2

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

April 25, 2002

SUBJECT: **Thiophanate-Methyl:** HED Human Health Risk Assessment for the Reregistration Eligibility Decision (RED) Document. Chemical No.102001. Barcode: D275774

FROM: Deborah C. Smegal, Toxicologist/Risk Assessor
José J. Morales, Chemist
Gary Bangs, Environmental Health Specialist
Sheila Piper, Chemist
Re-Registration Branch 3
Health Effects Division (7509C)

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

TO: Deanna Scher, Chemical Review Manager
Reregistration Branch 1
Special Review and Reregistration Division (7508C)

Attached is HED's human health risk assessment of the fungicide, thiophanate-methyl (TM), for purposes of issuing a Reregistration Eligibility Decision (RED) Document for this active ingredient. This assessment aggregates the risk estimates for carbendazim [methyl-2-benzimidazole carbamate (MBC)], which is a metabolite of TM, and is also registered for use in residential settings as a paint additive and for tree injection. Although MBC is also an environmental metabolite of benomyl, in April 2001, the benomyl registrant requested voluntary cancellation of all benomyl-containing products, with sales and distribution proposed to cease by December 31, 2001 (http://www.dupont.com, April 19, 2001). Therefore, potential exposures to MBC from benomyl use were not evaluated in this assessment. Cumulative risk assessment considering risks from other pesticides or chemical compounds having a common mechanism of toxicity is not addressed in this document. This assessment incorporates the public comments received during the Public Participation process. The disciplinary science chapters and other

supporting documents for the TM RED are also included as attachments as follows:

Report of the Hazard Identification Assessment Review Committee. J. Doherty and D. Smegal (3/7/2002; HED Doc No. 005041 for thiophanate-methyl) and D. Smegal (3/2001 for MBC)

Report of the FQPA Safety Factor Committee. B. Tarplee (For thiophanate-methyl: October 25, 2000; HED Doc No. 014363 and for MBC: July 1, 1999; HED Doc No. 013544 for MBC)

Revised Toxicology Chapter for Thiophanate-methyl and Carbendazim. D. Smegal and L. Hansen, March 14, 2002. D279278.

Occupational and Residential Exposure Assessment for Thiophanate-methyl. G.Bangs (March 15, 2001, D271922)

Occupational and Residential Exposure Assessment and Recommendations for the Risk Assessment Document for MBC. G. Bangs, March 2001, D273465.

Thiophante-methyl and its Metabolites Methyl 2-benzimidazolyl carbamate (MBC) and 2-Aminobenzamidazole (2-AB) Anticipated Residues, Acute, Chronic and Cancer Dietary Exposure Assessments for the Reregistration Eligibility Decision (RED) S. Piper, April 2002. D279277.

Thiophante-methyl Revision of Residue Chemistry Chapter for Reregistration Eligibility Decision. J. Morales (April 3, 2002; D279270)

Tier II Estimated Drinking Water Concentrations (EDWCs) for Human Health Risk for Thiophanate-Methyl (TM) and its degradate methyl-2-benzimidazole carbamate (MBC) on Oregon Pears and Turf. F, Khan, R. Pisigan to D. Scher and D. Smegal. April 2, 2002

Tier 1 Estimated Environmental Concentrations for Thiophanate-methyl and its major degradate, MBC. R. Pisigan/I. Abdel-Saheb, 1/19/2001.

Additional Estimated Environmental Concentrations for Thiophanate-methyl and its major degradate, MBC for application on Turf and Onions. R. Pisigan/I. Abdel-Saheb, 4/11/2001.

Review of Thiophanate-Methyl Incident Reports. J. Blondell and M. Spann. August 15, 1997. D230959.

HED's Hazard Identification Assessment Review Committee (HIARC) reviewed the toxicological database for TM (updated memorandum dated March 7, 2002) and its primary metabolite, carbendazim or MBC (memorandum dated March 2001) and selected toxicological endpoints for acute oral, chronic oral and for short-, intermediate and long-term dermal and inhalation exposure risk assessment. HED's FQPA Safety Factor Committee reviewed the hazard and exposure data for TM and recommended that the FQPA Safety Factor (as required by Food Quality Act of August 3, 1996) be reduced to 3X in assessing the risk posed by TM (memorandum dated October 25, 2000), and retained at 10X in assessing the risk posed by MBC (memorandum dated July 1, 1999).

This assessment has been revised to reflect the following mitigation measures:

- reduced maximum application rate on residential/public turf from 11-19.3 lb ai/acre to 2.74 lb ai/acre with a 14 day retreatment interval and 4 applications per season;
- only granular formulations are available to residents for broadcast turf treatment;
- liquid use on lawns will be restricted to pest control operators (PCOs);
- labels will be revised to specifically preclude belly grinder and hand application methods for residents only (but not PCOs); and
- PCO treatment of backyard fruit trees will be allowed only up to fruit set.

REVISED PRELIMINARY HUMAN HEALTH RISK ASSESSMENT:

THIOPHANATE-METHYL

April 25, 2002

Health Effects Division

Office of Pesticide Programs

U.S. Environmental Protection Agency

1.0 EXECUTIVE SUMMARY

The Health Effects Division (HED) has conducted a Human Health Risk Assessment for the active ingredient thiophanate-methyl (TM) for the purposes of making a reregistration eligibility decision (RED). This assessment evaluates all currently registered uses of TM, proposed new uses on canola, grapes, pears and pistachios, and two Section 18 emergency exemption requests on citrus (1 year only) and blueberries.

Thiophanate-methyl [dimethyl [(1,2-phenylene)bis(iminocarbonothioyl)] bis(carbamate)] is a systemic fungicide registered for use in a wide variety of agricultural, ornamental, and residential settings. The technical registrants are Cerexagri, Inc (formerly Elf-Atochem North America Agrichemicals), Nations Ag, Microflo and Gowan Pacific LLC. There are approximately 45 active registrations and 20 Special Local Need (SLN) registrations. There are approximately 62 tolerances. Major food/feed crops include: apples, dry beans, green beans, potatoes, sugar beets, and wheat. Non-agricultural uses include ornamentals, turf (sod farms, residential and recreational lawns), greenhouses, interior scapes, landscaping, and nursery use. There is potential exposure from agricultural, commercial operator, and residential uses. Due to the recent voluntary cancellation of the fungicide benomyl in 2001, the use of TM is expected to double in the next few years. The estimated annual usage is expected to range from 860,000 lbs ai/year (weighted average) to 1,495,000 lbs ai/year (estimated maximum) for agricultural uses. Non-agricultural use estimates (i.e., residential and golf course use) are not available.

Thiophanate-methyl formulations registered for use include dust (D), granular (G), wettable powder (WP), water-disperable granular (WDG), and flowable concentrate (FlC) and emulsifiable concentrate (EC) formulations, and ready-to-use liquid, ranging from 1.65% to 90% active ingredient (a.i). The dust formulation may be applied to potato seed-pieces at planting and the granular formulation may be applied as an in-furrow application to beans at planting. The remaining products may be applied as an in-furrow application at planting to onions (WP and WDG) or as postemergence broadcast applications to all other labeled crops using ground or aerial equipment.

Tolerances for residues of TM in/on plant and livestock raw agricultural commodities (RACs) are currently expressed in terms of TM, its oxygen analogue [dimethyl-4,4'-o-phenylene bis(allophanate)], and its benzimidazole-containing metabolites (calculated as TM). However, TM is metabolized by plants and animals and/or hydrolyzed under aqueous conditions to its major metabolite carbendazim or MBC (methyl 2-benzimidazole carbamate), which is also a systemic fungicide. Consequently, the HED Metabolism Committee recently recommended that the tolerance expression in 40 CFR §180.371 be modified to include residues of TM, and MBC (methyl 2-benzimidazole carbamate) in plant and animal commodities. Based on the Metabolism Committee recommendation, the residues of concern evaluated in the dietary risk assessment are TM, MBC and 2-AB (2-amine-1-H-benzimidazole) in plant commodities, and TM, MBC, and the hydroxylated metabolites of MBC (4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S) in animal commodities. There are two separate analytical methods that quantify the residues of concern, one method for plant commodities and one method for animal commodities (i.e., TM, MBC and 2-AB in plants and TM, MBC, 5–OH-MBC and 4-OH-MBC and 5-OH-MBC-S in animals).

Based on the revised tolerance expression, the current data collection methods are acceptable for all residues of concern in plant and animal commodities. However, the current enforcement method requires radiovalidation prior to EPA method validation.

Thiophanate-methyl is also degraded to MBC under environmental conditions. Therefore, MBC residues are present in food, drinking water and on lawns following TM use. In addition, MBC is registered for use as an in-can fungicide/preservative for paints, coatings, plaster and adhesives. MBC may be added to paints at a concentration of up to 0.5%. Therefore, residents could be exposed to MBC via dermal and inhalation exposure during painting activities. MBC also has a registered tree injection use: however, residential exposures resulting this use is considered to be negligible. Aggregate exposures to MBC (and metabolites of concern) resulting from TM, and MBC use have been estimated and evaluated in this report.

Hazard: Both TM and MBC are of low toxicity following acute oral, dermal and inhalation exposures (toxicity categories III/IV). TM is classified as a skin sensitizer, while MBC is not a skin sensitizer. TM and MBC share some common toxicological effects, including developmental and liver effects. Following oral exposures, the most sensitive target organs are the thyroid gland and liver for TM, and the liver for MBC. Dogs appear to be the most sensitive species for both compounds following chronic oral exposure. TM is generally less toxic than MBC for adverse developmental and liver effects. Both TM and MBC have been associated with an increased incidence of mouse liver tumors following chronic oral exposure. TM is classified as "likely to be carcinogenic to humans", while MBC is classified as a possible human carcinogen (group C). MBC has weak mutagenic activity that is primarily attributed to adverse effects on cellular spindle apparatus. In addition, both TM and MBC cause aneuploidy (i.e., abnormal number of chromosomes).

Both TM and MBC induce developmental toxicity. The developmental effects of MBC occurred in the absence of maternal toxicity, indicating increased fetal susceptibility. Fetal effects from TM exposure include an increase in supernumerary ribs, and reduced fetal weight, which occurred in the presence of maternal toxicity. In rats, adverse fetal effects attributed to maternal MBC exposure include decreased body weight, increases in skeletal variations and malformations, and ocular and brain malformations. TM induced adverse testicular effects in two chronic rat studies, including testis/leydig cell hyperplasia and other microscopic effects. MBC also induced adverse testicular effects such as reduced sperm counts, reduced testes size, and testicular pathology (i.e., atrophy and degeneration of the seminiferous tubules). Other reproductive effects observed only in the presence of parental toxicity include reduced pup weights.

Toxicity Endpoints. The toxicity endpoints used in this document to assess potential risks include acute dietary and chronic dietary reference doses (RfDs), and short-, intermediate- and/or long-term incidental oral, dermal and inhalation doses. HED's Hazard Identification Assessment Review Committee (HIARC) developed toxicity endpoints for both TM and its primary metabolite MBC based on exposure concerns. Because TM and MBC cause adverse developmental effects, HIARC identified two acute dietary reference doses (aRfDs) for each compound, one for females of child bearing age (13-50 years) and one for the general population, including infants and children.

Acute and Chronic RfDs. For TM, HIARC identified acute RfDs of 0.2 mg/kg/day and 0.4 mg/kg/day for females 13-50 yrs and the general population, respectively. The female 13-50 year aRfD is based on a adverse developmental effects (supernumerary ribs and decreased body weight in fetuses) in a rabbit developmental study, while the aRfD for the general population is based on tremors observed 2-4 hours following a single dose in dogs. The acute RfDs for MBC are 0.1 mg/kg/day and 0.17 mg/kg/day for females 13-50 yrs and the general population, respectively, based on adverse fetal effects (skeletal variations and other effects), and testicular effects, respectively. The TM chronic RfD (cRfD) is 0.08 mg/kg/day based on adverse thyroid effects and decreased body weight observed in a 1-year dog study, while the MBC cRfD is 0.025 mg/kg/day based on adverse liver effects from a 2-year dog study. An uncertainty factor of 100 (10X for interspecies extrapolation and 10X for intraspecies variability) was applied to the NOAELs to obtain all acute and chronic RfDs, except for the general population acute RfD for MBC, which has a total uncertainty factor of 300 (extra factor of 3) to account for the absence of a NOAEL.

Short-term (1-30 day) incidental oral endpoint: For TM and MBC, HIARC identified a short-term oral NOAEL of 10 mg/kg/day based on decreased body weight and food consumption following TM exposure of 20 mg/kg/day.

Dermal and Inhalation Endpoints. For TM, the short- and intermediate-term dermal endpoint is based on a NOAEL of 100 mg/kg/day based on decreased body weight and food consumption seen at 300 mg/kg/day in a 21-day rabbit dermal toxicity study. For MBC, the short- and intermediate term dermal NOAELs of 10 mg/kg/day based on adverse fetal effects noted in a rat developmental toxicity study at 20 mg/kg/day.

For TM, the short- and intermediate-term inhalation endpoints are based on an oral NOAEL of 10 mg/kg/day based on decreased maternal body weight and food consumption in the rabbit developmental toxicity study at 20 mg/kg/day. For MBC, the short-, and intermediate- term inhalation NOAEL is 0.96 mg/kg/day from a 90-day rat inhalation toxicity study with benomyl that observed adverse respiratory effects at 4.8 mg/kg/day. This study was selected to assess MBC in the absence of inhalation data for MBC.

The long-term TM dermal and inhalation endpoints are based on an oral NOAEL of 8 mg/kg/day from the chronic dog toxicity study that observed adverse thyroid effects and decreased body weight. Because an oral NOAEL was selected, absorption factors of 7% dermal and 100% inhalation were used in route-to-route extrapolation. The dermal absorption factor is based on a comparison of the oral developmental toxicity study and a 21-day dermal toxicity study in the same species (rabbit) with similar endpoints (decreased food consumption). The long-term dermal MBC NOAEL is 2.5 mg/kg/day based on liver toxicity noted in a 2-year dog toxicity study at 12.5 mg/kg/day (LOAEL). Because oral NOAELs were selected, a 3.5 percent dermal absorption factor was used for MBC, based on a rat dermal absorption study with benomyl.

Cancer. As previously noted, TM is classified as "likely to be carcinogenic to humans", while MBC is classified as a possible human carcinogen (group C). Both chemicals and are associated with hepatocellular tumors in certain strains of mice. HED estimated a unit risk Q_1^* of 1.16×10^{-2} $(mg/kg/day)^{-1}$ for TM is based on a dose-dependent increase in liver tumors in male CD-1 mice. HED estimated a unit risk Q_1^* of 2.39×10^{-3} $(mg/kg/day)^{-1}$ for MBC based on hepatocellular (adenoma and/or carcinoma) tumors in female CD-1 mice exposed to MBC.

FQPA Safety Factor: The Food Quality Protection Act (FQPA) Safety Factor Committee determined that the FQPA 10X safety factor should be reduced to 3X for TM and retained at 10X for MBC. In accordance with HED policy, a RfD modified by a FQPA safety factor is a population adjusted dose (PAD)[1].

The FQPA factor for TM is necessary, due to an incomplete toxicity database (acute and subchronic neurotoxicity studies are required due to evidence of neurotoxicity) and the requirement for a developmental neurotoxicity study has been 'reserved'. However, the FQPA factor was reduced to 3X because the available data provided no indication of increased susceptibility *in utero* exposure in the developmental studies in rats and rabbits or following pre- and/or postnatal exposure in the multi-generation reproduction studies in rats; and the dietary (food and drinking water) and non-dietary exposure assessments will not underestimate the potential exposures for infants and children from the use of TM. The 3X FQPA safety factor is applicable for all risk assessments for all population subgroups.

The 10X factor was retained for MBC due evidence of increased susceptibility following *in utero* exposure of MBC in the prenatal developmental toxicity study in rats and rabbits; and the need for developmental neurotoxicity studies in rats for MBC. The 10x FQPA safety factor is applicable for all risk assessments for females 13-50 years, infants, and children (1 - 6 years and 7-12 years).

Toxic Equivalency Factors: HED used a toxic equivalency factor (TEF) approach to sum exposure and risk estimates from TM and MBC as MBC equivalents consistent with USEPA guidance (USEPA 1999). A TEF approach was used because both TM and MBC share common toxicological effects (i.e., developmental and liver effects, and liver tumors), and because individuals are exposed to both compounds simultaneously on food commodities, in drinking water and on treated lawns. A non-cancer TEF is derived based on a ratio of the MBC PAD to the TM PAD. Using the TEF approach, TM exposure estimates were adjusted to account for the differences in toxicity endpoints between TM and MBC [i.e., acute PAD or aPAD is 0.067 mg/kg/day for TM, but 0.01 mg/kg/day for MBC, differing by a factor of 0.15]. For acute exposures to females of child bearing age (13-50 years), an TEF of 0.15 was used to convert TM exposures into MBC equivalents. For non-cancer chronic exposures, TEFs of 0.093 and 0.93 were used to convert TM exposures into MBC equivalents for females and children, and the general population, respectively. A cancer TEF value of 4.85 was used to convert the TM cancer exposure estimates to MBC equivalents (i.e., TM Q_1^* is 4.85 times more potent than the MBC Q_1^*).

---

[1] PAD= Population Adjusted Dose = $\frac{\text{Acute or Chronic RfD}}{\text{FQPA Safety Factor}}$

Dietary Exposure and Risk: The Agency conducted highly refined probabilistic acute, chronic and cancer dietary risk assessments for TM and MBC and other metabolites of toxicological concern for current and pending uses of TM. New and pending uses evaluated in this assessment include canola, grapes, pears, and pistachios and Section 18 emergency exemption petitions on citrus (1 year only) and blueberries. Because it is anticipated that the citrus tolerance for the Section 18 use will be established for only one year, for the cancer risk assessment, the lifetime exposure estimate attributable to this use was amortized. HED expresses dietary risk estimates as a percentage of the acute PAD (aPAD) or chronic PAD (cPAD). Dietary exposures that are less than the 100% of the aPAD or cPAD are below HED's level of concern.

Anticipated residues (ARs) were calculated using both USDA Pesticide Data Program (PDP) monitoring data for benomyl, measured as MBC, and field trial residue data, in addition to percent crop treated data. Field trial residue data are considered by the Agency as an upper-bound estimate of possible residues, and are designed for tolerance setting rather than to the requirements of dietary risk assessment. Where percent crop treated estimates indicated no TM use, a default minimum assumption of 1% crop treated was applied. Where residues were nondetectable, one-half the limit of quantitation (LOQ) was assumed for treated commodities.

The acute dietary risk estimates are less than HED's level of concern at the 99.9th percentile of exposure for all population subgroups for both TM and MBC. The acute dietary risk estimates range from 5% to 25% for TM and 4% to 89% for MBC of the acute PAD at 99.9th percentile exposure, with infants (< 1 year) being the highest exposed population subgroup. The chronic non-cancer dietary analysis indicates all risk estimates are below HED's level of concern for all population subgroups for either TM or MBC. The highest chronic dietary risk estimates are 2% and 26% of the chronic PAD, for TM and MBC, respectively, for the highest exposed population subgroup, children (1-6 years). The lifetime cancer risk estimates range from $6.4x10^{-7}$ to $1.1x10^{-6}$ for TM, and $7.7x10^{-8}$ to $9.3x10^{-8}$ for MBC, depending on the uses, and whether field trial or PDP data were used. Generally, HED is concerned when cancer risk estimates exceed $1x10^{-6}$ or one-in-one million.

In addition, total TM and MBC dietary risks were estimated using the TEF approach because both chemicals cause similar toxic effects following oral exposure, and because simultaneous exposure is plausible for these chemicals on food commodities given the rapid degradation of TM to MBC. The highest acute dietary risk estimate represents 51% of the aPAD for developmental effects for females 13-50 years of age. The highest total non-cancer chronic risk estimate is 29% of the cPAD for liver/thyroid effects, for children 1-6 years. The total TM and MBC lifetime cancer risk estimates range from $7.2x10^{-7}$ to $1.1x10^{-6}$ for existing TM registered uses. Cancer risk estimates range from $7.4x10^{-7}$ to $1.1x10^{-6}$ for existing uses and the amortized exposure associated with the Section 18 use on citrus. Cancer risk estimates range from $8.5x10^{-7}$ to $1.2x10^{-6}$ for existing and new uses, in addition to Section 18 for citrus (1 year only). The cancer risk estimates based on field trial data are slightly above the lifetime risk estimates the level the Agency generally considers to be negligible for excess lifetime cancer risk (i.e., $1x10^{-6}$). The cancer risk estimates based on benomyl/MBC PDP monitoring data are below $1x10^{-6}$ for TM existing and new uses, and considering the amortized Section 18 use for citrus.

Water Exposure and Risk: The available environmental fate data suggest that TM rapidly degrades to MBC in the environment (i.e., <1 to 2 days in aerobic soil, and water, respectively). Therefore, both TM and MBC are likely to be present in ground water or surface water following TM use. MBC has a low potential to leach to groundwater in measurable quantities from most typical agricultural uses based on its high soil organic carbon partition coefficient (Koc) of 2,100 l/kg, respectively. MBC is less mobile, and significantly more persistent in many soils, especially under anaerobic conditions than TM.

There are no drinking water monitoring data on the concentrations of TM or MBC from registered TM uses. Therefore, potential exposures and risks from TM and MBC residues in drinking water were assessed using modeling techniques (Tier 1 SCI-GROW for groundwater and Tier 2 PRZM/EXAMS for surface water) provided by the Environmental Fate and Effects Division (EFED). Inputs to the models included the highest annual TM use rates on pears and proposed rates on turf based on risk mitigation measures. For risk assessment purposes, groundwater estimated acute and chronic environmental concentrations (EECs) range from 0.006 to 0.033 ppb for TM and 0.51 to 3 ppb for MBC. For TM, long-term average EECs in surface water range from 0.41 to 1.13 ppb, while acute EECs range from 19.5 to 22.7 ppb based on the same assumptions. For MBC, long-term average EECs in surface water range from 5.98 to 23.4 ppb, while acute EECs range from 24.9 to 40.9 ppb. Under HED's interim approach for incorporating estimated exposures to residues of TM, MBC or both in drinking water, drinking water level of comparisons (DWLOCs) are compared to EECs. When EECs are greater than the DWLOCs, HED considers the estimate of aggregate risk to exceed HED's level of concern. In accordance with current OPP policy (S. Johnson 11/17/97), if the EECs exceed the DWLOCs, water monitoring data may be required to refine the drinking water exposure estimate.

Residential Exposure and Risk: Based on risk mitigation, most of the residential/non-occupational scenario risk estimates are below HED's level of concern for both residential handlers and postapplication exposures for both non-cancer and cancer assessments, except for incidental oral exposures to young children the day of treatment. Potential residential exposures are anticipated as a result of homeowner application and professional lawn care operator application. The Agency evaluated TM exposures to residential handlers during mixing, loading and application to turf and TM postapplication exposure to residues by adults and children on treated turf. The duration of exposure is short-term (1-30 days) for both residential handlers, and postapplication exposures. Exposure scenarios with risk estimates for TM that exceed HED's level of concern (i.e., MOEs <300) are: children playing on treated lawns (MOEs of concern range from 31 to 250) for hand to mouth activities and incidental granular ingestion. The scenarios with MOEs above 300 for TM that are not of concern are: high dermal contact (such as hand weeding, and playing), mowing activities, golfing, spot treatments of ornamentals, and broadcast lawn treatment with a push-type spreader. Residential handler cancer risk estimates range from 4.7×10^{-9} to 2.8×10^{-8}, while post-application cancer risk estimates range from 1.3×10^{-9} to 1.3×10^{-7}. Residential risk estimates utilized the submitted residue dissipation studies and a turf transfer study, as well as the EPA's updated (2001) SOPs for Residential Exposure Assessment.

Aggregate Exposure and Risk: As mandated by the FQPA amendments to the Federal Food, Drug and Cosmetic Act (FFDCA), the Agency must consider total aggregate exposure from food, drinking water, and residential sources of exposure to TM and MBC. This aggregate assessment considers exposure to TM and MBC from food, drinking water and residential uses. In addition, there may be concerns about possible residential exposure from TM spray drift. The Agency is currently developing methods to assess residential exposures and risks from spray drift, and these will be assessed in the future when new methods are available. Because both TM and MBC have common acute, short-term oral and chronic toxicity endpoints (i.e., developmental effects for acute, decreased body weight and food consumption for short-term, and liver effects and liver tumors for chronic), it is appropriate to add TM and MBC dietary (food and water) and residential risk estimates. In addition, because TM degrades to MBC, individuals may be exposed to both residues simultaneously on a given food commodity or via drinking water. Risk estimates were combined using the previously described TEF approach. The acute, short-term, and chronic non-cancer and cancer aggregate TM and MBC risk estimates exceed HED's level of concern for combined exposure to TM and MBC through food, drinking water sources and/or residential uses.

Aggregate food and drinking water risk estimates for acute and chronic non-cancer scenarios for TM and MBC, exceed HED's level of concern for infants and/or children (1-6 years) because the EECs are greater than the HED Drinking Water Levels of Comparison (DWLOCs). Aggregate risks for the short-term and cancer assessments also exceed HED's level of concern because residential and food exposure estimates alone, respectively exceed HED's level of concern (i.e., > $1x10^{-6}$ lifetime cancer risk estimate, and residential exposures have MOEs <300 for TM). As a result, the HED DWLOCs are effectively zero. For acute effects for infants (< 1 year), and for chronic non-cancer effects for infants and children (1-6 years) the estimated surface water concentrations of TM and MBC (as MBC equivalents) slightly exceed the DWLOC and HED's level of concern. However, the estimated groundwater concentrations do not exceed the DWLOC for either acute or non-cancer chronic effects, or HED's level of concern. The modeled EECs are based on conservative assumptions regarding the application and fate and transport of TM and MBC, and do not reflect dilution to source tap nor water treatment.

HED also conducted an aggregate exposure assessment for MBC resulting from registered uses of TM, and MBC. TM, which degrades to MBC, is registered for residential lawn and home orchard use, and is applied to golf courses. MBC is registered as an in-can paint preservative. The aggregate MBC exposure from all uses (TM and MBC) and TM risk estimates exceed HED's level of concern for acute, short-term, chronic non-cancer and cancer estimates. Dietary exposures to MBC (from TM use), residential exposures to TM, and exposures resulting from MBC's use as a paint additive were the most significant contributors to the aggregate risk estimates of concern.

Occupational Exposure and Risk: Occupational exposures to TM can occur during handling, mixing, loading and application activities. Because environmental fate data demonstrate that TM is converted to MBC, postapplication exposures were evaluated for both TM and MBC residues. Occupational postapplication exposure can occur for agricultural workers during scouting, irrigation, cultivation, harvesting and handling seeds, seedlings, and seed pieces.

Based on toxicological criteria and potential for exposure, HED has conducted dermal and inhalation exposure assessments for occupational handlers exposed to TM and dermal exposure assessments for occupational postapplication exposures to TM and MBC. Inhalation is not expected be a significant postapplication exposure route, except for possibly handling treated seeds for planting, for which limited non- chemical-specific data are available. The duration of exposure is expected to be short-, and intermediate-term for both occupational handler, and postapplication exposures during agricultural and harvesting activities, and long-term for a few postapplication activities. The exposure duration for short-term assessments is 1 to 30 days. Intermediate-term durations are 1 to 6 months, and long-term durations are greater than 6 months. For dermal and inhalation risk assessment, risk estimates are expressed in terms of the Margin of Exposure (MOE), which is the ratio of the NOAEL selected for the risk assessment to the exposure. For occupationally exposed workers, MOEs $\geq$100 (i.e., 10x for interspecies extrapolation and 10x for intraspecies variability) for dermal and inhalation exposures are considered to be below the Agency's level of concern.

The majority of occupational risk estimates for handlers exposed to TM do not exceed HED's level of concern with personal protective equipment (PPE) or engineering controls. HED identified 23 major handler scenarios, which when combined with the typical range of application rates resulted in over 190 scenarios. For mixing and loading wettable powder formulations to support aerial or chemigation applications, engineering controls (i.e., water-soluble packaging) are required to achieve the target MOE for many crops and use patterns. The MOEs were less than 100 for the highest application rate for loader/applicators using push-spreaders and belly grinders, for which no feasible engineering controls are available.

Cancer risks were estimated for the various handler scenarios assuming individual or farm-based ("private") applicators would apply less frequently than professional or "commercial" operators using only the average or "typical" application rates. With baseline clothing, most of the exposure scenarios had estimated cancer risks less than 10^{-4}, but greater than 10^{-6}. The estimates for private and commercial handlers range from $1.6x10^{-4}$ to $8.6x10^{-9}$, and from $1.5x10^{-3}$ to $2.6x10^{-8}$, respectively. With the addition of PPE, cancer risk estimates for all private and commercial handler scenarios were less than 10^{-4}. With PPE, cancer risk estimates for private and commercial handlers ranged from $1.9x10^{-8}$ to $2.5x10^{-5}$, and from $1.2x10^{-8}$ to $8.7x10^{-5}$, respectively. With the addition of engineering controls, where feasible, cancer risk estimates for all private handler scenarios were equal to or less than $6.8x10^{-7}$, and estimates for commercial applicators ranged from $1.3x10^{-7}$ to $4.5x10^{-6}$. Handler scenarios with high application rates, very high acreage crops (i.e., 1200 acres per day) or hand-held application equipment generally had cancer risk estimates greater than 10^{-6}, even with addition of PPE or engineering controls. Most hand application methods (hand-directed sprays, spreaders, etc.) do not have a practical means of enclosure or other engineering control. There are insufficient data to adequately assess the seedling or dip applications, and additional data are requested to support these uses. The agricultural handler assessments are believed to be reasonable representations of TM uses. Surrogate data from the Pesticide Handlers Exposure Database (PHED), Occupational and Residential Exposure Task Force (ORETF), or published literature, were used to assess handler exposure because no chemical-specific studies are available.

Chemical-specific postapplication dislodgeable foliar residue (DFR) data were submitted for apples, strawberries and turf and cut flowers. These data were used along with HED standard transfer coefficients derived using recently submitted Agricultural Re-entry Task Force (ARTF) data, to assess potential exposures to workers reentering treated sites. The occupational postapplication assessment is believed to be reasonably representative of TM uses.

The results of the short- and intermediate-term dermal postapplication assessments for workers exposed to TM and MBC indicate that the MOEs were less than 100 for grapes, citrus, almonds, cut flowers and some lawn-care activities at the current WPS-required restricted entry intervals (REIs) of 12 hours, and therefore exceed HED's level of concern. The REI represents the duration in days which must elapse before the Agency would not have a concern (MOE $\leq$ 100) for a worker wearing a long-sleeved shirt and long pants to enter the treated area and perform specific tasks. Overall, the days necessary to reach a target MOE ranged from 0 days to 67 days (cut flowers), although most crops had MOEs of 100 at postapplication day 1. Using translated apple DFR data, grapes required up to 28 days, citrus up to 3 days, and almonds about 2 days to attain an MOE of 100 for workers. High-contact activities on turf required 2 days to attain an MOE of 100 using a TM TTR study. Row crop reentry risk estimates using strawberry DFR data indicated 1 day was sufficient to achieve an MOE of 100 for all assessed scenarios. These risk estimates are less certain for crops which do not resemble strawberry plants in architecture and leaf surface. Cut flower risk estimates, using data for transfer coefficients and residues from TM studies, showed MOEs of 100 were not attained until 1-2 months (41-67 days) after application. Using 14 day average residues, cancer risk estimates for most activities on most crops were between 10^{-4} and 10^{-6}, although some high-contact activities exceeded 10^{-4}, notably those involving cut flowers.

A worker post-application exposure scenario was also assessed for the MBC metabolite of TM. The same assumptions as for TM exposure assessment were used along with the maximum MBC residue measured in the DFR studies. The highest MBC DFR value was used because of the uncertainties in the percentage of TM that degrades to MBC at any time in the environment, as well as the dissipation rate of MBC. The risk assessment indicates that noncancer risks to postapplication workers do not exceed the level of concern (MOE >100) from exposures to MBC residues as a degradate of TM. For short/intermediate-term risks, the MOEs range from 350 to 630,000 with a target of 100, while long-term MOEs ranged from 100 to 6,000. Cancer risk estimates range from 2.6×10^{-9} to 4.4×10^{-6}. TM residues alone were used to calculate the time required postapplication to achieve MOEs $\geq$100, as the highest detected MBC residue in the DFR studies resulted an MOE of 350 for short/intermediate-term exposure, and 100 for long-term exposures.

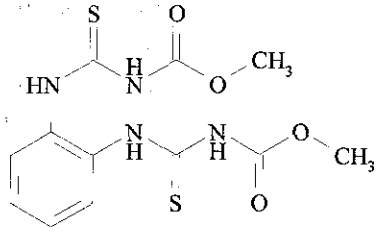
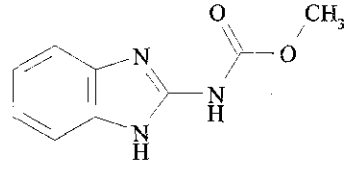
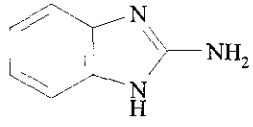
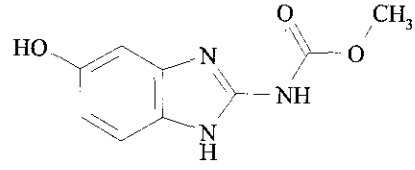
Data Gaps. The toxicological database is not complete, and several studies have been requested. Residue chemistry requirements are outstanding, including storage stability data to support the residue data for plant commodities. The current enforcement method still requires radio-validation prior to EPA method validation. The Agency has insufficient data to assess handler or post-application exposure during mixing, loading, or applying pesticides for seedling or bulb dip treatment, and additional data are requested to support these uses.

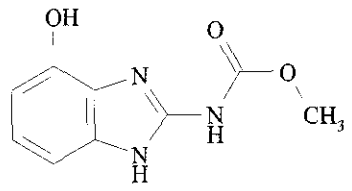
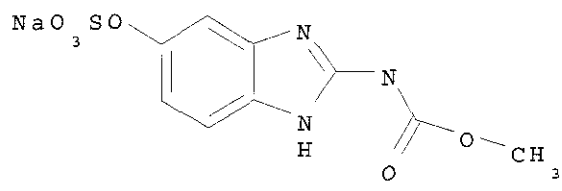
2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Thiophanate-methyl [dimethyl [(1,2-phenylene)bis(iminocarbonothioyl)] bis(carbamate)] (CAS Registry No.:23564-05-8) has an empirical formula of $C_{12}H_{14}N_4O_4S_2$, and a molecular weight of 342.4. Pure TM is a colorless crystalline solid with a melting point of 168 °C with decomposition. Technical TM is a pale brown powder which begins to decompose at ~163 °C. Thiophanate-methyl is slightly soluble in water (21.8 ppm) and sparingly soluble in most organic solvents at 25 °C (2.9 g/100 mL acetone; 7.8 x 10^{-1} g/100 mL methanol; 8.4 x 10^{-1} g/100 mL ethyl acetate; 7.3 x 10^{-2} g/100 mL dichloromethane; 1.8 x 10^{-2} g/100 mL n-octanol; 1.1 x 10^{-2} g/100 mL xylene; and 4.7 x 10^{-5} g/100 mL n-hexane). TM is a semi-volatile compound based on its vapor pressure of 1.3x10^{-5} mmHg.

The HED Metabolism Committee (S. Funk, 3/6/97) has concluded that the residues to be regulated in plant and animal commodities for purposes of tolerance enforcement will consist of TM and its metabolite methyl 2-benzimidazolyl carbamate (MBC). For purposes of dietary risk assessment, the residues of concern in plants will include TM, MBC, and 2-aminobenzimidazole (2-AB). In animal commodities, the residues of concern will include TM, MBC, and the hydroxylated metabolites of MBC (4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S). The chemical names and structures of these compounds are depicted in Figure A.

Figure A. Chemical structures of thiophanate-methyl residues of concern.

<table>
<tr>
<td> 
Thiophanate-methyl; dimethyl [(1,2-phenylene)bis (iminocarbonothioyl)]bis(carbamate)</td>
<td> 
MBC: methyl-2-benzimidazole carbamate</td>
</tr>
<tr>
<td> 
2-AB: 2-amine-1H-benzimidazole</td>
<td> 
5-OH-MBC: Methyl 2-(5-hydroxybenzimidazolyl) carbamate</td>
</tr>
</table>

	
4-OH–MBC: Methyl 2-(4-hydroxybenzimidazolyl) carbamate	**5-OH-MBC-S: sodium 5-(2-methoxycarbonylamino) benzimidazolyl sulfate**

TM rapidly degrades to carbendazim (MBC) in surface water (i.e., less than one day). MBC is also a white solid that has a molecular weight of 191.2 and is not very soluble in water (8 mg/L at pH of 7). MBC is more stable than TM, especially under aerobic conditions. MBC has a typical aerobic soil metabolism half life ($T_{½}$) of 320 days and aerobic and anaerobic aquatic metabolism half life of 61 days (Memorandum from I. Abdel-Saheb to D. Smegal, Drinking Water Assessment for TM, September 1999). The soil/water partition coefficient (K_{oc}) value for MBC is 2,100 l/kg, indicating that MBC is not very mobile in soils. MBC is not volatile based on its low vapor pressure of $1x10^{-7}$ mmHg at 20° C.

There are six TM end-use products (EP) with food/feed uses registered to Cerexagri, Inc (formerly Elf Atochem North America). These products include Topsin M® 70W, Topsin® M 5D, Topsin® M 4.5F, Topsin® M 5G, Topsin® M 85WDG and Topsin® M WSB. However, there are 36 active registrations and 22 special local need registrations. Most pertinent data requirements are satisfied for the TM product chemistry; however, additional data are required concerning OPPTS 830.1620, 830.1670, 830.6313, and 830.7050.

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile Overview

Adequacy of Toxicology Database/Data Gaps: At this time, the toxicology database for TM is incomplete. The Hazard Identification Assessment Review Committee (HIARC report dated March 7, 2002 from J. Doherty and D. Smegal to C. Eiden, HED Doc. No.005041) requested that rat acute and subchronic neurotoxicity screening studies be submitted and that a developmental neurotoxicity study be placed in 'reserve' status pending the results of these studies and a developmental neurotoxicity study with MBC. The HIARC also requested a 90 day rat inhalation study because an unacceptable 14-day inhalation study showed possible respiratory effects from TM exposure at lower concentrations than those associated with developmental effects and because there are potential long-term inhalation exposures associated with the green house use. Although the Cancer Assessment Review Committee (CARC, April 28, 1999 meeting) requested additional genotoxicity studies, the Agency has since determined that these studies are no longer necessary based on a review of additional data submitted by the registrant.

The quality of the currently available acceptable toxicity studies on TM is considered high.

Toxicology data for carbendazim (Methyl 2-Benzimidazole Carbamate) or MBC, the primary metabolite and environmental breakdown product of TM, are also considered in this assessment. In foods and the environment, TM rapidly transforms to MBC, hence environmental residues on plants and water to which people maybe exposed are primarily MBC. MBC is also registered for use as a systemic fungicide in paints in residential settings, but has no registered food uses in the US, nor import tolerances. The HIARC requested two toxicity studies with MBC, a 21 day dermal toxicity study in rats and a developmental neurotoxicity study in rats. In addition, the 2-generation rat reproduction and subchronic studies for MBC fail to meet the Subdivision F Guidelines. The available toxicology studies are summarized in Appendix A (Tables A-1 and A-2 for TM and MBC, respectively).

Acute Toxicity. Both TM and MBC possess a low order acute toxicity by oral, dermal and inhalation routes of exposure (categories III/IV). TM is only slightly irritating to the skin and is not an ocular irritant (both category IV), but is a dermal sensitizer. MBC is in category III for primary eye irritation. MBC is not a skin sensitizer. Acute toxicity values and categories for the technical grade of TM and MBC are summarized on Tables 1 and 2, respectively.

Subchronic/Chronic Systemic Toxicity: The liver and thyroid are the primary target organs of TM in several species following subchronic or chronic dietary exposure. In the Fischer-344 rat subchronic toxicity study, thyroid and liver enlargement, hepatocellular hypertrophy and thyroid hypertrophy/hyperplasia were observed, although alterations in thyroid hormone levels were not reported. In the chronic toxicity/carcinogenicity study on Fischer-344 rats, thyroid and liver were enlarged and alterations in circulating thyroid hormones [increased thyroid stimulating hormone (TSH); decreased T3/T4] were observed. Serum cholesterol was also increased. Microscopically, liver hypertrophy, lipofuscin pigmentation, focal fatty degeneration and necrosis were observed in males and hypertrophy and lipofuscin deposition in females. Thyroid hypertrophy and hyperplasia were seen in both sexes. In the beagle dog, similar thyroid and liver effects and related clinical chemistry alterations were also observed with subchronic or chronic exposure. Serum alkaline phosphatase was also increased following chronic exposure. In the 18-month CD-1 mouse carcinogenicity study, liver enlargement and hypertrophy, and enlarged thyroid and hypertrophy/hyperplasia, were also reported. However, thyroid effects were less pronounced than in the rat or dog, with enlargement and hypertrophy/hyperplasia and sporadic circulating hormone alterations observed only at high dose levels (>1000 mg/kg/day). The effects observed in the thyroid are consistent with disruption of the thyroid-pituitary homeostasis, but additional information is considered necessary to sufficiently support this mechanism.

Adverse testicular effects were observed in two chronic rat studies. In the 1971 study, adverse microscopic effects occurred following long-term exposures to 24.3 mg/kg/day TM. In the more recent 1993 study, significant testis/leydig cell hyperplasia was noted in all male dose groups, which was significantly elevated in the 3.3, 8.8 and 54.4 mg/kg/day groups but significantly decreased in the 280 mg/kg/day group. The testes is a known target organ of carbendazim (MBC), the primary metabolite of TM.

In addition to liver and thyroid effects, TM also appeared to cause mild anemia at the higher dose levels in rats, dogs and mice following subchronic or chronic exposure. In rats, TM caused toxicity to the kidney and increased urinary protein (males), lipofuscin pigmentation and increased severity of nephropathy were reported following chronic administration. An increase in systemic calcification was observed in males and to a lesser extent in females and was probably secondary to hyperparathyroidism. Decreased body weight/weight gain was observed in both sexes. Male rats appeared to be more sensitive than females based on greater severity of effects and high mortality at the highest dose tested (6000 ppm or 280.6 mg/kg/day, males and 334.7 mg/kg/day, females). Beagle dogs also showed decreased body weight. In the 1 year dog study, transient tremors at the highest dose tested (HDT of 200 mg/kg/day) were also observed. In the mouse carcinogenicity study, increased heart weight (females) and incidence of atrial thrombosis were observed.

TM is a carbamate but only limited data are available on its potential to inhibit cholinesterase (ChE). As a class of compounds, thiocarbamates do not produce consistent cholinesterase inhibition patterns. In the rat subchronic toxicity study, serum cholinesterase activity was increased in males by 22-38% relative to controls but decreased in females by 25-28% at ≥293.2 mg/kg/day. In the rat chronic toxicity/carcinogenicity study, males showed increases in serum ChE at 280.6 mg/kg/day (HDT) at 6 and 12 months (41-42%) whereas at 24 months, it was decreased (-38%). ChE activity in females was slightly decreased (18-35%) at 6 and 12 months at ≥63.5 mg/kg/day. RBC and brain ChE activities were not evaluated. ChE was not measured in the subchronic or chronic dog studies.

TM administered dermally to rabbits over a period of 21 days (5 days/week, 6 hrs/day) caused decreased food consumption in females at 300 and 1000 mg/kg/day and in males at 1000 mg/kg/day. Because this decrease was reported in both sexes and a dose-response was observed in females, it is considered treatment-related although no other signs of toxicity were observed. Comparison of this dermal LOAEL with an oral LOAEL (maternal toxicity, rabbit developmental toxicity study) suggests that TM is poorly absorbed into the skin. Dermal absorption was estimated at about 7% of the applied dose.

The only inhalation toxicity study submitted was a 14-day inhalation toxicity study on a formulation containing 5.2% TM. Local pulmonary effects were observed at the LOAEL of 0.0151 mg/L and decreased body weights at the HDT. However, in addition to testing a formulation and not the technical a.i., this study did not evaluate all of the standard parameters (e.g., clinical chemistry, hematology, organ weights, complete gross/microscopic tissue evaluation) and therefore does not provide adequate information on toxicity via the inhalation route.

Only one subchronic oral study in dogs was available for MBC. Although classified as unacceptable, both liver and testicular effects were noted at MBC doses as low as 35-40 mg/kg/day. Chronic toxicity studies are available for MBC in rats, mice and dogs. In all species, the most sensitive toxicological endpoint is liver toxicity that occurred at levels as low as 12.5 mg/kg/day for MBC, indicating that MBC may be more toxic than TM following chronic exposure. Dogs appear to be the most sensitive species for liver toxicity following chronic oral exposure to MBC.

Carcinogenicity. TM is classified as "likely to be carcinogenic to humans". TM caused a dose-related increase in the incidence of thyroid follicular cell tumors in male and female F-344 rats at the highest 2 dose levels tested (greater than or equal to54.4 mg/kg/day). In males, a positive increasing trend and a pair wise increase in incidence of adenomas, carcinomas and combined adenomas/carcinomas at the HDT were observed. In females, the incidence of adenomas was lower and showed a significant increasing trend but no pair wise increase. No carcinomas were observed. In both sexes, the incidence was increased above available historical control values; however, these data were not from the study lab or from the same supplier within 2-3 years of the study conduct. In CD-1 mice, statistically significant, dose-dependent increases in hepatocellular adenomas were observed in males at the highest 2 dose levels tested (greater than or equal to 476.6 mg/kg/day) and also in females at greater than or equal to 123 mg/kg/day. A significant increasing trend was also observed in both sexes. The combined incidence of adenoma and carcinoma was also increased in males, but the incidence of carcinomas alone was not increased. These incidences were above the available historical control values for studies from the same lab and for the same strain from the supplier, some within 2-3 years of the conduct of this study.

MBC is classified in group C (possible human carcinogens) because it induced liver tumors (hepatocellular adenoma and/or carcinomas) in mice. There is no evidence of carcinogenicity in rats for MBC. It is noted that the MBC rat studies only tested 36 rats/sex/dose (and only 20/sex/dose in the 250 mg/kg/day MBC dose group), when current guidelines require 50 rats/sex/dose.

Developmental/Reproductive Toxicity: Developmental toxicity was observed in the fetuses of rabbits exposed to 40 mg/kg/day TM and included increased incidence of supernumerary ribs and decreased fetal weight. These findings occurred at a dose that also caused maternal toxicity based on decreases in body weight gain (decreased 6%) and food consumption (decreased 24-70%). There were no abnormalities observed in the rat at gavage doses up to 1000 mg/kg/day or in the rat dietary developmental study as doses up to 163 mg/kg/day. Increased offspring sensitivity was not observed in the reproductive toxicity studies. In the 2-generation reproductive toxicity study, parental toxicity was observed at all doses tested (greater than or equal to13.7 mg/kg/day) based on mild hepatocellular hypertrophy and thyroid hypertrophy/hyperplasia, whereas offspring toxicity was observed at greater than or equal to 43.3 mg/kg/day as slightly reduced body weights of the F2b offspring during lactation. Although the offspring NOAEL and LOAEL (8 mg/kg/day and 32 mg/kg/day, respectively) were lower than the parental systemic NOAEL and LOAEL (greater than or equal to32 mg/kg/day and > 32 mg/kg/day, respectively) in the 3-generation reproductive toxicity study, liver and thyroid of parental animals were not evaluated and therefore the evidence for increased offspring susceptibility in that study is considered equivocal.

As noted previously, TM was associated with adverse testicular effects in the two chronic rat studies, including adverse microscopic effects at 24.3 mg/kg/day, and significant testis/leydig cell hyperplasia in males at doses as low as 3.3 mg/kg/day.

There is increased sensitivity of rat and rabbit fetuses as compared to maternal animals following *in utero* exposure to MBC, 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, i.e., some malformations noted but not statistically significant) at doses of 20 mg/kg/day which were not maternally toxic. At higher doses of 90 mg/kg/day, treatment-related malformations of the central nervous system (CNS) were observed which included exencephaly, domed head, anophthalmia, microphthalmia and bulged eyes. 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.

MBC was associated with adverse reproductive effects (decreased birth weight at weaning) in an unacceptable reproductive toxicity study in rats. MBC also caused adverse testicular effects characterized by premature release of immature germ cells, atrophy of a few seminiferous tubules and significant decrease in seminiferous tubule diameter following a single gavage dose with 50 mg/kg (Nakai et al. 1992). In addition, evidence of testicular effects has been demonstrated in the unacceptable 90-day subchronic dog study with MBC.

Genotoxicity. Although the acceptable submitted genotoxicity studies (*in vitro* CHO cytogenetic and rat liver unscheduled DNA synthesis assays) were negative, two published reports (mouse bone marrow micronucleus and BALB/c 3T3 cell transformation assays) demonstrated that TM is aneugenic. Although weak equivocal positive results were observed in a published Ames assay, TM was negative in a recently reviewed bacterial reverse gene mutation study.

In 1999, the CARC (April 28, 1999) determined that additional genotoxicity testing should be provided to adequately assess direct mutagenicity of TM: (1) a *Salmonella typhimurium* mammalian microsome gene mutation assay (pre-incubation modification) to resolve the equivocal results from the literature; (2) a mouse lymphoma L5178Y mammalian cell forward gene mutation assay, including colony sizing; (3) an *in vivo* mouse micronucleus assay should be performed and the Agency prefers that this assay include immunofluorescent antikinetochore-specific antibody staining. Finally, (4) the 2-aminobenzimidazole metabolite of TM should be tested at minimum in the *S. typhimurium* mammalian microsome gene mutation assay because of the structural alert for mutagenesis (i.e, the amine (NH_2) group attached to the imidazole ring). However, since the 1999 CARC meeting, HED reviewed an additional bacterial reverse gene mutation study, which included an independent repeat trial of the preincubation modification to the conventional plate incorporation protocol, and concluded that TM is negative for gene

mutations in *S. typhimurium* and *Escherichia coli* up to insoluble (625-5000 ug/plate) and cytotoxic (greater than or equal to 312.5 ug/plate -S9; 5000 micrograms/plate +S9) concentrations.

In light of this information, HED agrees that the need to conduct further mutagenicity testing (i.e., mouse lymphoma forward gene mutation assay with colony sizing and an *in vivo* micronucleus assay with antikinetochore-specific immunofluorescent antibodies) is not warranted. Since it has been established by the CARC that TM is an aneugen, nothing further would be gained from performance of a repeat micronucleus assay. Similarly, TM is now listed as negative for gene mutations and there is no evidence in the data base which suggest possible mutagenic activity. Therefore, it is concluded that the available data, including the recently reviewed bacterial reverse gene mutation assay, are adequate to characterize the mutagenic potential of TM.

MBC has marginal mutagenic activity in standard in vitro studies. In contrast, there is clear and reproducible evidence of aneuploidy (i.e., abnormal number of chromosomes) both in vitro and in vivo. There is also convincing evidence that the induction of aneuploidy by MBC is primarily attributed to adverse effects on cellular spindle apparatus. MBC is an established spindle poison that induces aneuploidy effects in both in vitro and in vivo test systems. For example, nondisjunction was reported in A. nidulans and many other test systems. MBC also produced positive effects in bone marrow antikinetochore micronucleus assays, which were consistent with a spindle effect. However, MBC is not clastogenic. Since the genotoxic activity of MBC is well known, MBC is frequently used as a test chemical (i.e., positive control) for the assessment of new assay systems for the detection of aneuploidy induction.

In mutagenicity studies with MBC, there is compelling evidence of aneuploidy induction following oral dosing in mice. Mutagenicity data support the evidence of developmental anomalies in rats and hepatocellular tumors in several strains of male and female mice.

Neurotoxicity. No acute or subchronic rodent neurotoxicity screening studies (§81-8 and §82-7) were submitted for TM. The HIARC (meeting of 4/8/99) determined that these studies should be submitted based on (1) potential clinical signs of neurotoxicity in the chronic dog study (transient tremors) and (2) existence of a common metabolite, MBC, with benomyl. In an earlier HIARC meeting (memorandum from J. Rowland to B. Madden, 12/3/97; HED Doc. No. 012418), it was determined that benomyl, which has a metabolite in common with TM (MBC), showed potential signs of neurotoxicity in the acute and subchronic rat neurotoxicity screening studies. In addition, in the rat developmental toxicity studies, both MBC (MRID No. 40438001) and benomyl (MRIDs 00148393, 00119017) caused developmental neurotoxic effects. Developmental neurotoxicity studies (§83-6) were therefore requested for benomyl and MBC. A developmental neurotoxicity study for TM is in 'reserve' status pending the receipt/evaluation of neurotoxicity studies and development of a policy on the need for a developmental neurotoxicity study for pesticides that cause thyroid toxicity. The Agency has concern for potential effects on the development of the nervous system if TM has antithyroid activity.

MBC does not appear to cause delayed neurotoxicity in hens. Developmental CNS malformations were noted in the MBC prenatal developmental toxicity study in rats, which included exencephaly, domed head, anophthalmia, microophthalmia and bulged eyes.

Metabolism/Pharmacokinetic Studies. There was no significant retention of TM or its metabolites in tissues and most of the administered dose was excreted within 24 hrs post-dosing. The extent of metabolism of parent compound and amount of radioactivity excreted in the urine and feces was greatest following a single oral low dose compared to a single oral high dose or repeated low dosing.

In the rat, MBC is excreted primarily in the urine with lesser amounts excreted in the feces, and MBC is poorly distributed to the tissues. MBC was rapidly absorbed and extensively metabolized in CD/BR rats following single oral doses up to 1000 mg/kg. The half-life of MBC was approximately 12 hours, and 98% of MBC was excreted by 72 hours post-administration. The primary reactions involved in the metabolism of MBC were oxidation of the phenyl ring, followed by conjugation to yield sulfate and glucoronide conjugates of 5-hydroxycarbendazim and 5,6-dihydroxycarbendazim. Subsequent phenyl ring oxidation and N-oxidation at the imidazole nitrogen led to significant levels of 5,6-hydroxy-oxo-carbendazim N-oxide glucuronide conjugate, especially in female rats.

Dermal Absorption. HED estimated a dermal absorption rate of 7% based on the results of an oral developmental toxicity study (LOAEL of 20 mg/kg/day) and a 21-day dermal toxicity study (LOAEL of 300 mg/kg/day) in the same species (rabbit) with similar endpoints (decreased food consumption). HED estimated a dermal absorption rate of 3.5% for MBC based on a dermal absorption study with benomyl. Benomyl was selected as a surrogate chemical because of similarities in toxicological effects and structure between benomyl and MBC.

Mechanism of Action. In order to characterize the mechanism of thyroid tumorigenesis, a series of short-term studies were undertaken to determine whether TM had antithyroid activity. These studies demonstrated that TM caused liver and thyroid enlargement, increased circulating TSH and decreased T3/T4 after 2 to 8 days' treatment with TM at 6000 ppm (equivalent to the HDT in the rat chronic toxicity/carcinogenicity study). Some liver microsomal enzymes, including UDP-glucuronosyltransferase, were increased. The effects on liver and thyroid weight were reversible, but reversibility of the alterations in circulating hormone levels and on microscopic effects were not evaluated. Supplementation of treated animals with T4 prevented thyroid enlargement and increased TSH but did not prevent liver enlargement. TM also appeared to have a mild inhibitory effect on microsomal thyroid peroxidase. These data were reviewed by the HED CARC. Although it was determined that the available evidence is consistent with disruption of thyroid-pituitary homeostasis by TM, additional data were considered necessary to adequately support this mechanism. The current Agency policy on rat thyroid tumors (US EPA, 1998) requires demonstration of the reversibility of the thyroid hormonal alterations and microscopic changes after withdrawal of treatment; these data demonstrated only reversibility of thyroid weight.

Other metabolites. The primary metabolites of MBC are 5-hydroxy-2-benzimidazolecarbamic acid, methyl ester (5-HBC) and 2-aminobenzimidazole (2-AB). The acute toxicity of 5-HBC and 2-AB could not be compared to MBC since they were not tested at levels higher than 3400 and 7500 mg/kg, respectively. MBC did not cause death in rats following single oral doses of 5000 mg/kg. Deaths (6/6) occurred with 2-AB following 10 doses at 670 mg/kg/day (2/6 occurred with MBC at 3400 mg/kg/day following repeated doses). 5-HBC was not tested higher than 200 mg/kg/day for 10 doses over 2 weeks. Testicular degeneration was observed with 5-HBC at 3400 mg/kg but not with 2-AB up to 7500 mg/kg.

Table 1
Acute Toxicity of Thiophanate-methyl

Guideline No.	Study Type	MRID #	Results	Toxicity Category
870.1100 (81-1)	Acute Oral, Rat	41644301	LD_{50} = >5000 mg/kg,	IV
870.1200 (81-2)	Acute Dermal, Rabbit	41644302	LD_{50} = >2000 mg/kg,	III
870.1300 (81-3)	Acute Inhalation, Rat	41482804	LC_{50} >1.7 mg/L males LC_{50} >1.9 mg/L females	III
870.2400 (81-4)	Primary Eye Irritation, Rabbit	40095501	slight ocular irritant	IV
870.2500 (81-5)	Primary Skin Irritation, Rabbit	40095502	Non-irritant	IV
870.2600 (81-6)	Dermal Sensitization, Guinea Pig	41482805	dermal sensitizer	N/A

N/A Not applicable

Table 2 Acute Toxicity of MBC					
Guideline No.	**Study Type**	**% a.i.**	**MRID or Accession No.**	**Results**	**Toxicity Category**
870.1100 (81-1)	Acute Oral, Rat	98	256025 (Acc No)	LD_{50} = >10,000 mg/kg,	IV
870.1200 (81-2)	Acute Dermal, Rabbits	75 INE 965	256025 (Acc No)	LD_{50} = >2,000 mg/kg formulation	III
870.1300 (81-3)	Acute Inhalation, Rat	75 INE 965	256025 (Acc No)	LC_{50} >5 mg/L	IV
870.2400 (81-4)	Primary Eye Irritation, Rabbit	>98	256025 (Acc No)	minimal to no irritation	III
870.2500 (81-5)	Primary Skin Irritation, Rabbit	75 INE 965	256025 (Acc No)	slight irritation at 24 hr, normal by 72 hr	IV
870.2600 (81-6)	Dermal Sensitization, Guinea Pig	98	256025 (Acc No)	not a dermal sensitizer	N/A
870.6100a (81-7)	Delayed neurotoxicity, hen	Not given	241931 (Acc No)	NOAEL = 2500 mg/kg	N/A

N/A Not applicable

3.2 FQPA Considerations

The HED FQPA Safety Factor Committee met on October 16, 2000 to re-evaluate the hazard and exposure data for TM and recommended that the FQPA safety factor (as required by the Food Quality Protection Act of August 3, 1996) should be reduced to 3x in assessing the risk posed by TM. In June 7, 1999, the HED FQPA Safety Factor Committee (SFC) met to evaluate the hazard and exposure data for benomyl and carbendazim or MBC, the primary metabolite of both benomyl and TM, and recommended that the FQPA safety factor should be retained at 10x in assessing the risk posed by both benomyl and MBC. FQPA SFC concluded (See memo from B. Tarplee October 25, 2000 HED Doc No. 014363) that the FQPA safety factor is necessary but can be reduced to **3X for TM** because:

- the toxicity database is incomplete (acute and subchronic neurotoxicity studies are required due to evidence of neurotoxicity) and the requirement for a developmental neurotoxicity study has been 'reserved';
- the HIARC evaluated the new 1997 prenatal developmental toxicity study in rabbits and classified this study as Acceptable for assessment of susceptibility;
- the HIARC agreed with the HED ToxSAC that the dietary prenatal developmental toxicity study in the rat was considered to be Acceptable for assessment of susceptibility;

- the HIARC concluded that the available data provided no indication of increased susceptibility *in utero* exposure in the developmental studies in rats and rabbits or following pre-/postnatal exposure in the multi-generation reproduction studies in rats; and
- the dietary (food and drinking water) and non-dietary exposure assessments will not underestimate the potential exposures for infants and children from the use of TM.

The Committee determined that **3X FQPA** safety factor for TM is applicable to **all population subgroups for dietary and non-dietary exposure assessments of all durations** since the toxicology database for TM is incomplete and the requirement for a developmental neurotoxicity study has been 'reserved'.

The FQPA SFC concluded (See memo from B. Tarplee July 1, 1999 HED Doc No. 013544) that the FQPA safety factor be retained at **10X for carbendazim or MBC**, the primary metabolite of TM, because of:

- evidence of increased susceptibility following *in utero* exposure of carbendazim, the primary metabolite of TM, in the prenatal developmental toxicity study in rats and rabbits; and
- the need for developmental neurotoxicity study in rats for carbendazim.

The Committee determined that **10X FQPA** safety factor for 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 for carbendazim or MBC.

The Committee determined that 10X FQPA safety factor for 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.

3.3 Dose-Response Assessment

3.3.1 Non-Cancer Endpoints

On September 26, 2000, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met to reassess the acute and chronic dietary, and dermal and inhalation endpoints for risk assessment for TM, and its primary metabolite carbendazim (MBC), respectively. The Committees decisions for TM are presented in the updated HIARC memorandum dated March 7, 2002 (J. Doherty and D. Smegal to C. Eiden, HED Doc. No.005041). The Committees decisions for MBC are presented in the HIARC memorandum dated March 2001 (D. Smegal to C. Eiden). To assess dietary exposure, HIARC developed acute and chronic RfDs for both TM and its primary metabolite, MBC, based on exposure concerns. Because TM and MBC cause developmental effects, HIARC developed two acute dietary RfDs (aRfD) for each compound, one for females of the child bearing age (13-50 years) and one for the general population, including infants and children.

Thiophanate-methyl

For TM, HIARC identified aRfDs of 0.2 mg/kg/day and 0.4 mg/kg/day for females 13-50 years and the general population, respectively. The aRfD for females (13-50 years) is based on a NOAEL of 20 mg/kg/day from a 1997 rabbit developmental study that observed an increased incidence of supernumerary ribs in fetuses of pregnant rats administered 40 mg/kg/day (LOAEL). The TM aRfD for the general population is based on a NOAEL of 40 mg/kg/day for tremors observed in 7 of 8 dogs, 2-4 hours following a single dose of 200 mg/kg (LOAEL). The cRfD is 0.08 mg/kg/day based on a NOAEL of 8 mg/kg/day for thyroid effects and decreased body weight in dogs chronically given 40 mg/kg/day. An uncertainty factor of 100 (10X for interspecies extrapolation and 10X for intraspecies variability) was applied to the NOAELs to obtain the RfDs. The cRfD is protective of adverse liver effects that had a NOAEL and LOAEL of 8.8 and 54 mg/kg/day, respectively in the chronic rat study.

For short- and intermediate-term incidental oral ingestion and inhalation exposures, HIARC selected the oral NOAEL of 10 mg/kg/day from the 1997 rabbit developmental study based on decreased maternal body weight and food consumption at 20 mg/kg/day (LOAEL) for use in risk assessment. The short- and intermediate-term dermal endpoints are based on a dermal NOAEL of 100 mg/kg/day from a 21-day dermal study in rabbits that observed decreased body weight and food consumption at 300 mg/kg/day (LOAEL). The long-term dermal and inhalation endpoints are based on the NOAEL of 8 mg/kg/day for thyroid effects and decreased body weight in the chronic dog study. Because an oral NOAEL was selected for all inhalation endpoints and the long-term dermal endpoint, a 100% inhalation absorption factor (i.e., equivalent to oral absorption), and a 7 percent dermal absorption factor were applied to these endpoints, respectively. The dermal absorption rate of 7% was estimated based on the results of an oral developmental toxicity study and a 21-day dermal toxicity study in the same species (rabbit) with similar endpoints (decreased food consumption).

MBC

The acute dietary RfDs for MBC are 0.1 mg/kg/day and 0.17 mg/kg/day for females (13-50 years) and the general population, respectively. The aRfD for females (13-50 years) is based on a NOAEL of 10 mg/kg/day from a rat developmental study in which decreased fetal body weight, increases in skeletal variations and a threshold for malformations were observed at 20 mg/kg/day (LOAEL). The aRfD for the general population is based on a LOAEL of 50 mg/kg/day for effects on the male reproductive system [sloughing (premature release) of immature germ cells 2 days post exposure, 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 post exposure]. This effect was seen at the lowest dose tested, therefore, a NOAEL could not be established for the aRfD for the general population. The cRfD of 0.025 mg/kg/day is based on an oral NOAEL of 2.5 mg/kg/day from a 2-year dog study in which histopathological lesions of the liver and chronic hepatitis in both sexes were observed at 12.5 mg/kg/day (LOAEL). An uncertainty factor of 100 (10X for interspecies extrapolation and 10X for intraspecies variability) was applied to the NOAELs to obtain the RfDs, except for the aRfD for the general population, which has a total uncertainty factor of 300 (extra factor of 3X) to account for the absence of a NOAEL.

For short-term incidental oral ingestion exposures, HIARC selected an oral NOAEL of 10 mg/kg/day from the 1997 rabbit developmental study with TM based on decreased maternal body weight and food consumption at 20 mg/kg/day (LOAEL) for use in risk assessment. TM was selected as a surrogate because there is no appropriate endpoint for infants and children in the MBC database. The intermediate-term incidental oral endpoint is based on adverse liver effects in the 90 day dog study with MBC. For MBC, HIARC identified short- and intermediate term dermal NOAELs of 10 mg/kg/day from a rat developmental study that observed adverse fetal effects at 20 mg/kg/day (LOAEL) for females 13-50 years. The long-term dermal NOAEL is 2.5 mg/kg/day from a 2-year dog study that observed liver toxicity at 12.5 mg/kg/day (LOAEL). Because oral NOAELs were selected, a 3.5 percent dermal absorption factor, based on a rat dermal absorption study with benomyl was used.

Due to an absence of inhalation toxicity data for MBC, the inhalation NOAEL of 0.96 mg/kg/day for benomyl based on respiratory effects was also used to assess inhalation exposures for MBC for all durations.

Population Adjusted Doses

The Population Adjusted Dose (PAD) is the term that OPP is now using to describe a reference dose (RfD) – either acute or chronic– that has been adjusted to take into account the FQPA Safety Factor. PAD (acute or chronic) = RfD (acute or chronic) ÷ FQPA Safety Factor. These PADs are referred to as aPAD and cPAD, respectively.

Depending on the determinations of the HED FQPA SFC, the FQPA safety factor may be the same or different for acute and chronic risk assessments, and may apply to either designated or all population subgroups. For TM, the FQPA safety factor was reduced to 3X, and was applied to all population subgroups for all exposure assessments. For MBC, the FQPA safety factor of 10 was

retained for both acute and chronic risk assessments, and applies to the following subgroups: females (13-50 years), all infants, children (1 - 6 years), and children (7 - 12 years). The doses and toxicological endpoints selected for various exposure scenarios and subgroups for TM and MBC are summarized in Tables 3 and 4, respectively.

3.3.2 Classification of Carcinogenic Potential

TM was classified as a "likely to be carcinogenic to humans" by the HED Cancer Assessment Review Committee (CARC) on April 28, 1999. A Q_1^* of 1.16×10^{-2} $(mg/kg/day)^{-1}$ was assigned based on the dose-dependent increases in liver tumors in male and female mice (quantitative risk assessment memorandum from L. Brunsman to D. Smegal dated November 8, 2001). The thyroid tumors in rats were also considered treatment-related because a dose-dependent increase was observed in both sexes (in males, toxicity at the HDT was excessive based on high mortality but the tumors were nonetheless considered treatment-related). Although evidence supporting a threshold mechanism for thyroid tumor induction based on disruption of thyroid-pituitary homeostasis was submitted, the CARC determined that additional information (e.g., demonstration of reversibility of treatment-induced thyroid hormonal alterations and morphological changes after cessation of treatment, additional genotoxicity studies) was required to adequately demonstrate this mechanism. Special mechanistic studies submitted in support of this mechanism are described in the toxicity chapter (memo from D. Smegal/L. Hansen to D. Scher, March 14, 2002, D279278, TXR No. 0050563).

MBC was classified as group C (possible human carcinogens) by the HED Cancer Peer Review Committee, and on 5/21/86, the Scientific Advisory Panel (SAP) concurred with this classification of MBC. The rationale for this classification is as follows: (1) the carcinogenic response for MBC is confined solely to the mouse liver, even with repeated experiments; (2) the liver tumors produced by MBC were observed in 2 related strains of mice (CD-1 and Swiss SPF) known to have high background incidence rates of liver tumors, whereas no liver tumors were produced by MBC in another strain of mice [NMRKf (SPF 71)] known to have a low background incidence rate of liver tumors; (3) MBC produced weak mutagenic effects consistent with spindle poison activity rather than gene mutation or DNA repair activity.

The Cancer Peer Review Committee noted the occurrence of mostly malignant hepatocellular tumor response with MBC in two stains of mice, and the presence of unusually occurring and malignant hepatoblastomas with MBC in male SPF Swiss mice. In addition, the mutagenicity information indicates that the aneuploidy known to be produced by MBC could theoretically result in a loss of tumor suppressor genes and a potential oncogenic effect.

HED estimated a unit risk Q_1^* of 2.39×10^{-3} $(mg/kg/day)^{-1}$ for MBC (memorandum from L. Brunsman to D. Smegal, November 18, 1999, HED Doc no 013859). This estimate is based on the outcome of the re-evaluation of the hepatocellular (adenoma and/or carcinoma) tumors in CD-1 female mice with dose levels of 0, 500, 1500 or 7500 ppm MBC (MRID 00154676, 00096513, Wood et al. 1982). The Q_1^* was estimated using the $(mg/kg/day)^{3/4}$ species scaling factor. Details of the quantitative estimate are presented in the Toxicity Memorandum.

Table 3
Summary of Doses and Toxicological Endpoints for Thiophanate-methyl

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary, Females 13-50 yrs	NOAEL=20 mg/kg/day UF = 100 **Acute RfD**= 0.2 mg/kg/day	FQPA SF = 3 **aPAD**= acute RfD / FQPA SF = 0.067 mg/kg/day	1997 Rabbit Developmental Study LOAEL=40 mg/kg/day based on supernumerary ribs in fetuses of exposed dams and decreased fetal weight.
Acute Dietary, General Population	NOAEL=40 mg/kg/day UF = 100 **Acute RfD**= 0.4 mg/kg/day	FQPA SF = 3 **aPAD**= acute RfD / FQPA SF = 0.13 mg/kg/day	Chronic oral toxicity dog study LOAEL= 200 mg/kg/day based on tremors 2-4 hours post-dosing in 7 of 8 dogs.
Chronic Dietary	NOAEL=8 mg/kg/day UF = 100 **Chronic RfD**= 0.08 mg/kg/day	FQPA SF = 3 **cPAD**= chronic RfD / FQPA SF = 0.027 mg/kg/day	Chronic oral toxicity dog study LOAEL= 40 mg/kg/day based on thyroid effects and decreased body weight.
Short-and Intermediate Term Incidental Ingestion	Oral NOAEL =10 mg/kg/day	**LOC for MOE = 300** for all residential populations **LOC for MOE = 100** for occupational workers	1997 Rabbit Developmental Study LOAEL= 20 mg/kg/day based on decreased maternal body weight and food consumption.
Short- and Intermediate-Term Dermal	Dermal NOAEL = 100	**LOC for MOE = 300** for all residential populations **LOC for MOE = 100** for occupational workers	21-Day Rabbit Dermal Toxicity Study LOAEL = 300 mg/kg/day based on decreased body weight (28%) and food consumption (15%).
Short-and Intermediate Term Inhalation (a)	Oral NOAEL =10 mg/kg/day (inhalation absorption rate=100% relative to oral absorption)	**LOC for MOE = 300** for all residential populations **LOC for MOE = 100** for occupational workers	1997 Rabbit Developmental Study LOAEL= 20 mg/kg/day based on decreased maternal body weight and food consumption.
Long-Term Dermal and Inhalation (a)	NOAEL=8 mg/kg/day (dermal absorption rate =7% relative to oral absorption; inhalation absorption rate=100% relative to oral absorption)	**LOC for MOE = 300** for all residential populations **LOC for MOE = 100** for occupational workers	Chronic oral toxicity dog study LOAEL= 40 mg/kg/day based on thyroid effects and decreased body weight.
Cancer (a)	$Q1^* = 1.16 \times 10^{-2}$ $(mg/kg/day)^{-1}$ (dermal absorption rate =7% relative to oral absorption; inhalation absorption rate=100% relative to oral absorption)	$Q1^* = 1.16 \times 10^{-2}$ $(mg/kg/day)^{-1}$	78-week mouse study based on male mouse liver adenoma and/or carcinoma and/or hepatoblastoma combined tumor rates

* The reference to the FQPA Safety Factor refers to any additional safety factor retained due to concerns unique to the FQPA.
UF = Uncertainty Factor
PAD = Population Adjusted Dose (includes UF and FQPA safety factor)
LOC= Level of Concern
MOE = Margin of Exposure
(a) Since an oral value was selected, 7% dermal absorption factor and 100% inhalation absorption factor (equivalent to oral absorption) should be used for route-to-route extrapolation.

Table 4
Summary of Doses and Toxicological Endpoints for MBC

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary, Females 13-50 years	NOAEL=10 mg/kg/day UF = 100 **Acute RfD=** 0.1 mg/kg/day	FQPA SF = 10 **aPAD=** acute RfD / FQPA SF = 0.01 mg/kg/day	Rat Developmental Study with MBC LOAEL= 20 mg/kg/day based on decreased fetal body weight and increases in skeletal variations and a threshold for malformations in fetuses of exposed dams
Acute Dietary, General Population, including infants and children	LOAEL=50 mg/kg/day UF = 300 **Acute RfD=** 0.17 mg/kg/day	FQPA SF = 10 for infants and children FQPA SF=1 general pop. **aPAD=** acute RfD / FQPA SF = 0.017 mg/kg/day (infants and children) = 0.17 (general pop.)	Single Dose Rat Study (Nakai et al. 1992) LOAEL= 50 mg/kg/day based on adverse testicular effects including sloughing (premature release) of immature germ cells 2 days post exposure, 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 post exposure.
Chronic Dietary	NOAEL=2.5 mg/kg/day UF = 100 **Chronic RfD=** 0.025 mg/kg/day	FQPA SF = 10 for children and females 13-50 yrs FQPA SF=1 general pop. **cPAD=** chronic RfD / FQPA SF = 0.0025 mg/kg/day (children and females) = 0.025 (general pop.)	2 year dog study with MBC 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.
Short-Term Incidental Ingestion	Oral NOAEL =10 mg/kg/day	**LOC for MOE = 1000** for all residential populations **LOC for MOE = 100** for occupational workers	1997 Rabbit Developmental Study with thiophanate-methyl LOAEL= 20 mg/kg/day based on decreased maternal body weight and food consumption.
Intermediate-Term Incidental Ingestion	Oral NOAEL =11 mg/kg/day (rounded to10 mg/kg/day)	**LOC for MOE = 1000** for all residential populations **LOC for MOE = 100** for occupational workers	90 day dog feeding study with MBC LOAEL= 35 mg/kg/day based on adverse liver effects.
Short-and Intermediate Term Dermal (a)	Oral NOAEL =10 mg/kg/day (dermal absorption rate = 3.5% relative to oral absorption)	**LOC for MOE = 1000** for children and females (residential) **LOC for MOE = 100** for occupational workers	Rat Developmental Study with MBC LOAEL= 20 mg/kg/day based on decreased fetal body weight and increases in skeletal variations and a threshold for malformations in fetuses of exposed dams
Long-Term Dermal (a)	Oral NOAEL =2.5 mg/kg/day (dermal absorption rate = 3.5% relative to oral absorption)	**LOC for MOE = 1000** for children and females (residential) **LOC for MOE = 100** for occupational workers	2 year dog study with MBC 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.
Short-, Intermediate- and Long Term Inhalation	Inhalation NOAEL= 0.96 (10 mg/m^3)	**LOC for MOE = 1000** for children and females (residential) **LOC for MOE = 100** for occupational workers	90 day rat inhalation study with benomyl LOAEL= 4.8 mg/kg/day (50 mg/m^3)based on Olfactory degeneration in the nasal cavity

Table 4 Summary of Doses and Toxicological Endpoints for MBC			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF* and Endpoint for Risk Assessment**	**Study and Toxicological Effects**
Cancer (a)	$Q1^* = 2.39 \times 10^{-3}$ $(mg/kg/day)^{-1}$ (dermal absorption rate =3.5% relative to oral absorption; inhalation absorption rate=100% relative to oral absorption)	$Q1^* = 2.39 \times 10^{-3}$ $(mg/kg/day)^{-1}$	2 year mouse study with MBC based on hepatocellular (adenoma and/or carcinoma) tumors in female CD-1 mice

* The reference to the FQPA Safety Factor refers to any additional safety factor retained due to concerns unique to the FQPA.
UF = Uncertainty Factor
PAD = Population Adjusted Dose (includes UF and FQPA safety factor)
LOC= Level of Concern
MOE = Margin of Exposure
(a) Since an oral value was selected, 3.5% dermal absorption factor should be used for route-to-route extrapolation.

3.3.3 Toxic Equivalency Factors

In this assessment, risk estimates for TM and MBC + other metabolites of concern were added together to account for total risk estimates for target organs of concern. This is considered appropriate because both chemicals have aPADs that are based on the similar developmental effects for females, identical endpoints for short-term incidental oral exposures, and the liver is a target organ of chronic exposure. In addition, individuals may be exposed to both TM and MBC residues simultaneously on a given food commodity. A toxic equivalency factor (TEF) approach was used to sum risk estimates from TM and MBC as MBC equivalents consistent with USEPA (1999) guidance. Using the TEF approach, all TM dietary exposure estimates were adjusted upwards to account for differences in aPADs and cPADs between TM and MBC. A TEF was not estimated for the aPADs for the general population because the target organs are different for TM (tremors) and MBC (testicular effects), nor for short- and intermediate-term dermal exposures. The TEFs were estimated for the cPADs because both TM and MBC cause adverse liver effects following chronic exposure. The TEFs used in this assessment are shown on Table 5 below.

Table 5 Toxic Equivalency Factors (TEFs) Used to Convert Thiophanate-methyl Exposures into MBC Equivalents			
Toxicological Endpoint/ Population Subgroup	**PAD or NOAEL/ Uncertainty Factor**		**Toxic equivalency Factor (a)**
	Thiophante Methyl (mg/kg/day)	**MBC (mg/kg/day)**	
Acute PAD, females 13-50 years	0.067	0.01	0.15 (d) (developmental effects)
Acute PAD, general population	0.13 (tremors)	0.17 (testicular effects)	Not relevant (b)

Table 5
Toxic Equivalency Factors (TEFs) Used to Convert Thiophanate-methyl Exposures into MBC Equivalents

Toxicological Endpoint/ Population Subgroup	PAD or NOAEL/ Uncertainty Factor		Toxic equivalency Factor (a)
	Thiophante Methyl (mg/kg/day)	MBC (mg/kg/day)	
Short-term incidental oral	10/300(UF)=0.03 (e)	10/1000 (UF)=0.01 (e)	0.3 (Decreased body weight and food consumption)
Intermediate-term incidental oral	10/300(UF)= 0.03 (e) (Decreased body weight and food consumption)	10/1000 (UF)=0.01 (e) (liver)	Not relevant (b)
Short- and intermediate-term dermal	100 /300(UF)=0.33 (e) (dermal study) (Decreased body weight and food consumption)	10 / 1000(UF)= 0.01 (e)(oral study) (developmental)	Not relevant (b)
Chronic PAD, females, infants and children	0.027 (thyroid/liver) (c)	0.0025 (liver)	0.093
Chronic PAD, gen population		0.025(liver)	0.93
Cancer (Q_1*)	1.16×10^{-2}	2.39×10^{-3}	4.85 (liver tumors)

(a) MBC PAD divided by TM PAD. For cancer, TM Q1* divided by MBC Q1*.
(b) A TEF was not calculated because the toxicity endpoints are different. Therefore, aggregate TM and MBC exposures were not combined.
(c) The RfD for TM is protective of both thyroid and liver effects. The NOAEL/LOAEL for thyroid effects are 8 and 40 mg/kg/day, while the NOAEL/LOAEL for liver effects are 8.8 and 54 mg/kg/day.
(d) The aPADs were aggregated because both TM and MBC cause adverse effects on the fetal skeletal system and decreased fetal body weight, although the effects occurred in the presence of maternal toxicity for TM, but in the absence of maternal toxicity for MBC.
(e) Uncertainty factor includes the FQPA factor, which is 300 for TM and 1000 for MBC.

3.4 Endocrine Disrupter Effects

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program

(EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, TM and MBC may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT AND CHARACTERIZATION

4.1 Summary of Registered Uses

Thiophanate-methyl [dimethyl [(1,2-phenylene)bis(iminocarbonothioyl)]bis(carbamate)] is a systemic fungicide registered for use on vegetables, fruits, soybeans, nuts, and wheat, and on ornamental plantings. There are approximately 62 tolerances for food and/or feed commodities. TM is manufactured by Nippon Soda Company Ltd of Japan, under the trade name Topsin M®. The registrants are Cerexagri, Inc (formerly Elf-Atochem North America Agrichemicals), Nations Ag, Microflo and Gowan Pacific LLC. TM formulations registered for use on food/feed crops include dust (D), granular (G), wettable powder (WP), water-disperable granular (WDG), and flowable concentrate (FlC) formulations. The dust formulation may be applied to potato seed-pieces at planting and the granular formulation may be applied as an in-furrow application to beans at planting. The remaining products may be applied as an in-furrow application at planting to onions (WP and WDG) or as postemergence broadcast applications to all other labeled crops using ground or aerial equipment.

The following uses are being supported by Cerexagri: almonds; apples; apricots, bananas; beans, dry; beans, lima and snap; cherries; cucurbits; nectarines; onions; peaches; peanuts; pecans; plums and prunes; potatoes; soybeans; strawberries; sugar beets; and fall seeded wheat. The registrant stated that the following uses will not be supported: post harvest uses on all commodities; and sugarcane. More recently (10/01) the registrant has indicated it is supporting uses on celery, and foliar applications to potatoes. However, celery was not included in this assessment because data are required to support this use. In addition, petitions are pending for uses on canola, grapes, pears and pistachios, while Section 18 requests have been submitted for uses on blueberries and citrus.

Total usage of TM is likely to increase substantially in the next few years based on pesticide survey information on TM and benomyl for the years 1991 through 2000, and a survey of growers conducted by USDA in 2001 about future use of TM after the cancellation of benomyl in 2001. BEAD estimates that total domestic usage of TM over the next few years will range from 860,000 lbs ai/year (weighted average) to 1,495,000 lbs ai/year (estimated maximum) for agricultural uses on about 1,400,000 acres treated [F. Hernandez, Quantitative Usage Assessment (QUA) memo dated November 2, 2001]. BEAD estimates that TM has or will have its largest agricultural markets in terms of total pounds of ai allocated to sugar beets (17%), canola (10%), dry beans (10%), apples (8%), citrus (8%), green beans (7%), potatoes (6%), and wheat (6%). BEAD estimates that most of the usage is in CA, FL, ID, MI, MN, MT, ND, and WA. Crops with a high percentage their total U.S. planted acres treated (i.e., percent crop treated), or estimated to be

treated in the future, include strawberries (32%), celery (25%), sugar beets (24%), blueberries (23%), pistachios (22%), apples (21%), and melons (14%). Crops with less than 1 percent of the crop acres treated include onions, peanuts, soybeans, and wheat.

Comprehensive lists of TM end-use products (EPs) and of use patterns with food/feed uses which are subject to re-registration are summarized in the Thiophanate Methyl Revision of Residue Chemistry Chapter (Memorandum from J. Morales to D. Smegal, April 2002, D279270).

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

As noted previously, TM is registered on a wide variety of food crops and has approximately 62 tolerances on food and/or feed commodities. Tolerances for TM residues in/on plant and livestock raw agricultural commodities (RACs) are currently expressed in terms of TM, its oxygen analogue [dimethyl-4,4'-o-phenylene bis(allophanate)], and its benzimidazole-containing metabolites, (calculated as TM) [40 CFR§ 180.371]. However, the HED Metabolism Committee (S. Funk, 3/6/97) concluded that the residues to be regulated in plant and animal commodities for purposes of tolerance enforcement consist of TM and its metabolite methyl 2-benzimidazolyl carbamate (MBC). The tolerance definition listed under 40 CFR §180.371 should be changed to reflect the decision of the Metabolism Committee. The conclusions specified in the "Tolerance Reassessment Summary" section of the Thiophanate Methyl Revision of Residue Chemistry Chapter (Memorandum from J. Morales to D. Smegal, April 2002, D279270) reflect this decision.

Adequate plant and animal metabolism data are available for reregistration and risk assessment purposes. However, some storage stability data are required to support the residue data for plant commodities.

The Codex Alimentarius Commission has established maximum residue limits (MRLs) for TM residues in/on various plant and animal commodities (see *Guide to Codex Maximum Limits For Pesticide Residues, Part A.1, 1995*). Codex MRLs for TM are currently expressed as carbendazim (MBC). The Codex MRL residue definition and the U.S. tolerance definition are currently incompatible and will remain incompatible even after the U.S. tolerance definition is revised, as the revised U.S. tolerance definition will include both TM and MBC, while the Codex MRL definition only includes MBC.

Plant Metabolism. The qualitative nature of the residue in plants is adequately understood based on adequate apple, lima bean, sugar beet, and wheat metabolism studies. The HED Metabolism Committee (S. Funk, 3/6/97) concluded that the residues of concern for dietary risk assessment in plants include TM and its metabolites MBC and 2-AB. For purposes of tolerance enforcement, the regulated residues consist of TM and MBC. For dietary risk assessment, 2-AB was included with the parent and MBC. Concentrations of 2-AB in plant commodities were estimated using the ratio of 2-AB to TM or MBC in the various plant commodities from the metabolism studies along with residue data for TM and MBC.

Animal Metabolism. The qualitative nature of the residue in animals is understood based upon adequate ruminant and poultry metabolism studies. The HED Metabolism Committee (S. Funk, 3/6/97) concluded that the residues of concern in animal commodities include TM, MBC, and the hydroxylated derivatives of MBC (4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S). For purposes of tolerance enforcement, the regulated residues consist of TM and MBC. For dietary risk assessment, the hydroxylated MBC metabolites were included along with the parent and MBC. Concentrations of 4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S in animal commodities were estimated using the ratio of these metabolites to TM or MBC in the animal commodities from the metabolism studies along with residue data for TM and MBC.

Residue Analytical Methods - Plants and Animals.

Adequate analytical methodology is available for collecting residue data on TM and its metabolites (MBC, 2-AB and the hydroxylated metabolites of MBC) in plant and animal commodities; however, new enforcement analytical methods for plant and animal RACs are required.

Methods for determination of residues in/on plant commodities: A single enforcement method for determining parent and MBC in plant commodities is listed in the Pesticide Analytical Manual (PAM), Vol. II, as Method I. As this method is a spectrophotometric method, it is no longer considered acceptable for enforcing tolerances. The two additional methods listed in PAM Vol. II, Methods A and B, are also spectrophotometric methods for plant commodities. In addition, Method A is for determining the metabolite allophanate, which is no longer a residue of concern.

The registrant, Cerexagri, has proposed a HPLC/UV enforcement method (Method BR-93-28; 1996; MRID 43986601; 43986600) for TM residues in/on plant commodities and a successful independent laboratory validation (ILV) trial using potatoes and peanut hay. The Agency has concluded that method BR-93-28 is adequate for determining residues of TM and MBC in/on plant commodities and has a validated limit of quantitation (LOQ) of 0.05 ppm and 0.5 ppm for potatoes and peanut hay, respectively for both TM and MBC. However, the HPLC/UV Method BR-93-28 must still be radio validated using samples from a plant metabolism study prior to Agency validation.

Data from analysis of TM residues in plants have been collected using adequate versions of the proposed enforcement method. Except for minor changes in clean-up procedures and solvent systems, these methods are essentially the same as the proposed enforcement method.

Methods for determination of residues in/on animal commodities: The registrant has proposed a HPLC/UV enforcement analytical method (Elf Atochem Method KP-10-04) for determining residues of TM and MBC in animal commodities, which recently underwent a successful ILV trial (MRID 44526101). The validated method LOQ is 0.05 ppm for TM and MBC in muscle, liver and eggs, and MBC in milk. Prior to Agency validation, the method should be radio validated using samples from an animal metabolism study.

Data on residues of TM, MBC, 4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S in milk and tissues from the ruminant feeding study were collected using adequate HPLC/UV methods that are modified versions of the above methods for plants. These methods involve extraction of residues into acidic methanol (following acid hydrolysis for milk and kidneys), solvent partitioning, and, if necessary, column clean-up prior to determining residues by reverse-phase HPLC with UV detection. The limit of quantitation for each analyte is 0.05 ppm.

Multiresidue methods: The FDA PESTDATA database indicates that TM and MBC are completely recovered using FDA Multiresidue Protocol A (PAM I Section 242.2). Additional multiresidue method (MRM) recovery data are required for TM and MBC through FDA MRM protocols A through G.

Storage Stability. Requirements for storage stability data are not satisfied for purposes of reregistration. To support the residue data for plant commodities, data are required depicting the frozen storage stability of TM and MBC in representative raw and processed plant commodities held in frozen storage for up to 5 years. In 1997, the Agency required TM and MBC fortification of several crops, including celery, sugar beets, wheat grain, apples, and soybeans. The requested storage stability study was begun by the registrant in 2/97 and is on-going.

Acceptable storage stability data are available indicating that MBC is stable at <0 °C for at least 2 years in apples, snap beans, spinach, sugar beet roots, tomatoes, and wheat grain. Data are also available indicating TM is stable at ≤ -10 °C for at least 3 years in apples, cucumbers, snap beans, sugar beet roots, and wheat grain, and for at least 2 years in soybeans.

For animal commodities, adequate data are available indicating that residues of TM, MBC, and 5'-OH-MBC are stable in frozen cattle tissues, and whole milk up to 9 months and in frozen eggs for up to 10 months. Available data indicate residues of 5'-OH-MBC and either TM or MBC are stable in poultry liver or muscle, respectively, for up to 8.5 months. These data adequately support the frozen storage intervals for samples from the ruminant and poultry feeding studies.

Magnitude of the Residue in Plants. Provided issues pertaining to storage stability of the residues are adequately resolved, reregistration requirements for magnitude of the residue in plants are fulfilled for the following crops/commodities: apple, beans (dry and succulent), bananas, cherry, cucurbit vegetables, onions (dry bulb), peaches/nectarines, plums (fresh prunes), strawberry, and wheat grain. Adequate field trial data depicting residues of TM and MBC following applications made according to the maximum or proposed federally registered use patterns have been submitted for these commodities. Geographical representation is adequate and a sufficient number of trials reflecting representative formulation classes were conducted.

The Agency has determined that recently submitted field trial data for almonds, peanuts, pecans, and soybeans are adequate and therefore, pending submissions of supporting storage stability data, the residue data requirements are fulfilled for these crops. However, field trial residue data are required on apricots, celery, dried peas, onions (green), potatoes, sugar beets, and wheat forage, hay, and straw.

Pending Petitions. Petitions are currently pending for new uses of TM on canola, grapes, pears and pistachios. Although deficiencies relating to other guidelines (i.e, MRM testing, and storage stability data) remain outstanding, adequate field trial data depicting residues of TM and MBC following applications made according to the proposed use patterns have been submitted for these crops.

Grapes/Pears (PP# 5F4550). The available field trial data support establishing tolerances for TM residues in/on grapes at 5 ppm and in/on pears at 3 ppm.

Canola (PP#2E6368). The available field trial data conducted in ND in 2001 support a tolerance of 0.2 ppm in/on canola seeds provided the proposed label is amended to include a 40 day PHI and registration is restricted to use in MN, ND and MT.

Pistachio (PP#2E6355). The available residue data from almond field trial will be translated to support a similar use of TM on pistachios.

Section 18 Emergency Exemptions. The registrant has recently submitted preliminary residue data from blueberries and citrus field trials to support section 18 requests for TM use on these crops.

Blueberry (MRID 45520602). The 2 blueberry field trials conducted in MI in 2001 are adequate to support Section 18 Emergency Exemption tolerance of 1.5 ppm in MI, but are inadequate to establish a permanent tolerance which would require and additional 6 tests in Regions 1, 2, 5 and 12. These data do not support post harvest application to plants, which should be removed from all labels.

Citrus Fruits (MRID 45520603). The 2 citrus field trials conducted in FL in 2001 are adequate to support Section 18 Emergency Exemption tolerance of 0.5 ppm in FL. An additional 21 field trials are required to establish a permanent tolerance (11 trials for oranges, 5 trials for grapefruits, and 5 trials for lemons).

Magnitude of the Residue in Processed Food/Feed. Provided issues pertaining to storage stability of the residues are resolved, requirements for magnitude of the residue in processed food/feed commodities are fulfilled for apples, canola, grapes, plums, potatoes, soybeans, sugar beets, and wheat. Based on the available processing studies, tolerances are not required for residues in processed commodities of apples, canola, grapes, plums, potatoes, sugar beets and wheat. Residues did not concentrate in apple juice, grape juice, raisins, prunes and sugar beet dried pulp and molasses processed from RACs bearing detectable residues. Residues concentrated slightly in wet apple pomace, but not enough to warrant establishing a separate tolerance. Data are required depicting TM residue in aspirated grain fractions derived from treated soybeans, which will be used to establish a tolerance. The registrant-submitted a peanut processing study that is inadequate and can not be upgraded because the samples were frozen for about 6 years prior to processing, and about 6 months prior to analysis, and therefore, a new peanut processing study is required.

Magnitude of the Residue in Meat, Milk, Poultry, and Eggs. Tolerances have been established for TM residues in ruminant (cattle, goats, and sheep) commodities at 0.1 ppm (negligible or N) in fat, meat, and meat-by-products (exc. liver and kidney), 2.5 ppm in liver, 0.2 ppm in kidney, and 1.0 ppm in milk [40 CFR §180.371]. Tolerances have also been established for TM residues in hog and horse commodities at 0.1 ppm (N) in fat, meat, and meat-byproducts (exc. liver) and 1.0 ppm in liver. For poultry commodities, tolerances have been established at 0.1 ppm (N) in fat, meat, and meat-by-products (exc. liver), 0.2 ppm (N) in liver, and 0.1 ppm (N) in eggs.

An adequate ruminant feeding study is available reflecting the dosing of dairy cattle for 28 days at levels equivalent to 67.1, 205, and 839 ppm in the diet (approximately 3.6x, 11x and 45x the theoretical dietary burden for beef cattle). Based upon the results of this study and the LOQs of residues of concern in milk and tissues, tolerances for residues in milk and in fat, meat, and meat-by-products of cattle, goats, horses, and sheep should be reassessed to 0.15 ppm.

Considering the maximum theoretical dietary burden for swine (0.09 ppm) and the results of the ruminant feeding study, the Agency also concludes that a 40 CFR §180.6(a)(3) situation exists with respect to TM residues in hog commodities. Therefore, tolerances for residues in hog commodities should be revoked.

The currently established tolerances for poultry commodities should be revoked because an adequate 28-day poultry feeding study showed that there is no reasonable expectation of residues.

Confined Accumulation in Rotational Crops. Adequate data have been submitted characterizing ^{14}C-residues in rotated lettuce, carrots, and wheat; metabolism in these rotational crops is similar to the metabolism in the primary crops. Parent, TM, levels were <0.01 ppm in all crops. TM residues of concern (MBC and 2-AB) were found at levels of >0.01 ppm in lettuce from 30- and 120-day plant-back intervals and in wheat from 30- and 365-day plant-back intervals, indicating that limited rotational field trials are required. TM residues of concern (MBC and 2-AB) were found at levels of <0.01 ppm in carrot from 30- and 120-day plant-back intervals.

Field Accumulation in Rotational Crops. An adequate limited field rotational crop study is available. Residues of both TM and MBC were <0.01 ppm in/on all RAC samples harvested at normal maturity. Labels should be amended to specify a 30-day plant back interval for crops without labeled uses of TM.

4.2.2 Food Exposure

As noted previously, TM is registered for use on a wide variety of food crops, and has approximately 62 tolerances for food and/or feed commodities. Tolerances have been established for TM residues in plant and animal commodities in 40 CFR §180.371. Many of the established tolerances are being revised. Appendix B provides a Tolerance Reassessment summary for TM.

The Agency conducted highly refined probabilistic acute, chronic and cancer dietary risk assessments for the current and pending uses of TM. The registrant, Cerexagri, has requested additional uses following the voluntary cancellation of benomyl in 2001. This assessment

evaluates (1) all current federally approved registered uses for TM; (2) a Section 18 on citrus (1 year) and blueberries; and (3) new uses on canola, grapes, pears and pistachios. Details of the dietary assessment are provided in memo from S. Piper to D. Scher/D. Smegal, D279277, April 2002.

The acute, chronic and cancer dietary exposure assessments were conducted using the Dietary Exposure and Evaluation Model (DEEM™) system. DEEM™, developed by Novigen Sciences, Inc., calculates acute and chronic dietary exposure estimates to residues in food for the U.S. general population and various population subgroups. The software contains food consumption data from the USDA Continuing Survey of Food Intake by Individuals (CFSII) from 1989-1992. For chronic and cancer dietary risk assessments, the 3-day average of the consumption data for each subpopulation is combined with average residues in commodities to determine the average exposure in mg/kg/day. For acute dietary risk assessment, the entire distribution of single day food consumption events is combined with a distribution of residues in a probabilistic analysis (referred to as a "Monte Carlo" analysis) to obtain a distribution of exposures in mg/kg/day.

Dietary assessments were separately performed for TM and the sum of the metabolites MBC and 2-AB for plant commodities, and TM and sum of the metabolites of concern (MBC, 4-OH-MBC, 5-OH-MBC and 5-OH-MBC-S) in livestock commodities. Anticipated residues (ARs) (based on maximum supported use patterns) used in dietary risk assessment are calculated using both USDA Pesticide Data Program (PDP) monitoring program data, and field trial residue data submitted by the registrant. In addition, percent crop treated data from Biological Economic Analysis Division (BEAD) were used (Quantitative Usage Analysis for TM dated 11/2/2001)].

The Agency conducted two exposure assessments for TM. The first assessment relied exclusively on TM field trial data. Field trial residue data are considered by the Agency as an upper-bound estimate of possible residues, and are more suited to the requirements of tolerance setting than to the requirements of dietary risk assessment. Field trial results reflect treatments at the maximum rates, the maximum number of applications and shortest pre-harvest intervals, and do not necessarily reflect residues at the time of food consumption. For commodities assessed using field trial data, actual residue data for TM and MBC, in conjunction with data derived from metabolism studies (i.e., ratio of MBC:2-AB) were used to estimate exposures. For animal commodities, the ratios of hydroxylated metabolites to MBC or TM in various commodities were based on livestock studies. Field trial data were used to assess the Section 18 request for citrus. Because this use was granted for only one year, the exposure estimates for cancer risk were amortized to reflect only one years use.

The Agency conducted a second TM dietary assessment using PDP monitoring data for benomyl, measured as MBC to estimate TM residues. MBC is a common metabolite of benomyl and TM. PDP data were available for apples, bananas, beans, cucurbits, peaches and strawberries. The PDP analytical method employs a hydrolysis step that converts any benomyl present to MBC. MBC is then quantitated and corrected for molecular weight, and results are measured as the sum of benomyl and MBC. Therefore, using MBC data to estimate TM residues may be a conservative approach in that it may overestimate TM residues. However, there is more uncertainty with this exposure analysis because it is extrapolated from limited plant metabolism

studies. Therefore, overall, this analysis may be considered a lower bound estimate of risk from TM residues in food, relative to using field trial data.

Percent crop treated data were available for almonds, apples, apricots, beans (succulent or dried), green beans, bananas, blueberries, canola, celery, cherries, citrus, cucurbits (cantaloupe, cucumbers, melons, pumpkins, squash, watermelons), garlic, grapes, nectarines, onions (bulb and green), peaches, peanuts, pears, pecans, pistachios, plums/prunes, potatoes, soybeans, strawberries, sugar beets, and wheat. These data were used for the acute and chronic dietary assessments. Where percent crop treated estimates indicated no TM use, a default minimum assumption of 1% crop treated was applied. Where residues were nondetectable, one-half the limit of quantitation was assumed for treated commodities.

Surrogate field trial data from similar crops were used, if necessary, to assess crops without field trial data. Examples include: onions used as a surrogate to assess green onions; watermelon data used to assess pumpkins, peach data used to assess nectarines; and plum data used to assess apricots.

TM residues may be either concentrated or reduced by activities such as drying (dried fruits), processing (juice, catsup, etc.), washing, peeling, and cooking. Processing studies were available for apples, potatoes, plums (prunes) and soybeans. All other processed commodities used default DEEM processing factors. As noted previously, the requirement for a processing study on peanuts remains outstanding. These processing factors are used together with the anticipated residue estimates in or on the associated RAC to estimate the residue in various processed fractions.

HED expresses dietary risk estimates as a percentage of the acute and chronic population adjusted dose (PAD). The PAD is the adjusted RfD reflecting the retention or reduction of the FQPA safety factor for all populations. The PAD is the Reference Dose (RfD), which is derived from an exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control, along with the application of uncertainty factors. The percent of the PAD is calculated as the ratio of the exposure value to the PAD (exposure/PAD x 100 = % PAD). As shown on Table 3, for TM there are two PADs pertaining to acute dietary exposure and one PAD for chronic exposure. For MBC, there are three PADs pertaining to acute dietary exposure and two PADs for chronic exposure, as shown on Table 4. Exposures less than 100% of the PAD do not exceed HED's level of concern. For this analysis, it was assumed that the metabolites 2-AB, 5-OH-MBC, 4-OH-MBC and 5-OH-MBC-S have the same toxicity as MBC.

In addition, cancer risks were estimated using a cancer unit risk estimate of 1.16×10^{-2} $(mg/kg/day)^{-1}$ for TM and 2.39×10^{-3} $(mg/kg/day)^{-1}$ for MBC and other metabolites of concern. Cancer risks are calculated by multiplying the 70 year exposure estimate for the U.S. population by the Q_1^*, and are expressed as a probability of developing cancer.

4.2.2.1 Acute Dietary

As noted previously, the Agency conducted two refined, acute probabilistic dietary assessments. The first assessment relied on TM field trial data (upper-bound estimate), while the second assessment utilized benomyl/MBC PDP monitoring data for the available commodities (i.e., apples, bananas, beans, cucurbits, peaches and strawberries) to estimate TM residues. Both assessments incorporated maximum percent crop treated estimates from the Biological and Economic Analysis Division (BEAD). All MBC exposures and risks were estimated using PDP monitoring data, where available.

Exposure (consumption x residues) was compared to the appropriate acute population adjusted dose shown previously on Tables 3 and 4 and listed in the footnotes of Table 6. As noted previously, there are a total of five aPADs, two for TM and three for MBC. The aPADs for TM differ based on the toxicological endpoint of concern (i.e., developmental effects for females, and tremors for the general population). A FQPA safety factor of 3X is applied to these populations. The aPADs for MBC also differ by toxicological endpoint (i.e., developmental effects for females and testicular effects for the general population). A FQPA safety factor of 10X is applied to females (13-50 years) and children subpopulations, but a FQPA safety factor of 1X is applied to all other population subgroups. The acute dietary risk analysis estimates the distribution of single day exposures for the overall U.S. population and certain subgroups. The analysis evaluates exposure to the chemical for each food commodity.

Table 6 summarizes the acute probabilistic dietary risk estimates for the U.S. Population and the most highly exposed subpopulations. For the U.S. population and all subpopulations, exposure estimates for either TM or MBC + other metabolites of concern are less than 100% of the aPADs, and therefore, are not of concern for all TM registered uses, new pending uses, and the two Section 18s on citrus and blueberries. As shown on Table 6, the highest exposed population, infants, had MBC exposure estimates that result in 89% of the aPAD.

In addition, risk estimates for TM and MBC and other metabolites of concern were added together for females (13-50 years) to account for total risk estimates for developmental effects. This is considered appropriate because both chemicals have aPADs that are based on developmental effects for females, and because individuals may consume both residues simultaneously on a given food commodity. Both TM and MBC caused adverse effects on the developing fetal skeletal system and decreased fetal body weight. The dietary risks for TM and MBC were not combined for children or the general population because the aPADs are based on different effects (i.e., tremors for TM, and testicular effects for MBC). A toxic equivalency factor (TEF) approach was used to sum dietary risk estimates from TM and MBC as MBC equivalents consistent with USEPA guidance (USEPA 1999). Using the TEF approach, all TM dietary exposure estimates were adjusted downwards to account for the differences in aPADs between TM and MBC (i.e., aPAD is 0.067 mg/kg/day for TM, but 0.01 mg/kg/day for MBC, therefore a factor of 0.15 was applied to the TM dietary estimate). As shown on Table 6, this approach is identical to summing the %aPADs for TM and the %aPAD for MBC. The total dietary risk estimate for females (13-50 years) for TM and MBC is 51% and is below HED's level of concern.

The uncertainties in the acute dietary exposure estimates are discussed below following the chronic dietary exposure assessment discussion.

Table 6. Summary of Thiophanate-methyl/MBC Acute Dietary Probabilistic Exposure Analysis (Tier 3) by DEEM (99.9th Percentile of Exposure) Current uses, new uses and Section 18s (including citrus)

Population (a)	Thiophanate-methyl Estimate				MBC+other metabolites Estimate (from Thiophanate-methyl Use) Benomyl/MBC PDP Data		Thiophanate-methyl and MBC	Total Risk Estimate for Thiophanate-methyl and MBC
	Benomyl/MBC PDP Data (Lower Bound)		Field Trial (Upper Bound)					
	Exposure (mg/kg/day) (b)	% aPAD (c)	Exposure (mg/kg/day) (b)	% aPAD (c)	Exposure (mg/kg/day) (b)	% aPAD (c)	Total Exposure in MBC Equivalents (mg/kg/day) (d)	% aPAD (e)
U.S. Population	0.006886	5	0.013595	10	0.006007	4	NA	NA
All Infants <1 year	0.028839	22	0.032922	25	0.015175	89	NA	NA
Children 1-6 years	0.015613	12	0.031548	24	0.011348	67	NA	NA
Children 7-12 years	0.007845	6	0.014899	11	0.006829	40	NA	NA
Females 13-50	0.004665	7	0.009167	14	0.003680	37	0.0044 - 0.00505	44 - 51

NA= Not appropriate due to different toxicological endpoints for TM and MBC.

(a) In addition to the U.S. population -all seasons, the most highly exposed subgroup within each of the infants, children, and females is listed.

(b) 99.9th percentile of exposure.

(c) Percent of aPAD = (Exposure ÷ aPAD) x 100%. aPAD for the general population = 0.13 and 0.17 mg/kg/day for TM and MBC, respectively, aPAD for females (13-50) = 0.067 and 0.01 mg/kg/day for TM and MBC, respectively and aPAD for children subgroups = 0.13 and 0.017 mg/kg/day for TM and MBC, respectively.

(d) TM dietary exposure adjusted using the toxic equivalency factor (TEF) of 0.15 for females 13-50 years to account for the differences in the aPADs for TM and MBC. Example, TM exposure = 0.009167 mg/kg/day * 0.15 = 0.00138 mg/kg/day (in MBC equivalents) + 0.00368 = 0.00505 mg/kg/day.

(e) Percent of MBC aPAD = (Total exposure in MBC equivalents ÷ aPAD for MBC) x 100%. This is also equivalent to: %aPAD from TM + %aPAD from MBC. This is considered appropriate because the aPADs are based on developmental effects for females 13-50 years.

4.2.2.2 Chronic Cancer and Non-Cancer Dietary

A refined Tier 3 chronic exposure analysis was performed using the DEEM ™ exposure modeling software. The input values for the Tier 3 analyses included average residues from field trials and incorporated average percent of the crop treated information from BEAD. As noted previously, there is one cPAD for TM and two cPADs for MBC. These cPADs were presented previously on Tables 3 and 4, and are shown in the footnotes of Table 7. Exposure was compared to the relevant cPAD for each chemical and subpopulation. A summary of the residue information included in this analysis can be found in the attached memorandums from S. Piper to D. Scher/D.Smegal, April 2002, D279277.

As shown in Table 7, non-cancer chronic risk estimates for all population subgroups are below the Agency's level of concern (<100% cPAD), even when considering all existing, and new pending TM uses, and the Section 18s for citrus and blueberries. The most highly exposed population subgroups are children (1-6 years) for MBC and other metabolites of concern at 26% of the cPAD, and for TM at 2.3% of the cPAD. Similar to the acute dietary risks, a total dietary risk estimate was calculated, because of similar adverse effects, and the potential for simultaneous exposure to these chemicals on food commodities. A TEF approach was used to sum dietary risk estimates from TM and MBC as MBC equivalents. Using the TEF approach, the TM dietary exposure estimates for the general population and children were adjusted downwards to account for the differences in cPADs between TM and MBC (i.e., general population cPAD is 0.027 mg/kg/day for TM, but 0.025 mg/kg/day for MBC, therefore a factor of 0.93 was applied to the TM dietary estimate). For females and children, the dietary exposure estimates were adjusted downwards using a TEF of 0.093 to account for the difference in the cPADs (i.e., 0.027 mg/kg/day for TM and 0.0025 mg/kg/day for MBC). This approach is identical to summing the %cPADs for TM and the %cPAD for MBC. As shown on Table 7, the highest total dietary risk estimate of 29% for children 1-6 years, was also below the cPADs, and therefore, does not exceed HED's level of concern.

Table 7 also presents the lifetime (70 year) cancer risk estimates for the U.S. general population. As noted previously, this assessment incorporates the existing uses of TM, in addition to several new uses and the citrus Section 18 use. The cancer risk estimates are presented separately for three scenarios: (1) TM existing uses; (2) TM existing and new uses on canola, grapes, pears and pistachios; and (3) TM existing uses, new uses and the Section 18s use for citrus. The citrus use was only evaluated for 1 year, and therefore, exposure was amortized over a 70 year lifetime. The cancer risk estimates for TM range from 6.4×10^{-7} to 1.1×10^{-6}, depending on the use scenario and whether PDP data for benomyl/MBC, or field trial data were used to assess TM exposures. For MBC, the cancer risk estimates range from 7.7×10^{-8} to 9.3×10^{-8}. The total TM and MBC dietary cancer risk estimates range from 7.2×10^{-7} to 1.1×10^{-6} for existing uses, 7.4×10^{-7} to 1.1×10^{-6} for existing and new uses, and 8.5×10^{-7} to 1.2×10^{-6} for existing and new uses, in addition to the Section 18 emergency exemption (citrus for 1 year only). The cancer risk estimates based on field trial data are slightly above the lifetime risk estimates the level the Agency generally considers to be negligible for excess lifetime cancer risk (i.e., 1×10^{-6}). The cancer risk estimates based on benomyl/MBC PDP monitoring data are below 1×10^{-6} for TM existing use, new uses, and considering the amortized Section 18 citrus use. It is appropriate to add the cancer risk estimates

from TM and MBC because both chemicals cause mouse liver tumors, and because both chemicals are found concurrently on food items treated with TM.

Uncertainties of Dietary Exposure Estimates

The Agency believes that the Tier 3 risk assessment presented is the most refined to date for acute dietary exposure to TM and MBC. However, there are some uncertainties associated with this exposure estimate as follows. Overall, HED considers the risk estimates to be conservative and health protective.

(a) The consumption database used in the dietary exposure analysis (CSFII, 1989-1992) has a limited number of individuals in the age group infants less than one year old.

(b) Residues based on field trial data do not necessarily represent residues potentially present at the time of consumption, and may result in an overestimation of exposure and risk.

(c) There are uncertainties in estimating TM residues based on PDP monitoring data for benomyl/MBC. The PDP analytical method employs a hydrolysis step that converts any benomyl present to MBC. MBC is then quantitated and corrected for molecular weight, and PDP results were measured as the sum of benomyl and MBC. Therefore, using MBC data to estimate TM residues may be a conservative approach in that is may overestimate TM residues. However, there is more uncertainty with this analysis because it is based on extrapolation from limited plant metabolism studies, and overall, provides a lower bound estimate of TM residues in food.

(d) Relative amounts of TM and MBC were determined from plant metabolism studies. Because TM degrades to MBC, over time more MBC and less TM may be present in food at the time of consumption. In addition, for the acute dietary assessment, it is conservative to add the 99.9th percentile exposure estimates for TM and MBC, because as TM residues decline, MBC residues increase. Consequently, individuals could be exposed to high-end (i.e., 99.9th) residues of either TM or MBC, not both at the same time. This uncertainty only affects the total acute dietary risk estimates for females (13-50 years), because the TM and MBC dietary risk estimates for children were not combined due to lack of common toxicological endpoints.

(e) Data reflecting possible reduction of residues by washing or peeling commodities are not available. These data may lead to lower dietary exposure estimates. Although the registrant submitted an apple washing study, the Agency determined this study is unacceptable for risk assessment due to several deficiencies. Note also that PDP samples are washed prior to analysis.

(f) No cooking factors could be incorporated in this dietary exposure analysis. If the registrant has any such data they should be supplied to the Agency. If reduction of residues is noted upon cooking, this could lead to lower acute dietary exposure estimates.

(g) In the absence of adequate toxicity data for the metabolites 2-aminobenzimidazole (2-AB) 5-OH-MBC, 4-OH-MBC and 5-OH-MBC-S it was assumed that all four metabolites are toxicologically equivalent to MBC on a gram basis.

(h) Data from four plant metabolism studies (apple, sugar beets, wheat and lima beans) were used to extrapolate to all other registered plant uses to estimate the ratio of TM:MBC residues.

Table 7
Summary of Thiophanate-methyl and MBC Tier 3 Chronic Dietary Exposure Analysis by DEEM
Current uses, new uses and Section 18s (including citrus)

Population Subgroup/ Use Scenario (a)	Thiophanate-methyl Estimate				MBC +other metabolites (from Thiophanate-methyl) Benomyl/MBC PDP Data		Thiophanate-methyl and MBC Total Exposure in MBC Equivalents (mg/kg/day) (e)		Total Risk for Thiophanate-methyl and MBC
	Benomyl/MBC PDP Data (Lower Bound)		Field Trial (Upper Bound)						
	Exposure (mg/kg BW/day)	%cPAD (b)	Exposure (mg/kg BW/day)	%cPAD (b)	Exposure (mg/kg BW/day)	%cPAD (b)	Benomyl/MBC PDP Data (Lower Bound)	Field Trial (Upper Bound)	%cPAD (c)
US Population	0.000194	0.7	0.000224	0.8	0.000258	1	0.000435	0.000460	1.7-1.8
All infants (< 1 yr)	0.000306	1.1	0.000435	1.6	0.000295	12	0.000326	0.000338	13-14
Children (1-6 years)	0.000499	1.8	0.000613	2.3	0.000662	26	0.000706	0.000717	28-29
Children (7-12 years)	0.000295	1.1	0.000351	1.3	0.000404	16	0.00043	0.000437	17-18
Females 13-50	0.000151	0.6	0.000165	0.6	0.000200	8	0.00021	0.000210	8.5
Males (13-19 yrs)	0.000161	0.6	0.000175	0.6	0.000239	1	0.00039	0.000400	1.6

(a) In addition to the U.S. population -all seasons, the most highly exposed subgroup within each of the infants, children, females, and males groups is listed.

(b) Percent of cPAD = (Exposure ÷ cPAD) x 100%. cPAD for TM = 0.027 mg/kg/day. cPAD for MBC= 0.025, 0.0025 and 0.0025 mg/kg/day for the general population, females 13-50 yrs and children, respectively.

(c) Percent of MBC cPAD = (Total exposure in MBC equivalents ÷ cPAD for MBC) x 100%. This is also equivalent to the sum of the %cPAD for TM and MBC+2-AB. This is considered appropriate because the cPADs are based on the same adverse effect (liver) for TM and MBC.

(d) TM dietary exposure adjusted using the toxic equivalency factors (TEFs) of 0.093 for females and children, and by a TEF of 0.93 for the general population to account for the differences in the cPADs for TM and MBC. Example, TM exposure = 0.000194 mg/kg/day * 0.93 = 0.00018 mg/kg/day in MBC equivalents + 0.0001255 = 0.000435 mg/kg/day.

Table 8
Summary of Thiophanate-methyl and MBC Tier 3 Cancer Dietary Exposure Analysis by DEEM

Population Subgroup/ Use Scenario	Thiophanate-methyl Estimate				MBC +other metabolites (from Thiophanate-methyl) Benomyl/MBC PDP Data		Thiophanate-methyl and MBC	Total Risk for Thiophanate-methyl and MBC
	Benomyl/MBC PDP Data (Lower Bound)		Field Trial (Upper Bound)					
	Exposure (mg/kg BW/day)	Lifetime Cancer Risk Estimate (a)	Exposure (mg/kg BW/day)	Lifetime Cancer Risk Estimate (a)	Exposure (mg/kg BW/day)	Lifetime Cancer Risk Estimate (a)	Total Exposure in MBC Equivalents (mg/kg/day) (b)	Lifetime Cancer Risk Estimate (c)
US Population								
Existing TM Uses	0.000055	6.4×10^{-7}	0.000085	9.8×10^{-7}	0.000032	7.7×10^{-8}	0.000298-0.000444	7.2×10^{-7}– 1.1×10^{-6}
Existing and Section 18 (1 yr citrus)	0.000057	6.6×10^{-7}	0.000087	1.0×10^{-6}	0.000035	8.4×10^{-8}	0.000311-0.000457	7.4×10^{-7}– 1.1×10^{-6}
Existing and new uses, and Section 18 (1 yr citrus)	0.000066	7.6×10^{-7}	0.000096	1.1×10^{-6}	0.000039	9.3×10^{-8}	0.000359-0.000505	8.5×10^{-7}– 1.2×10^{-6}

(a) Lifetime cancer risk = Exposure x Q1*.
(b) TM dietary exposure adjusted using the toxic equivalency factors (TEFs) of 4.85 to estimate MBC equivalents.
(c) Total lifetime cancer risk estimate is the sum of TM and MBC cancer risks. Range represents lower and upper bound based on use of PDP data and field trial data, respectively. Both chemicals cause mouse liver tumors.

4.3 Drinking Water Exposure/Risk Pathway

The Agency currently lacks sufficient water-related exposure data from monitoring to complete a quantitative drinking water exposure analysis and risk assessment for TM and MBC. Therefore, the Agency is presently relying on water-quality models to estimate environmental concentrations (EECs) of pesticides in ground and surface water to estimate drinking water exposures to TM and MBC. Generic Estimated Environmental Concentrations (GENEEC) and/or the Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS) (both product estimates of pesticide concentration in a farm pond) predict EECs for pesticides in surface water. The Screening Concentration in Ground Water (SCI-GROW) (an empirical model based on actual monitoring data collected for a number of pesticides that serve as benchmarks) predicts EECs for pesticides in ground water. These models take into account the use patterns and environmental profile of a pesticide, but do not include consideration of the impact that processing raw water for distribution as drinking water may have on the removal of pesticides from the source water. The primary use of these models by the Agency at this stage is to provide a coarse screen for assessing whether a pesticide is likely to be present in drinking water at concentrations that would exceed human health levels of concern.

The SCI-GROW model generates a single EEC value of pesticide concentrations in ground water. That EEC is used to assess drinking water exposures in assessments of both acute and chronic dietary risk. It is not unusual for the ground water EEC to be significantly lower than the surface water EECs. The GENEEC model generates several time-based EEC values of pesticide concentration in surface water, ranging from 0-days (peak) to 56-days (average). The GENEEC peak (maximum)EEC is used in assessments of acute dietary risk; the GENEEC 56-day (average) EEC is used in assessments of chronic (non-cancer and cancer) dietary risk. PRZM/EXAMS provides longer duration values (up to a 36-year mean) of pesticide concentrations in surface water, and is mainly used when a refined EEC is needed.

A drinking water level of comparison (DWLOC) is the concentration of a pesticide in drinking water that would result in risk estimates below HED's level of concern, when considering total aggregate exposure to that pesticide from food, water, and residential uses. HED uses DWLOCs in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. DWLOC values are not regulatory standards for drinking water, however, they do have an indirect regulatory impact through aggregate exposure and risk assessment. In the absence of monitoring data for a pesticide, the DWLOC is used as a point of comparison against the conservative EECs provided by computer modeling (SCI-GROW, GENEEC, PRZM/EXAMS). A DWLOC may vary with drinking water consumption patterns and body weights for specific subpopulations.

HED back-calculates DWLOCs by a two-step process: exposure [food + (if applicable) residential exposure] is subtracted from the PAD to obtain the maximum exposure allowed in drinking water; DWLOCs are then calculated using that value and HED default body weight and drinking water consumption figures. In assessing human health risk, DWLOCs are compared to EECs. When EECs are greater than DWLOCs, HED considers the aggregate risk [from food + water + (if applicable) residential exposures] to exceed HED's level of concern.

4.3.1 Environmental Profile

The Environmental Fate and Effects Division (EFED) provided EECs for TM and its primary degradate, MBC, based on Tier 1 modeling (using GENEEC, and SCI-GROW) and Tier 2 modeling (PRZM/EXAMS) (Attached memos from F. Khan/R. Pisigan April 2002, R. Pisigan/I. Abdel-Saheb, 1/19/01, 4/11/01). The available environmental fate data suggest that TM rapidly degrades to MBC following application to ornamentals, turf and agricultural crops. MBC has a low potential to leach to groundwater in measurable quantities from most typical uses based on its high soil organic carbon partition coefficient (Koc) of 2,100 l/kg. The available data indicate that the primary metabolite of TM, MBC, is less mobile and significantly more persistent in many soils, especially under anaerobic conditions. The MBC aerobic soil half-life is 320 days, while the aerobic and anaerobic aquatic metabolism half-lives are 61 and 743 days, respectively. EFED concludes that MBC will probably not reach ground water to any significant concentration due to its high Koc. EFED (EFED; memo by R. Pisigan/I. Abdel-Saheb, January 19, 2001, and April 11, 2001) has provided EECs (screening-level drinking water assessment) using simulation models to estimate the potential concentrations of TM and MBC in ground and surface water.

4.3.2 Estimated Environmental Concentration (EECs)

EFED conducted screening-level assessments to generate EECs for TM and MBC using the simulation models SCI-GROW (Tier 1) for ground water and Tier 2 (PRZM/EXAMS) for Oregon pears and turf for surface water. The surface water modeling was conducted based on the environmental profile and the maximum seasonal application rate proposed for TM uses based on the product label for Oregon pears (0.7 lbs ai TM/acre with 8 treatments per year at 7 day intervals), and proposed turf rates based on risk mitigation (5.45 lbs ai/A/season on fairways and 21.8 lb ai/A/season on greens and tees). The groundwater model estimates for turf and onions were conducted using maximum applications on current labels that the registrant has agreed to modify based on risk mitigation. Consequently, the groundwater EECs are very conservative, and are likely to be much lower based on recently adopted risk mitigation measures. TM and MBC have the potential to pollute surface waters by erosion of soil particles to which these chemicals are adsorbed or via dissolution in runoff water, especially in areas with large amounts of annual rainfall that could result in large volumes of runoff. EFED notes that MBC ground and surface water EECs and are expected to provide the highest environmental exposures resulting from TM use. The EECs are shown on Table 9.

Table 9 EFED ESTIMATED ENVIRONMENTAL CONCENTRATION (EECs)				
Chemical	Ground Water SCI-GROW (µg/L) (a) (acute and chronic)	Surface Water (µg/L) PRZM/EXAMS		
		Acute (Peak)	Long-Term Non-Cancer (1/10 Year)	Long-Term Cancer (36 yr mean)
Thiophanate-methyl	0.033 (turf) 0.006 (onions)	22.67 (turf) 19.5 (pears)	0.92 (turf) 1.13 (pears)	0.41 (turf) 0.8 (pears)
MBC	3 (turf) 0.51 (onions)	24.85 (turf) 40.9 (pears)	8.8 (turf) 23.4 (pears)	5.98 (turf) 19.04 (pears)

(a) SCI-GROW (Screening Concentration in Ground Water) is an empirical model for predicting pesticide levels in ground water. The value from SCI-GROW is considered an upper bound concentration estimate.

4.4 Residential Exposure/Risk Pathway

This assessment for TM reflects the Agency's current approaches for completing residential exposure assessments based on the guidance provided in the *Draft: Series 875-Occupational and Residential Exposure Test Guidelines, Group B-Postapplication Exposure Monitoring Test Guidelines*, the *Draft: Standard Operating Procedures (SOPs) for Residential Exposure Assessment*, and the *Overview of Issues Related to the Standard Operating Procedures for Residential Exposure Assessment* presented at the September 1999 meeting of the FIFRA Scientific Advisory Panel (SAP). The Agency is, however, currently in the process of revising its guidance for completing these types of assessments. Modifications to this assessment shall be incorporated as updated guidance becomes available. This will include expanding the scope of the residential exposure assessments by developing guidance for characterizing exposures from other sources already not addressed such as from spray drift; residential residue track-in; exposures to farm worker children; and exposures to children in schools.

4.4.1. Residential Handler

Exposure Scenarios

Potential residential exposures can occur as a result of residential application of liquid, and granular formulations to lawns. There are several granular home lawn products produced by the Scotts Company for residential application to lawns. All are a combination fertilizer/pesticide, or "weed and feed" formulations, ranging from 2 to 5% TM by weight. It should be noted, that the current labels do not permit residents to treat home orchards, although a pest control operator (PCO) may treat home orchards. The following four residential handler scenarios were evaluated:

(1) Applying with a ready-to-use hose-end sprayer (ornamental treatment only);
(2) Mixing/Loading/Applying liquids with a low pressure hand wand (ornamental treatment only);
(3) Mixing/Loading/Applying with a backpack sprayer (ornamental treatment only); and
(4) Loading/Applying granular formulations with a push type spreader.

Application of granules with a belly grinder and by hand were excluded because as part of risk mitigation, the registrant recently agreed to modify the labels to specifically preclude these application methods. In addition, as part of risk mitigation, residents will no longer be permitted to apply liquid formulations of TM for broadcast treatment. Use by residents will be restricted to granular products for broadcast turf treatment, and liquid treatments for ornamentals. The labels will be revised to preclude residential use of liquid formulations for broadcast turf treatment.

Exposure Data and Assumptions

The duration of exposure is expected to be short-term (1-30 days) for residential handlers during application of TM products to turf and ornamentals. Intermediate- and long-term exposures of residential applicators are not anticipated based on TM's use pattern and information from the registrant. Based on toxicological criteria and potential for exposure, HED has conducted a dermal and inhalation exposure assessments. Only exposures to TM were evaluated, because MBC is formed during environmental degradation of TM.

Residential usage patterns were estimated based on the new maximum label rate agreed to as part of risk mitigation, label application frequency, estimated seasonal length, and persistence of TM. Based on label information, TM may be applied repeatedly to treat fungal infections. However, consultation with EPA agronomists (scientists) and information supplied by the registrant indicate that typical use is once per season over a lifetime. Therefore, it was estimated that thiophante methyl formulations could be applied once in season, and that residents treat 0.5 acres for broadcast application. In addition, a 0.25 acre treated area was assumed for ornamental treatment with a ready-to-use hose end sprayer based on the label. No chemical-specific data were submitted for residential handler risk assessment, so the PHED values were used, as cited in the Draft SOPs for Residential Exposure Assessments (12/97). For all residential equipment, the exposure estimates assume that individuals wear short pants, short sleeves and no gloves.

HED also estimated cancer risks based on the number of years typically working in the home garden (50 years) and lifetime (70 years), which are population defaults recommended by EPA's Exposure Factors Handbook. Therefore, cancer risks are based on 50 applications in a lifetime. A cancer risk assessment is considered appropriate because TM has been assessed as a carcinogen using a model for carcinogenesis that assumes any exposure at any point in time may result in carcinogenic effects.

Risk Characterization

A summary of the short-term and cancer risk estimates for residential handler is presented in Table 10. As noted previously, non-cancer risk estimates are expressed in terms of the MOE. MOEs greater than 300 do not exceed HED's level of concern for residents. Cancer risks are presented as a probability of developing cancer over a lifetime.

Residential application of TM formulated products to lawns and ornamentals at the new maximum label rate (based on risk mitigation) resulted in risk estimates that are below the Agency's level of concern (i.e., total MOE < 300). Total dermal and inhalation MOEs range from MOEs of 5,800 to 35,000 for both broadcast (granular) and ornamental treatment scenarios for all equipment types. The broadcast treatment estimates are based on treatment of 0.5 acre lawn per day, which is considered to be in the high-percentile range of lawn sizes. Recent lawn size survey data suggest that 0.5 acre represents 73% of the 2,300 respondents, while nearly 16% of the respondents had lawn sizes that ranged from 0.57 to 1 acre (Outdoor Residential use and Usage Survey and National Gardening Association Survey 1999). In this study, 2,300 respondents of 4,100 knew the size of their lawn. A spot treatment was assumed to be 1,000 ft^2.

Lifetime cancer risk estimates for applying TM formulated products once per year for 50 years (i.e., 50 times in a lifetime) range from $4.7x10^{-9}$ to $2.8x\ 10^{-8}$ for ornamental treatment using a backpack sprayer and a ready to use hose-end sprayer, respectively. Cancer risk estimates for the other application methods are in between these ranges.

4.4.2 Postapplication Residential/Recreational

Exposure Data and Assumptions

Potential residential postapplication exposures to adults and children may occur as a result of residential application or professional lawn care operator application of TM products. Specifically, adult and child exposures were evaluated as a result of ornamental, golf course, and recreational and home lawn uses. Guidance from the Agency's Residential SOPs (Draft 1997, and February 22, 2001 update, ExpoSac policy 12) was used to address the exposures of children contacting recently treated turf. The SOPs use a high contact activity based on the use of Jazzercise® to represent the exposures of an actively playing child. All residential scenarios, where possible, utilized the TM specific study data, which were modified by the new reduced application rates based on recently adopted risk mitigation measures.

The following residential postapplication scenarios were evaluated:

(1) Dermal exposure to adults and young children involved in a high exposure activity, such as heavy yardwork or playing on treated turf;
(2) Dermal exposure to adults mowing or other moderate contact activity for 2 hours;
(3) Dermal exposure to adults involved in a low exposure activity, such as golfing or walking on treated turf;
(4) Incidental oral exposure to children (1-6 years) playing on treated turf
    (4a) object to mouth (i.e., turf mouthing),
    (4b) hand to mouth,
    (4c) granular ingestion, and
    (4d) incidental soil ingestion.

The Agency believes that TM exposures are short-term duration and can occur over a single day or up to one month. This is supported by the length of time that residues took to decline in the TM turf transferable residue (TTR) study (i.e., residues still present up to two weeks after application) and the fact that several areas may be treated at different times. For example, a golf course or lawn might be treated over several weeks. MBC risks from treated turf were not evaluated because they are considered to be negligible relative to TM risks (i.e., at least ten fold lower), based on chemical-specific TTR data. Inhalation exposures are thought to be negligible in outdoor post-application scenarios relative to dermal and oral exposures because of the low vapor pressure of TM (1.3×10^{-5} mmHg) and MBC (1×10^{-7} mmHg) and because the uses (and primary exposures) are outdoors allowing for significant dilution. As such, inhalation exposures are not considered in the post-application exposure assessment.

Table 10
Short-Term Exposure and Risk Estimates (MOE) for Homeowner Lawn /Garden Application with Thiophanate-methyl

Equipment Type	Dermal Unit Exposure (mg/lb ai) (a)	Inhalation Unit Exposure (mg/lb ai) (b)	lb ai / acre (c)	Acres/ day (d)	Dermal Dose (non-absorbed) (mg/kg/day) (e)	Inhalation Dose (mg/kg/day) (f)	Dermal MOE (g)	Inhalation MOE (h)	Total MOE (i) (Target≥300)	Cancer Risk Estimate (50 applications per lifetime)
(1) Applying with a RTU hose-end sprayer (ORETF data)	2.6	0.011	1.8 (ornamentals)	0.25 (11,000 ft^2) (2 quarts product)	0.017	7.1E-5	6,000	140,000	5,800	2.8E-8
(2) Mixing/Loading/Applying Liquids with a Low Pressure Handwand	100	0.03	0.0075 lb ai/gal	5 gal	0.054	1.6E-5	1,900	620,000	1,900	8.5E-8
(3) Mixing/Loading/ Applying with a Backpack Sprayer	5.1	0.03	0.0075 lb ai/gal	5 gal	0.0027	1.6E-5	37,000	620,000	35,000	4.7E-9
(4) Loading/Applying with a Push-type Spreader (ORETF data)	0.68	0.00091	2.72	0.5	0.013	1.8E-5	7,600	570,000	7,500	2.1E-8

(a) Dermal unit exposure from PHED or ORETF where noted, represents short-sleeved shirt and shorts, no gloves; open mixing/loading and application by same person.
(b) Inhalation unit exposure from PHED or ORETF where noted; no respirator.
(c) Application rates based on labels or mitigation.
(d) Amounts of acreage treated per day are from the Residential SOP for area treated in a single day for each exposure scenario of concern.
(e) Daily Dermal Dose (mg/kg/day) = [Dermal Exposure (UE mg/lb ai * lb ai/acre] / Body Weight (70 kg)].
(f) Daily Inhalation Dose (mg/kg/day) = [Inhalation Exposure (UE mg/lb ai * lb ai/day = mg ai/day] / Body Weight (70 kg)].
(g) Dermal MOE = NOAEL (100 mg/kg/day) / Daily Dermal Dose mg/kg/day). Dermal NOAEL from a dermal study, therefore, no adjustment is made for dermal absorption.
(h) Inhalation MOE = NOAEL (10 mg/kg/day) / Daily Inhalation Dose (mg/kg/day).
(i) Total MOE = 1/ (1/MOE dermal + 1/MOE inhalation).

Dermal contact with treated turf residues was evaluated for both adults and young children (1-6 years). The standard SOP recommended-assumptions were used, including 2 hours/day for yardwork and/or playing, 2 days/year for mowing, 14 days/year for dermal contact, and short-term transfer coefficients of 14,500 and 5,200 cm^2/hour for adults and children, respectively. Chemical-specific turf transfer residue data for the day of treatment were also used for the non-cancer assessment. The golfing scenario assumed adults could contact treated turf on the day of treatment (DAT 0 residues), 4 hours/day for 3 days/year based on the number of applications per year. The SOP-recommended transfer coefficient of 500 cm^2/hour was used. The body weights used in the assessment are 15 kg, and 70 kg for the child (1-6 years), and adults (male and female), respectively. For the cancer assessment, it was assumed that individuals could contact TM residues over a 50 year period based on the Residential SOPs.

Residential risk estimates utilized the turf transfer study, as well as the EPA's original (12/97) and revised 2001 SOPs for Residential Exposure Assessment (ExpoSac Policy 12, February 22, 2001). Wherever available, reported usage data are used in this process to define the application frequency. As noted previously, the application rates are based on recent risk mitigation measures to reduce turf application rates from 11-19.3 lb ai/acre to 2.7 lb ai/acre on residential lawns, and 5.45-8.16 lb ai/acre on golf courses. All non-cancer risks (i.e., MOEs) for turf exposure were based on the new maximum label application rate of 2.72 lb ai/acre for residential turf, except for golf course exposures, which were assessed at a maximum rate of 5.45 lb ai/acre for fairways.

Residential Risk Estimate Characterization

A summary of the short-term risk estimates for residential/recreational postapplication dermal and incidental oral exposures is presented in Table 11. As noted previously, non-cancer risk estimates are expressed in terms of the MOE. MOEs $\geq$ 300 for exposures to TM do not exceed HED's level of concern for residents, children or other non-occupationally exposed individuals (i.e., golfers). Cancer risk estimates are expressed as a probability of developing cancer over a lifetime. Postapplication exposures were only evaluated for TM because MBC exposures and risks are considered to be negligible in comparison based on risk mitigation measures.

As shown on Table 11, two short-term MOEs for children playing on treated turf were less than 300 and therefore, exceed HED's level of concern (MOEs range from 31 to 250) for hand to mouth activities and incidental granular ingestion. Consequently, the aggregate MOE for children based on combined dermal and oral exposures is also below 300 (total MOE=170 for treated turf). All other short-term MOEs were greater than 300 for adults and children during high dermal contact (such as hand weeding, playing etc), and adults involved in mowing and golf activities, and therefore, do not exceed HED's level of concern. These MOEs were based on turf transfer residue (TTR) data provided by the registrant for the day of treatment, and transfer rates recommended in the EPA Residential SOPs.

HED also estimated cancer risks using the same residential exposure scenarios. The lifetime cancer risk estimates ranged from $1.3x10^{-9}$ to $1.3x10^{-7}$ for the scenarios evaluated (mowing and dermal contact, respectively). These cancer risks are below the Agency's level of concern (generally one in one million (10^{-6})). The highest cancer risk estimates are based on dermal

contact with treated turf 2 hours/day, 14 days per year for 50 years, which yields a cancer risk estimate of $1.3x10^{-7}$ for contact with 14-day average residues following turf treatment.

The Residential SOPs are considered to be conservative scenarios for determining risk estimates. The adult and toddler transfer coefficients are based on the Jazzercise protocol and an upper percentile exposure duration value. Where study data were used with the SOP formulae, these risk estimates were better refined, and hence, less conservative. Therefore, the dermal exposure estimates related to lawn skin contact (which were based on study data) are more refined than the estimates of incidental ingestion of TM residues.

The median frequency of postapplication exposure to golf course turf is based on data provided by golfing associations. Therefore, the risk estimates associated with golfing are believed to be average, or not over-estimated. The residential exposure to treated lawns is based upon exposure to transferable residues at the earliest possible opportunity and high transfer coefficients. While this is a high-end scenario, it is not worst-case because the time of exposure is short, based on behavioral data, and the risk estimate is based on actual data supplied by the registrant, which did not use the highest rate or number of applications for turf.

Mitigating circumstances for homeowner/residential exposure to TM residues may include the watering-in of both liquid and granular formulations on turf. There is some evidence from the study data submitted that watering or rainfall increases the residue dissipation rate [see summaries of Turf TTR study; also Apple study, NY (wet) vs. WA (dry) data]. Turf labels variously call for watering or irrigation within 24 hours or less. This instruction, however, does not prevent contact with turf prior to watering-in.

Table 11
Potential Post-Application Exposures and Risks for Residential/Non-Occupational Uses of Thiophanate-methyl (Short- term)

Application Rate lb ai/A	TM Maximum Potential Dose (a) (mg/kg/day)			TM MOE (unitless) Target MOE≥300		TM Cancer Risk Estimate (c)
	Child 1-6 years (15 kg)	Adult		Child 1-6 years	Adult	
		Non-Cancer	Cancer (LADD)			
(1) Dermal Contact with Treated Turf						
2.72	0.099	0.059	1.1E-5	1000	1700	1.3E-7
(2) Dermal Contact During Mowing Treated Turf						
2.72	NA	0.002	1.1E-7	NA	49,000	1.3E-9
(3) Dermal Contact During Golfing						
5.45	NA	0.0082	6.6E-7	NA	12,000	7.6E-9
(4a) Object to Mouth						
2.72	0.01	NE		990	NE	

Table 11
Potential Post-Application Exposures and Risks for Residential/Non-Occupational Uses of Thiophanate-methyl (Short- term)

Application Rate lb ai/A	TM Maximum Potential Dose (a) (mg/kg/day)			TM MOE (unitless) Target MOE≥300		TM Cancer Risk Estimate (c)
	Child 1-6 years (15 kg)	Adult		Child 1-6 years	Adult	
		Non-Cancer	Cancer (LADD)			
(4b) Hand to Mouth						
2.72	0.04	NE		250	NE	
(4c) Granular Ingestion						
2.7 (1.6% ai)	0.32	NE		31	NE	
(4d) Incidental Soil Ingestion						
2.72	0.00014	NE		73,000	NE	
Aggregate MOE (b)				170	NE	

NA = Not applicable
NE = Not evaluated, because scenario not applicable to this population.
(a) Potential Dose not adjusted for absorption, except for cancer LADD, which includes a 7% dermal absorption factor..
(b) Aggregate MOE for children 1-6 years includes dermal, turf mouthing, hand to mouth and incidental soil ingestion. There is a common endpoint of decreased body weight and food consumption for oral and dermal exposures.
(c) For turf, cancer risks for TM based on 14 day average residues from a TTR study. Cancer risks based on contact 14 days/year, 2 days/year and 3 days/year for 50 years for dermal lawn contact, mowing and golfing, respectively.

MOE_{dermal} = NOAEL / (Max Potential Dose * dermal/oral route conversion) . TM: dermal NOAEL = 100 mg/kg/day (no absorption necessary).
MOE_{oral} = oral NOAEL / (Max Potential Dose). TM oral NOAEL = 10 mg/kg/day
LADD = [Absorbed Dermal Dose * Exposure Days/Yr * 50 years] / [70 years lifetime * 365 days/year]
Cancer Risk = LADD * cancer Q_1, where Q1* = 1.16×10^{-2} (mg/kg/day)-1 for TM.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

For establishing a pesticide tolerance, the Food Quality Protection Act amendments to the Federal Food, Drug, and Cosmetic Act (FFDCA, Section 408(b)(2)(A)(ii)) require "that there is reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there are reliable information." Aggregate exposure is the total exposure to a single chemical (or its residues) that may occur from dietary (i.e., food and drinking water), residential, and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal, and inhalation). Aggregate risk assessments were conducted for acute (1 day), short-term (1-30 days), and chronic (several months to lifetime) exposures to TM and MBC. The aggregate risk assessments for chronic exposures includes a non-cancer and a cancer assessment. An aggregate assessment was not conducted for intermediate-term duration because there are no intermediate-term residential exposures. In all, four aggregate risk assessments were conducted.

As part of the aggregate assessment, HED conducted the aggregate assessments under two scenarios: (1) one that considered TM and MBC exposures resulting exclusively from TM uses and, (2) TM and MBC from all uses, including TM and registered MBC uses. These aggregate assessments are referred to as Aggregate 1 and Aggregate 2, respectively.

Aggregate 1 Assessment. Because TM and MBC have some common acute and chronic toxicity endpoints [developmental effects for females (13-50 years), and liver effects and tumors for chronic exposures for all subpopulations], and individuals are likely to consume both residues simultaneously on a given food commodity, it is appropriate to add TM and MBC dietary risk estimates for females (13-50 years) under the acute dietary assessment, and for all subpopulations under the chronic dietary assessment. In addition, there are short-term residential and other non-occupational exposures (e.g., golf course use) to TM, or to MBC resulting from TM uses. Therefore, residential/non-occupational dermal exposures are also anticipated to occur for the Aggregate 1 assessment. Consequently, aggregate exposures and risks from exposure to these compounds in food and water sources, and as a result of residential/non-occupational uses will be characterized for TM and MBC (resulting from TM uses) under the Aggregate 1 assessment.

Aggregate 2 Assessment. Dietary exposures to MBC may occur from benomyl or TM application to food crops because MBC is the primary environmental and metabolic degradate of both fungicides. However, in April 2001, the benomyl registrant requested voluntary cancellation of all benomyl-containing products, with sales and distribution proposed to cease by December 31, 2001 (http://www.dupont.com, April 19, 2001). Consequently, MBC exposures from benomyl uses were not evaluated in this assessment. Although MBC exposures (dermal and oral) can also occur from registered residential and recreational TM uses including lawn treatment, golf courses and home orchards, these exposures were considered to be negligible relative to TM exposure, and therefore, were not quantitatively evaluated. In addition, MBC is registered for tree injection and as an in-can fungicide/preservative in paints, coatings, plaster, and adhesives in residential settings. Therefore, residents could be exposed to registered MBC products via dermal and inhalation exposure during painting activities, and via inhalation of vapors in painted rooms. Residential exposures resulting from tree injection uses are considered to be negligible.

Therefore, the Aggregate 2 assessment includes MBC exposures from all dietary (food and water from TM uses) and residential/recreational uses (from TM and MBC use). In addition, TM risk estimates were combined with the total MBC risk estimates, where appropriate (i.e., females for acute exposures and all population subgroups for chronic exposures) because of common toxicity endpoints and simultaneous exposure on TM-treated commodities.

5.1 Acute Aggregate Risk

The acute aggregate risk estimate to TM and MBC addresses exposure from food and water. For the Tier III acute dietary exposure analysis, dietary exposures based on both PDP monitoring data and field trial data were used in conjunction with percent crop treated data to assess dietary exposures.

5.1.1 Aggregate 1: Thiophanate-methyl and MBC (from TM Use)

5.1.1.1 Aggregate Acute Risk Assessment

The TM acute dietary risk estimates range from 5% to 25% of the aPAD for TM, with infants (<1 years old) being the highest exposed population subgroup. For MBC, the acute dietary risk estimates range from 4% to 89%, with highest risk estimates for infants (< 1 yrs old). Thus, the acute dietary (food) risk estimate associated with TM or MBC exposure are below exceeds the Agency's level of concern. [The acute aggregate risk assessment conducted under scenario 1 is the same as that conducted for the acute dietary risk assessment.]

Because TM and MBC have a common acute toxicity endpoint for females (13-50 years) based on developmental effects, it is appropriate to add TM and MBC acute dietary risk estimates for this subpopulation. In addition, individuals are likely to consume both residues simultaneously on a given food commodity. The total TM and MBC acute dietary risk estimate ranges from 44-51% of the aPAD for developmental effects for females of child bearing age (13-50 years) depending on whether PDP or field trial data are used to estimate TM dietary exposure. Acute dietary risk estimates were not combined for TM and MBC for other populations because the acute oral endpoint for these other populations is based on different effects (i.e., tremors for TM and testicular effects for MBC).

The acute aggregate assessment includes both dietary and drinking water exposures to TM and MBC. Drinking water monitoring data are not available, therefore, HED calculated drinking water level of comparisons (DWLOCs), which are discussed below to account for potential drinking water exposures to TM and MBC.

5.1.1.2 Acute DWLOC Calculations

A drinking water level of comparison (DWLOC) is the concentration of a pesticide in drinking water that would result in risk estimates below HED's level of concern, when considering total aggregate exposure to that pesticide from food, water, and residential uses. HED uses DWLOCs in the risk assessment process as a surrogate measure of potential exposure associated with pesticide

exposure through drinking water. In the absence of monitoring data for a pesticide, the DWLOC is used as a point of comparison against the conservative EECs provided by computer modeling (SCI-GROW, GENEEC, PRZM/EXAMS).

HED back-calculates the acute DWLOCs by a two-step process: exposure [food + (if applicable) residential exposure] is subtracted from the acute PAD to obtain the maximum exposure allowed in drinking water; DWLOCs are then calculated using that value and HED default body weight and drinking water consumption figures. A DWLOC may vary with drinking water consumption patterns and body weights for specific subpopulations. In assessing human health risk, the acute DWLOCs are compared to acute (maximum) EECs. When EECs are **greater** than DWLOCs, HED considers the aggregate risk estimates [from food + water + (if applicable) residential exposures] to exceed HED's level of concern (HED SOP 99.5 "Standard Operating Procedures for Incorporating Estimates of Drinking Water Exposure into Aggregate Risk Assessment, August 1, 1999).

DWLOCs based on simultaneous dietary exposure to both TM and MBC (as MBC equivalents) were estimated using the aPAD for MBC and by combining the 99.9th percentile dietary exposure for both chemicals. As noted previously, a TEF approach was used to convert the TM dietary exposure into MBC equivalents. Table 12 presents the total dietary exposure estimate as MBC equivalents.

The acute DWLOC values are also presented in Table 12. For each population subgroup listed, the acute PAD and the acute dietary (food) exposure (from Table 6) as MBC equivalents, for that subgroup were used to calculate the acute DWLOC for the subgroup, using the formulas in footnotes of Table 12.

Using conservative screening-level models, the acute (maximum) estimated environmental concentrations (EECs) of TM in groundwater (SCI-GROW) range from 0.006 to 0.033 µg/L, while the surface water EECs range from 19.5 to 22.7 µg/L. Because thiophante-methyl rapidly degrades to MBC within hours to days, EFED also provided EECs for MBC in groundwater (SCI-GROW) that range from 0.51 to 3 µg/L, and surface water EECs that range from 24.9 to 40.9 µg/L. As noted previously, a TEF approach was used to convert the TM dietary exposure into MBC equivalents (i.e., factor of 0.15 was applied to the TM dietary exposure estimates for females) in order to aggregate TM and MBC dietary and drinking water exposures and risks.

The acute DWLOCs are shown on Table 12. For infants (< 1 year), the surface water EECs (but not groundwater) for MBC (24.9 to 40.9 ppb) are greater than the DWLOC of 18 ppb, indicating that aggregate food and drinking water exposure could exceed HED's level of concern. For children (1-6 years) and females of child bearing age (13-50 years) the acute EECs for surface water and groundwater are less than the acute DWLOCs, indicating that food and drinking water are not of concern for these subpopulations. For females (13-50 years), the TM and MBC EECs were converted to MBC equivalents of 43 and 3 ppb for surface and ground water, respectively because it is reasonable to assume that peak TM and MBC concentrations will occur on the same day, and because TM and MBC share a common toxicological effect for females (developmental effects). As noted previously, when EECs are greater than DWLOCs, HED considers the

aggregate risk [from food + water] to exceed HED's level of concern. It should be noted that neither SCI-GROW, nor PRZM/EXAMS models reflect concentrations after dilution (from source to treatment to tap) or treatment of drinking water.

HED concludes that acute aggregate exposure TM and MBC in food and water exceeds the HED's level of concern for infants, but is not of concern for children (1-6 years) and females (13-50 years).

Table 12
DWLOCs FOR ACUTE AGGREGATE I DIETARY EXPOSURE
Thiophanate-methyl AND MBC (From TM Use)

Population Subgroup (a)	MBC Acute PAD (mg/kg/day)	Total Food Exposure as MBC Equivalents (mg/kg/day) (b)	Max. Water Exposure (mg/kg/day) c)	Surface Water (µg/L)	Ground Water SCI-GROW (µg/L)	MBC Acute DWLOC (µg/L) (d,e,f)	Aggregate Risk of Concern
U.S. Population	0.17	0.006007 (MBC only)	0.164	24.9-40.9 (MBC)	0.51 to 3 (MBC)	5,700	No
All Infants (< 1 Year)	0.017	0.015175 (MBC only)	0.001825	19.5-22.7 (TM)	0.006 to 0.033 (TM)	18	Yes for surface water
Children (1-6 years)	0.017	0.011348 (MBC only)	0.00565			57	No
Females (13-50 yrs)	0.01	0.0044-0.00505	0.00495-0.0056	43 (MBC equivalents) (g)	3 (MBC equivalents) (g)	150-170	No

(a) In addition to the U.S. population (all seasons), the most highly exposed subgroup within each of the infants, children, female groups is listed.

(b) 99.9th percentile exposure. Values are from Table 6. Values for females based on TM and MBC exposure due to a common endpoint (developmental effects). TM exposure adjusted using the appropriate TEF of 0.15 for females. Values for other populations based on MBC alone due to different endpoints (testicular effects for MBC and tremors for TM).

C) Maximum Water Exposure (mg/kg/day) = Acute PAD (mg/kg/day) - Acute Food exposure (mg/kg/day).

(d) DWLOC (µg/L) = Maximum water exposure (mg/kg/day) x body wt (kg) ÷ [(10^{-3} mg/µg) x (L water /day)].

(e) HED default body weights are: general U.S. population, 70 kg; adult females, 60 kg; and infants/children, 10 kg.

(f) HED default daily drinking water rates are 2 L/day for adults and 1 L/day for children.

(g) EECs for pears were adjusted to MBC equivalents as follows: 19.5 ppb * 0.15 (TEF)= 2.925 + 40.9 ppb = 43 ppb; 0.033 ppb * 0.15 (TEF)=0.00495 + 3 ppb = 3 ppb.

5.1.2 Aggregate 2: Thiophanate-methyl and MBC from all Uses

As noted previously, in April 2001, the benomyl registrant requested voluntary cancellation of all benomyl-containing products, with sales and distribution proposed to cease by December 31, 2001 (http://www.dupont.com, April 19, 2001). Consequently, MBC dietary exposures from benomyl uses were not evaluated in this assessment. MBC has no registered food uses in the U.S. Therefore, HED did not conduct an aggregate assessment of all MBC acute dietary exposure resulting from registered uses of both TM and benomyl.

5.2 Short-Term Aggregate Risk

5.2.1 Aggregate 1: Thiophanate-methyl and MBC (from Thiophanate-methyl Uses)

Short-term aggregate risk estimates were not conducted for TM and MBC because most of the short-term non-occupational exposures for children during post application activities result in MOEs less than 300 for TM, and therefore already exceed HED's level of concern based on a screening-level assessment using the residential SOPs. Any additional short-term exposures through food and drinking water would result in MOEs that would further exceed HED's level of concern. Therefore, DWLOCs for short-term exposures to TM and MBC in drinking water were not calculated, because the DWLOCs are effectively zero.

As shown on Table 11, short-term MOEs for incidental ingestion of TM residues on treated turf were of concern and ranged from 31 to 250, except incidental soil ingestion. The TM dermal and oral aggregate MOEs for a child (1-6 years) playing on a treated lawn is 170. The postapplication MOEs for children and adults for dermal contact with treated turf are above 300 and do not exceed HED's level of concern.

5.2.2 Aggregate 2: Thiophanate-methyl and MBC from All Uses

5.2.2.1 Aggregate Short-Term Risk Assessment

For this assessment, HED evaluated the aggregate exposures to MBC resulting from registered uses of TM and MBC. As noted previously, MBC is a major metabolite of TM. The short-term aggregate risk estimate includes average dietary exposure (food and water) to MBC from TM uses. Estimated exposure from the residential uses of MBC as a paint additive were also added to the average chronic dietary MBC exposure. TM exposures were also considered due to similar toxic endpoints and concurrent exposure to TM and MBC on food commodities.

As noted in the Aggregate 1 assessment, the short-term non-occupational exposures for children during post application activities result in MOEs less than 300 for TM, and therefore already exceed HED's level of concern based on a screening-level assessment using the residential SOPs. Therefore, any additional short-term exposures through food and drinking water would result in MOEs that would further exceed HED's level of concern. Nevertheless, HED conducted an aggregate assessment of TM and MBC from all uses for informational purposes.

Table 13 presents the aggregate exposure estimates for MBC from diet and residential/non-occupational uses. Based on TM uses, it was assumed that children (1-6 years) could be exposed to TM residues through dermal contact with treated residential turf, and through turf mouthing, and incidental ingestion of residues on turf (i.e., hand to mouth activities). Incidental soil ingestion by children (1-6 years) was also evaluated for TM, but not MBC. Female residents were assumed to have TM dermal exposures through contact with treated residential turf. Potential dermal exposures from mowing and golf activities were approximately an order of magnitude lower, and therefore, would have a negligible contribution to female exposure. As noted previously, MBC exposures are considered to be negligible from TM turf use, and therefore, were not quantitatively evaluated. Residents that apply TM products to lawn and ornamentals are only expected to be exposed to TM, and not MBC, because MBC is formed in the environment after application. Therefore, dermal exposures during an application of TM liquid formulation to ornamentals were also included in the TM aggregate exposure assessment for females 13-50 years. The results of this exposure analysis are presented in detail in the Occupational /Residential Exposure Chapter for the Reregistration Eligibility Document for Thiophante-Methyl (April 2002).

In addition, based on MBC registered uses, it was assumed that adult residents could be exposed to MBC during painting activities (e.g., dermal and inhalation exposure during painting) and through the diet (food and water). The dermal and inhalation exposures associated with airless sprayers were used in the aggregate assessment. Details of the residential exposure assessment for registered MBC uses are presented in the attached memorandum from G. Bangs to D. Smegal, March, 2001, D273465. For this painting scenario, an adult resident was assumed to apply 2 gallons of paint containing 0.5% ai MBC, and wear short pants, short-sleeved shirt and no gloves. Exposure estimates were based on data from PHED. However, due to the very low vapor pressure of MBC relative to other pesticides, the risk estimates for MBC inhalation exposure are considered to be conservative. Post application exposure to paint vapors containing MBC is considered a long-term exposure and consequently is considered in the cancer aggregate assessments (below). Inhalation exposures were not aggregated with non-cancer risks because the endpoint of concern (respiratory effects) is different than the chronic oral endpoint (liver effects).

All oral exposures were compared to the short-term oral endpoint for MBC in accordance with HED policy. Only exposure and risk estimates associated with common toxicological endpoints were aggregated. Therefore, both oral and dermal exposures and MOEs were aggregated. For females, both oral and dermal MBC risk estimates were aggregated because both endpoints are based on a NOAEL of 10 mg/kg/day for developmental effects and decreased body weight and food consumption. The TM dermal exposure estimates were adjusted for 7% dermal absorption in calculating the dermal risk estimates. It is not appropriate to aggregate the inhalation MOEs with the oral and dermal MOEs because the inhalation NOAEL is based on respiratory effects.

As shown on Table13, aggregate MOEs are of concern for children 1-6 years and females (i.e., <1000 for MBC equivalents) due to exposures on treated lawns, and while applying MBC-containing paint, respectively. Consequently, any additional exposure from drinking water would only result in further exposures of concern.

5.2.2.2 Short-Term DWLOC Calculations

Aggregate potential MBC exposures, along with the EFED estimated EECs are presented on Table 14. The long term EFED MBC EECs range from 8.8 to 23.4 µg/L from TM use. As shown, the combined potential short-term exposure to MBC from food and residential use alone exceed HED's level of concern for children 1-6 years and females 13-50 years, and therefore any water exposure would only contribute to the exposures of concern. For these subpopulations, the short-term DWLOCs are effectively zero. In conclusion, aggregate potential short-term exposure to MBC and TM resulting from food, water and residential use due to TM, and MBC uses exceeds HED's level of concern for children (infants, and 1-6 years of age) and females 13-50 years, due primarily to TM post-application exposures on turf and MBC's use as a paint additive. This analysis is considered reasonable because HED aggregated some (but not all) of the possible residential/recreational use scenarios associated with TM uses (i.e., excluded potential exposures to golfers, individuals mowing treated lawns) with dietary exposures to ensure this analysis is as realistic as possible.

Table 13
Summary of Aggregate Short-Term Exposure
Chronic Diet and Short-Term Residential Use
Aggregate 2: Thiophanate-methyl and MBC (From All Uses)
(Excludes Water)

Population Subgroup	Thiophanate-methyl Target MOE≥1000 MBC Equivalent			MBC +other metabolites (from Thiophanate-methyl) (h) Target MOE≥1000	MBC (from MBC Uses) Target MOE≥1000		Total Aggregate MOE Estimate (c) MBC Equivalents, unless noted		
	Chronic Diet Exposure as TM and MBC equivalents (mg/kg BW/day) / MOE (a,g)	Short-Term Residential Exposure (mg/kg/day)/ MOE		Chronic Diet Exposure (mg/kg BW/day)/ MOE (g)	Short-Term Residential Exposure (mg/kg/day)/ MOE		Dermal Target MOE≥300	Inhalation Target MOE≥1000	Oral and/or Dermal Target MOE≥1000
		Oral TM/ MBC (g)	Dermal TM (b) Target ≥300 TM		Dermal (b)	Inhalation (d)			
Children (1-6 years)	0.000613 (TM)= 0.00018 (MBC Equiv) MOE= 56,000 (↓BW and FC)	**0.05 (f) as TM = 0.015 as MBC equivalents** **MOE =670 (MBC equiv) (↓BW and FC)**	0.099 (0.0069 absorbed) MOE = 1000 (↓BW and FC) (TM)	0.00066 MOE = 15,000 (↓BW and FC)	NA	NA	1000 (TM only, ↓BW and FC)	NA	**630 (↓BW and FC) (i)**
Females 13-50 yrs	0.000165 (TM)= 0.0000495 (MBC Equiv) MOE = 200,000 (↓BW and FC/ developmental)	NE	0.076 (0.0052 absorbed) (e) MOE =1315 (↓BW and FC)	0.000198 MOE= 50,500 (↓BW and FC /developmental)	0.457 (0.016 absorbed) **MOE = 620** (developmental/ ↓BW and FC)	0.0042 **MOE = 230** (respiratory)	1315 (TM only; ↓BW and FC)	**230 (respiratory)**	**620 (TM and MBC uses) (i) (↓BW and FC / developmental)**

TM = Thiophanate-methyl; NE = not evaluated.; BW = body weight; FC= food consumption

(a) Dietary exposure from Table 7, based on upper-bound field trial exposure estimates. MOE for TM, as MBC equivalents, calculated based on the MBC toxicity endpoints: short-term oral NOAEL of 10 mg/kg/day for decreased body weight and food consumption. TM converted to MBC equivalents based on the TEF approach, with TEFs of 0.3 for all populations since the short-term oral endpoint for thiophanate methyl is used to assess MBC short-term oral exposures, but total uncertainty factor (including FQPA factor) is 300 for TM and 1000 for MBC.

(b) For dermal TM exposures, the dermal NOAEL of 100 mg/kg/day based on decreased body weight and food consumption was used to assess dermal exposures to both children and females 13-50 yrs. Dermal exposure adjusted for 7% for TM to estimate absorbed doses. For MBC exposures, an oral NOAEL of 10 mg/kg/day was used

with a dermal absorption factor of 3.5%.

(c) Sum of MOEs for MBC. For females 13-50, inhalation MOE was not aggregated with oral and dermal MOEs because the endpoint (respiratory effects) is different than the dermal and oral NOAEL based on developmental effects and decreased body weight and food consumption.

(d) Inhalation NOAEL of 0.96 mg/kg/day, based on respiratory effects, was used to assess MBC inhalation exposure.

(e) For females 13-50 yrs, dermal exposure from dermal lawn contact, in addition to spot treatment for ornamentals (handler exposure) (i.e., 0.059 and 0.017 mg/kg/day). Postapplication dermal exposure from mowing lawns and golfing were approximately an order of magnitude lower.

(f) For TM includes turf mouthing, hand to mouth, and incidental soil ingestion for lawns treated with liquid or granular formulation at 2.72 lb ai/acre. TM converted to MBC equivalents based on the TEF approach using a TEF of 0.3. This excludes the incidental granular ingestion scenario, which is considered to be an episodic event.

(g) MOE based on short-term oral endpoint of 10 mg/kg/day for decreased body weight and food consumption.

(h) MBC residential exposures from TM use are considered negligible relative to TM exposures and therefore, were not quantitated.

(i) Excludes dermal TM MOE because a TEF was not developed due to different dermal endpoints for MBC and TM.

Table 14
Aggregate MBC DWLOCs for Short-Term Exposures
Aggregate 2: MBC From All Uses

Population Subgroup	NOAEL or LOAEL (mg/kg/day)	Target MOE	Maximum Exposure (MBC Acute PAD) (mg/kg/day)	MBC Average Chronic Food Exposure (mg/kg/day) (a)	Residential Exposure (as MBC Equivalents) (mg/kg/day) (b)	Potential MBC Max. Water Exposure (mg/kg/day) (c)	Long-Term Surface Water EEC (µg/L)	Long-term Ground Water EEC SCI-GROW (µg/L)	Short-Term MBC DWLOC (µg/L) (d,e,f)
Children (1-6 years)	10	1000	0.01	0.00046	0.015	None (no room)	8.8 to 23.4 (MBC) 0.92 to 1.13 (TM)	0.51 to 3 (MBC) 0.006-0-.003 (TM)	Zero (No room)
Females (13-50 years)	10	1000	0.01	0.00021	0.016 (g)	None (no room)			Zero (No room)

TM = thiophanate-methyl

(a) Values from Table 13 represent the sum of MBC dietary exposure from Thiophante methyl use as MBC equivalents. Includes TM dietary exposure (as MBC equivalents)

(b) Values based on oral MBC and TM (as MBC equivalent) exposures from lawn use. For females, absorbed dermal exposure from MBC paint application was used to calculate DWLOC since this exposure is higher than dermal exposure from TM uses. Inhalation exposures were not included because of a different toxicity endpoint (respiratory effects).

(c) Potential maximum water exposure (mg/kg/day) = Acute PAD (mg/kg/day) - [Chronic Food Exposure + short-term Residential Exposure (mg/kg/day)]. Includes MBC residential exposure from Thiophante Methyl use for children or MBC as a paint additive for females.

(d) DWLOC (µg/L) = Maximum water exposure (mg/kg/day) x body wt (kg) ÷ [(10^{-3} mg/µg) x water consumed daily (L/day)].

(e) HED default body weights are: adult females, 60 kg; and children, 10 kg for children.

(f) HED default daily drinking water rates are 2 L/day for adults and 1 L/day for children.

(g) MBC exposures as a paint additive and excludes residential exposure from TM uses (which were much lower than paint exposures).

5.3 Chronic Non-Cancer and Cancer Aggregate Risk

The chronic aggregate risk estimate for TM and MBC addresses exposure from food and water. For the Tier III chronic dietary exposure analysis, PDP monitoring data and field trial data level residues, in conjunction with percent crop treated data were used to assess dietary exposures.

5.3.1 Aggregate 1: Thiophanate-methyl and MBC (from Thiophanate-methyl Use)

5.3.1.1 Aggregate Chronic Non-Cancer and Cancer Risk Assessment

Non-Cancer Aggregate

The TM chronic noncancer dietary risk estimates are less than 2.3% of the cPAD for TM, with children (1-6 yrs) being the highest exposed population subgroup (2.3% of the cPAD). For MBC, the chronic noncancer dietary risk estimates range from 17% to 26%, with highest risk estimates for children 1-6 years (26% of the cPAD). Thus, the chronic dietary (food) risk estimate associated with TM or MBC exposure individually is below the Agency's level of concern.

Because TM and MBC have common chronic toxicity (liver effects), and because individuals are likely to consume both chemical residues on TM-treated commodities, it is appropriate to add TM and MBC chronic dietary risk estimates. Although the chronic PAD for TM is based specifically on thyroid effects, the liver is a target organ of this chemical and the cancer effects are based on mouse liver tumors (i.e., the NOAEL for thyroid effects is 8 mg/kg/day, while the NOAEL for liver effects is 8.8 mg/kg/day). The aggregate chronic dietary risk estimates include exposure to TM and MBC residues in food and water; there are no TM uses that could result in chronic residential exposure. Average chronic dietary food risk estimates are below the Agency's level of concern. The total dietary exposure to TM and MBC for the highest exposed population subgroup, children 1-6 years, is 29% of the cPAD for liver/thyroid effects, leaving 71% of the cPAD available for exposure through drinking water. As noted previously, all TM dietary exposures were converted to MBC equivalents using the TEF approach. The DWLOCs were then estimated using the cPAD for MBC.

Cancer Aggregate

The cancer aggregate risk estimate also includes chronic dietary exposures from TM and MBC residues estimated in food and water, and from residential uses of TM, because both chemicals cause mouse liver tumors. As noted previously, the cancer risks are presented separately for three scenarios: (1) TM existing uses; (2) TM existing and new uses on canola, grapes, pears and pistachios; and (3) TM existing uses, new uses and the Section 18 use for citrus. The total TM and MBC dietary cancer risk estimates range from 7.2×10^{-7} to 1.1×10^{-6} for existing uses, 7.4×10^{-7} to 1.1×10^{-6} for existing and new uses, and 8.5×10^{-7} to 1.2×10^{-6} for existing and new uses, in addition to the Section 18 emergency exemption (citrus for 1 year only). The citrus use was only evaluated for 1 year, and therefore, exposure was amortized over a 70 year lifetime. The cancer risk estimates based on TM field trial data are slightly above the lifetime risk estimates the level the Agency generally considers to be negligible for excess lifetime cancer risk (i.e., 1×10^{-6}). The

cancer risk estimates using benomyl/MBC PDP monitoring data to estimate TM residues are below $1x10^{-6}$ for TM existing uses, new uses, and considering the amortized Section 18 use for citrus. It is appropriate to add the cancer risk estimates from TM and MBC because both chemicals cause mouse liver tumors, and because both chemicals are found concurrently on food items treated with TM. Cancer risk estimates associated with residential uses of TM are below HED's level of concern for cancer based on recently adopted risk mitigation measures.

5.3.1.2 Chronic Non-Cancer and Cancer DWLOC Calculations

As noted previously, all TM dietary exposures were converted to MBC equivalents using the TEF approach. The DWLOCs were then estimated using the cPAD for MBC and by combining the average dietary exposure as MBC equivalents.

The chronic non-cancer DWLOC values are presented in Table 15. For each population subgroup listed, the chronic PAD and the chronic dietary (food) exposure (from Table 7) for that subgroup were used to calculate the chronic DWLOC for the subgroup, using the formulas in footnotes of Table 15. Note that under the cancer risk assessment that DWLOC values for cancer effects are effectively zero because chronic dietary exposure to TM and MBC residues on food alone are equal to or slightly exceed $1x10^{-6}$ for TM existing uses, new uses and the recently approved Section 18 requests. Consequently, any additional water exposure will further contribute to potential exposures of concern.

Using conservative screening-level models, the estimated long-term concentrations of MBC in groundwater (SCI-GROW) range from 0.51 to 3 µg/L, while surface water EECs range from 8.8 to 23.4 µg/L for non-cancer (1 in 10 year) and 5.98 to 19.04 µg/L for cancer assessment (36 year mean). The estimated long-term concentrations of TM in groundwater (SCI-GROW) range from 0.006 to 0.033 µg/L, while the surface water EECs range from 0.92 to 1.13 µg/L for non-cancer (1 in 10 year) and 0.41 to 0.8 µg/L for cancer assessment (36 year mean) depending on use pattern. As noted previously, TM degrades to MBC in water within a few days. In addition, the TM and MBC EECs were converted to MBC equivalents because it is reasonable to assume that individuals could be exposed to long-term average TM and MBC concentrations simultaneously, and because TM and MBC share common toxicological effects (i.e., liver effects).

As shown on Table 15, the non-cancer DWLOCs are below the surface water EECs (as MBC equivalents) for infants and children (1-6 years), indicating that aggregate food and water could exceed HED's level of concern. The DWLOCs for infants and children range from 18-22 µg/L, which are slightly less than the MBC (equivalent) EECs for surface water of 23.5-24.4 µg/L for use on pears. However, the DWLOCs are greater than the surface water EEC resulting from turf use and the groundwater EEC (MBC equivalent) of 3 µg/L. As noted previously, when EECs are less than DWLOCs, HED considers the aggregate risk [from food + water] to not exceed HED's level of concern. Therefore, HED concludes that chronic (non-cancer) and cancer aggregate exposure to TM and MBC (from TM use) exceeds HED's level of concern. It should be noted, however, that the EECs do not reflect dilution from source to tap nor do they reflect water treatment, and therefore, may not reflect the actual concentrations that individuals may consume.

Table 15
DWLOCs for Chronic Non-Cancer and Cancer Aggregate Dietary Exposure
Aggregate 1: Thiophanate-methyl and MBC (from Thiophanate-methyl Use)

Population Subgroup (a)	MBC Chronic PAD (mg/kg/day)	MBC Q_1* $(mg/kg/day)^{-1}$	Total Chronic Food Exposure as MBC Equivalents (mg/kg/day) (b)	Max. Water Exposure (mg/kg/day (c)	Surface Water (µg/L)	Ground Water SCI-GROW (µg/L)	Chronic MBC DWLOC (µg/L) (d,e,f)
Non-Cancer							
U.S. *Population*	0.025	$2.39x10^{-3}$	0.000435-0.000460	0.0245	MBC: 23.4 (pears) 8.8 (turf)	MBC: 0.51 - 3	858
All Infants (< 1 Year)	0.0025		0.000311-0.000338	0.00216-0.00217	TM: 1.13 (pears) 0.92 (turf)	TM: 0.006 -0.033	22
Children (1-6 years)			0.000706-0.000717	0.00178-0.00179			18
Females (13-50 years)			0.000210	0.00229	23.5-24.4 (MBC equivalents) (h)	3 (MBC equivalents) (h)	69
Cancer --U.S. Population							
Existing TM uses	NR	$2.39x10^{-3}$	0.000298-0.000444	No room (g)	MBC: 19 (pears) 5.98 (turf)	MBC: 0.51 - 3	zero (g)
Existing and new uses			0.000311-0.000457		TM: 0.8 (pears) 0.41 (turf)	TM: 0.006 -0.033	
Existing and new uses, and Section 18s (1 year Citrus)			0.000359-0.000505		22.9 (MBC equivalents) (h)	3.16 (MBC equivalents) (h)	

NR=not relevant

(a) In addition to the U.S. population (all seasons), the most highly exposed subgroup within each of the infants, children, female groups is listed.

(b) Values are from Table 7, and represent the sum of TM and MBC dietary exposure. TM values were converted to MBC equivalents using the TEF approach.

(c) Maximum Water Exposure (mg/kg/day) (non-cancer) = Chronic PAD (mg/kg/day) - [Chronic Food Exposure (mg/kg/day) Maximum water exposure (cancer) = (1x10-6/Q1*) - chronic food exposure. TM has no registered residential uses expected to result in long-term exposure

(d) DWLOC (µg/L) = Maximum water exposure (mg/kg/day) x body wt (kg) ÷ [$(10^{-3}$ mg/µg) x (L water/day)].

(e) HED default body weights are: general U.S. population, 70 kg; adult females, 60 kg; and infants/children, 10 kg.

(f) *HED default daily drinking water rates are 2 L/day for adults and 1 L/day for children.*

(g) Food only dietary risk estimate is greater than $1x10^{-6}$ for existing uses, new uses and recently approved Section 18s, and for all scenarios where field trial data were used to estimate TM exposure and risk.

(h) EECs were adjusted to MBC equivalents as follows: For cancer 0.8 ppb * 4.85 (TEF)= 3.88 + 19 ppb = 22.9 ppb; 0.033 ppb * 4.85 (TEF)=0.16 + 3 ppb = 3.16 ppb. For non-cancer: 1.13 ppb * 0.093 or 0.93 (TEF)= 0.1 or 1 + 23.4 ppb = 23.5 - 24.4 ppb ; and 0.033 ppb * 0.093 or 0.93 (TEF)= 0.003 or 0.03 + 3 ppb = 3 ppb

5.3.2 Aggregate 2: Thiophanate-methyl and MBC From All Uses

5.3.2.1 Aggregate Chronic Non-Cancer and Cancer Risk Assessment

Chronic aggregate exposure includes all MBC chronic dietary exposure resulting from registered uses of TM. In addition, TM and MBC have the same toxic effects (i.e., liver effects) and therefore were added together. Chronic residential exposures to MBC are not anticipated based on registered uses for TM. While there are potentially chronic inhalation exposures to MBC vapors from use of MBC as a paint additive, these exposures were not considered in the non-cancer aggregate assessment because the endpoint of concern (respiratory effects) is different from the chronic oral endpoint of concern (liver effects). However, these potential chronic inhalation exposures are assessed in the cancer aggregate assessment below.

Non-Cancer Aggregate

The Aggregate 2 assessment is identical to the Aggregate 1 assessment for non-cancer effects because all benomyl food uses were recently proposed for cancellation by the benomyl registrant in April 2001. Therefore, the chronic non-cancer Aggregate 2 assessment includes chronic exposures to TM and MBC in food and drinking water through thiophante-methyl uses.

Cancer Aggregate

For this assessment, HED evaluated the aggregate exposures to MBC resulting from registered uses of TM and MBC. Chronic aggregate cancer exposure, includes all MBC chronic dietary exposure resulting from both TM and MBC. In addition, TM and MBC have the same toxic effects (i.e., liver effects), both have Q_1*s based on mouse liver tumors, and therefore were added together. Chronic residential exposures to MBC are not anticipated based on registered uses for thiophante methyl. There are potential chronic inhalation exposures to MBC from MBC's registered use as a paint additive (i.e., dermal and inhalation exposures to a resident painter, and chronic inhalation to vapors in a painted room). Therefore, these MBC inhalation exposures were included in the aggregate risk estimates.

As shown on Table 16 the aggregate cancer dietary risk estimates (food only) for MBC and TM, combined for existing uses, new uses and the recently approved Section 18s ranges from $1.6x10^{-6}$ to $2.3x10^{-6}$. The total cancer risk estimates for TM for some residential uses is $1.5x10^{-7}$, while the cancer risk estimate associated with MBC paint additive use is $2.2x10^{-7}$. The combined cancer risk estimate for TM and MBC exposures from dietary and selected residential uses (i.e., lawn treatment and postapplication exposure) ranges from $1x10^{-6}$ to $2.6x10^{-6}$, depending on whether the dietary exposures were based on PDP or field trial data. These risk estimates are just at or slightly above $1x10^{-6}$, which is generally the Agency's level of concern.

5.3.2.2 Chronic/Cancer DWLOC Calculations

As noted previously, all TM dietary exposures were converted to MBC equivalents using the TEF approach. The DWLOCs were then estimated using the Q_1^* for MBC and by combining the average dietary exposure as MBC equivalents.

As shown on Table 16 the aggregate cancer dietary risk estimates (food only) for MBC and TM, combined ranges from 7.2 $x10^{-7}$ to 1.2$x10^{-6}$, while combined food and residential exposures result in cancer risks as high as 1.6$x10^{-6}$. Therefore, the cancer DWLOC is effectively zero because any additional exposure contribution from water will only further contribute to exposures of potential concern. Therefore, the aggregate exposure to TM and MBC from all uses on food, residential settings, in addition to potential residues in water exceeds HED's level of concern for carcinogenic effects. The cancer risk estimates for MBC use as a paint additive are conservative, because they are based on high end assumptions for occupancy, air exchange rates used in the air model, and assume no degradation or matrix effects of the paint.

Therefore, HED concludes the aggregate exposure to TM and MBC from all food and residential uses, as well as potential residues in water exceeds HED's level of concern for carcinogenic effects. As noted previously, the EECs do not reflect dilution from source to tap nor do they reflect water treatment.

Table 16
Aggregate 2: Summary of Aggregate Cancer Risk Estimates
Thiophanate-methyl and MBC Tier 3 Chronic Dietary
Exposure Analysis by DEEM
(Excludes Water)

Population Subgroup (a)	Thiophanate-Methyl as MBC equivalents		MBC +other metabolites (from Thiophante Methyl)		MBC (from MBC Use as Paint Additive)		Total Thi Methyl an
	Exposure (mg/kg BW/day) (d)	Lifetime Cancer Risk Estimate (a)	Exposure (mg/kg BW/day)	Lifetime Cancer Risk Estimate (a)	Exposure (mg/kg BW/day) (c)	Lifetime Cancer Risk Estimate (a)	Lifetime Ca Estima
US Population							
Diet: Existing Uses	0.000267-0.000412	6.4×10^{-7}-9.8×10^{-7}	0.000032	7.7×10^{-8}	None		7.2×10^{-7} to
Diet: Existing TM uses, new uses and recently granted Section 18	0.000320-0.000466	**7.6×10^{-7}-1.1×10^{-6}**	0.000039	9.3×10^{-8}			**8.5×10^{-7} to**
Residential	0.0000645 (e)	1.5×10^{-7}	Negligible		9×10^{-5}	2.2×10^{-7}	
Total		**7.9×10^{-7} to 1.3×10^{-6}**		7.7×10^{-8} to 9.3×10^{-8}		2.2×10^{-7}	**1.1×10^{-6} to** (TM and

(a) Lifetime cancer risk = Dietary Exposure x Q1*, where Q1* is 2.39×10^{-3} $(mg/kg/day)^{-1}$ for MBC and 1.38×10^{-2} $(mg/kg/day)^{-1}$ for TM.
(b) Total cancer risk is the sum of cancer risks from TM and MBC.
(c) Sum of exposure to both residential handler during paint activities and to vapors following painting.
(d) Dietary TM exposure adjusted by a TEF of 4.85 based on differences in the Q1* potency estimates for TM and MBC.
(e) TM exposure based on treatment of ornamentals (LADD=2.3E-6 mg/kg/day) and dermal postapplication lawn exposure (LADD=1.1E-5 mg/kg/day), with an adjustment for TEF (i.e., multiplied by 4.85) to convert to MBC equivalents.

Table 17
Aggregate 2: Aggregate MBC DWLOCs for Chronic Exposures
Thiophanate-Methyl and MBC (all uses)

Population Subgroup	MBC Chronic PAD (mg/kg/day)	Q1* $(mg/kg/day)^{-1}$	Total Food as MBC Equivalents (mg/kg/day) (a)	MBC Equivalents (from Thiophanate-Methyl Residential Use)	MBC (from MBC as Paint Additive) (mg/kg/day)	Potential MBC Max. Water Exposure (mg/kg/day) (b)	Long-Term Surface Water EEC (µg/L)	Long-term Ground Water EEC SCI-GROW (µg/L)	Chronic/ Cancer DWLOC (µg/L) (c,d,e)
Non-Cancer (Same as Aggregate 1)									
Cancer									
US Population	0.025	2.39×10^{-3}	0.000298 to 0.000505-(i)	0.0000645 (f)	0.00009 (h)	Zero	MBC: 19 (pears) 5.98 (turf) TM: 0.8 (pears) 0.41 (turf) 22.9 (MBC equivalents) (j)	MBC: 0.51 - 3 TM: 0.006 -0.033 3.16 (MBC equivalents) (j)	Zero

NA = not applicable.

(a) Exposure from Table 8 for cancer exposure estimates.

(b) Non-cancer Maximum Water Exposure (mg/kg/day) = cPAD (mg/kg/day) - [Chronic Food Exposure]. Cancer Maximum Water Exposure (mg/kg/day) = $(1 \times 10^{-6} / Q_1^*)$ - [Chronic Food Exposure+ residential exposures]. MBC Cancer water exposure estimate also incorporates TM because MBC and TM Q1*s are both based on mouse liver tumors, and both are present on the same food

(c) DWLOC (µg/L) = Maximum water exposure (mg/kg/day) x body wt (kg) ÷ [$(10^{-3}$ mg/µg) x water consumed daily (L/day)].

(d) HED default body weights are: general U.S. population, 70 kg; adult females, 60 kg; and infants/children, 10 kg.

(e) HED default daily drinking water rates are 2 L/day for adults and 1 L/day for children.

(f) Based on treating ornamentals and postapplication dermal contact with treated lawns.

(g) MBC inhalation exposure not considered for non-cancer because the toxicity endpoint (respiratory effects) differs from the oral endpoint.

(h) Sum of exposure to both residential handler during paint activities and to vapors following painting.

(i) Cancer dietary exposure from Table 8, which is the sum of total TM and MBC exposure (as MBC equivalents).

(j) EECs were adjusted to MBC equivalents as follows: For cancer 0.8 ppb * 4.85 (TEF)= 3.88 + 19 ppb = 22.9 ppb; 0.033 ppb * 4.85 (TEF)=0.16 + 3 ppb = 3.16 ppb.

6.0 CUMULATIVE EXPOSURE AND RISKS

The Food Quality Protection Act (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

HED has recently developed a framework that it proposes to use for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance was issued for public comment on June 30, 2000 (65 FR 40644-40650) and is available from the OPP Website at: http://www.epa.gov/fedrgstr/EPA-PEST/2000/June/Day-30/6049.pdf
In the draft guidance, it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed. The proposed guidance on cumulative risk assessment of pesticide chemicals that have a common mechanism of toxicity is expected to be finalized by the summer of 2001.

Before undertaking a cumulative risk assessment, HED will follow procedures for identifying chemicals that have a common mechanism of toxicity as set forth in the "*Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity*" (64 FR 5795-5796, February 5, 1999).

HED did not perform a cumulative risk assessment as part of this reregistration review for TM because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of TM. If HED identifies other substances that share a common mechanism of toxicity with TM, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment once the final guidance HED will use for conducting cumulative risk assessments is available.

It is possible that TM and MBC may express toxicity and carcinogenicity through a common mechanism as the other benzimidazole compounds and, consequently these pesticides may be considered as a group when performing cumulative risk assessments in the future. It is also noted that both TM and MBC are structurally related to several other benzimidazole compounds (primarily veterinary drugs) that are suspect carcinogens including albendazole, fenbendazole, mebendazole, oxfendazole and thiabendazole. Most of the benzimidazole compounds are regulated by the Center for Veterinary Medicine, Food and Drug Administration (FDA) as animal drugs. The potential carcinogenic effects of these compounds were reviewed by the Center for Veterinary Medicine, Food and Drug Administration (FDA). Thiabendazole also has agricultural uses.

7.0 OCCUPATIONAL EXPOSURE

Thiophanate-methyl ([1,2-phenylene)-bis(iminocarbonothioyl)]bis[carbamate]) is a systemic fungicide registered for use in a wide variety of agricultural, ornamental, and residential settings. There are 36 active registrations and 22 special local need registrations. Major food/feed crops include: almonds, apples, dry beans, green beans, peaches, potatoes (seed pieces), soybeans, sugar beets and wheat. Non-agricultural uses include ornamentals, turf (sod farms, residential and recreational lawns), greenhouses, interior scapes, landscaping, and nursery use including seedling and bulb treatment. TM is applied by most ground and aerial methods, and also applied as a seed or seed piece treatment in dry or slurry form and a dip treatment for seeds. There is a potential for exposure from agricultural, commercial operator, and residential uses.

TM is formulated as a wettable powder (WP), water-dispersible granules (WDG), flowable concentrate (FC), emulsifiable concentrate (EC), granular (G), and ready-to-use liquid ranging from 1.65% to 90% active ingredient.

Occupational exposures to TM can occur during pesticide handling (mixing, loading and application activities) or post-application work. Because environmental fate data demonstrate that TM converts to MBC, postapplication exposures were assessed for both TM and MBC residues. Occupational postapplication exposure can occur for agricultural workers during scouting, irrigation, cultivation, harvesting and handling seeds and seedlings. Details of the occupational exposure assessment are presented in the attached memorandum from G. Bangs to D. Smegal April 2002.

7.1 Occupational Handler

Exposure Scenarios

Based on the registered use patterns, HED has identified 23 major exposure scenarios for which there is potential occupational handler exposure during mixing, loading, and applying products containing TM to agricultural crops and turf/ornamentals. These scenarios are as follows:

(1) mixing/loading wettable powders for: (a) aerial/chemigation, (b) groundboom, (c) airblast, (d) lawn handgun, and (e) dip application;
(2) mixing/loading dry flowable/WDG for: (a) aerial/chemigation, (b) groundboom, (c) airblast, (d) lawn handgun, and (e) dip application;
(3) mixing/loading liquid flowable concentrates for: (a) aerial/chemigation, (b) groundboom, (c) airblast, (d) lawn handgun, and (e) dip application;
(4) loading granular formulations for: (a) mechanical ground application for turf, and ornamental broadcast;
(5) loading dusts for seed treatment;
(6) applying sprays aerially;
(7) applying with a groundboom sprayer;
(8) applying with an airblast sprayer;
(9) applying sprays with a handgun sprayer;

(10) applying granular products to turf with tractor-drawn spreader;
(11) applying dip treatments;
(12) applying dust as a potato seed treatment;
(13) mixing/loading/applying liquids using a high pressure handwand;
(14) mixing/loading/applying wettable powder using a low pressure handwand;
(15) mixing/loading/applying liquids using a low pressure handwand;
(16) mixing/loading/applying dry flowables using a low pressure handwand;
(17) mixing/loading/applying with a backpack sprayer;
(18) mixing/loading/applying: (a) liquids, (b) dry flowables (WDG), and (c) wettable powders using a handgun sprayer;
(19) loading/applying granules to turf and ornamentals using a belly grinder;
(20) loading/applying granules to turf using a push-type spreader;
(21) loading/applying dust as a seed treatment (dry) in planter box (i.e., peanuts);
(22) loading/applying wettable powder/DF solution as a seedling or bulb dip treatment; and
(23) flagging aerial spray applications.

These occupational scenarios reflect a broad range of application equipment, application methods and use sites. There are currently insufficient data to evaluate scenarios:11 (applying dip treatments), 16 (mixing/loading/applying dry flowables using a low pressure handwand) and 22 (loading/applying wettable powder/DF solution as a seedling or bulb dip treatment). Although there are no data to assess scenario 16, HED believes exposure resulting from this registered use scenario would be less than scenario 14 (i.e., mixing/loading/applying wettable powder using a low pressure handwand). Additional data are requested for the registered uses of scenarios 11 and 22. The crops on which TM is used, and application rates, are summarized below for the different TM formulations. The application rate ranges reflect maximum single-treatment rates for various crops or groups of crops.

For the agricultural handlers, the estimated exposures initially are assessed assuming handlers are using baseline attire (i.e., long-sleeve shirt, long pants, shoes, and socks). If risk estimates exceed the level of concern for a given scenario with baseline attire, then exposures are assessed with the addition of personal protective equipment (i.e., chemical-resistant gloves, double-layer body protection, and/or a respirator) as required. In general, the Agency uses the least PPE necessary to achieve risk estimates that do not exceed the level of concern. Also, if the risk estimates for *inhalation* exposures result in a MOE that is at least two-fold greater than the target MOE (i.e., MOE $\geq$ 200) at baseline (no respirator), then the inhalation exposures will not contribute significantly to an aggregate (dermal + inhalation) MOE. Therefore, addition of PPE, a respirator, is not warranted for that scenario. If the risk estimates exceed the Agency's level of concern (i.e., if MOE < 100) for a given scenario even with the addition of PPE, then the risks are assessed with the use of engineering controls (i.e., closed system mixing/ loading and enclosed cabs or cockpits for applying and flagging).

Exposure Data Sources and Assumptions

No chemical-specific data on handler exposure were submitted to the Agency for TM. Therefore, potential exposures resulting from handling and applying TM were estimated using data from the Pesticide Handlers Exposure Database (PHED) Version 1.1. PHED is a software system consisting of two parts -- a database of measured exposure values for workers involved in the handling of pesticides

under actual field conditions and a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the database contains values for over 1,700 monitored individuals (i.e., replicates). While data from PHED provides the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pounds of active ingredient handled) may not accurately represent labeled uses in all cases. For example, the agricultural groundboom scenario data in PHED may overestimate exposure from golf course ground application methods.

Occupational and Residential Exposure Task Force (ORETF) data were used to assess scenarios 18a, b and c, (mixing/loading/applying liquid, dry flowables or wettable powders using a handgun sprayer) and 20 (loading/applying granules to turf using a push-type spreader) (MRID 44972201). Scientific literature data were used to assess scenarios 5 (loading dusts), and 12 (applying dusts as a potato seed treatment) and 21 [loading/applying dust as a seed treatment (dry) in a planter box].

Potential exposures were calculated using unit exposures from PHED, ORETF or literature studies, multiplied by the amount of TM handled per day (i.e., lb ai/day). The amount of TM assumed handled per day was derived from the various application rates and the number of acres (or gallons of spray solution) that could be applied in a single day. Cancer risks were estimated only for the typical application rate, in accordance with HED policy.

The duration of exposure is expected to be short-, and intermediate-term for occupational handlers. The exposure duration for short-term assessments is 1 to 30 days, while intermediate-term durations are 1 to 6 months. Maximum application rates were used to assess non-cancer exposure and risks, while the typical application rate was used to assess cancer risks. The standard default body weight of 70 kg was used to assess both non-cancer and cancer effects.

Cancer risks were estimated for the various handler scenarios using two categories of handlers: private and commercial. "Private" handlers are assumed to mix, load, apply, or otherwise handle TM as part of their duties on a single agricultural establishment of a typical size. "Commercial" handlers are assumed to be either custom "for-hire" applicators or individuals who handle TM on a very large agricultural establishment. The Agency assumes that private handlers would handle TM less frequently than commercial handlers. Except where specific information is available (such as greenhouses and golf courses), commercial handlers are assumed to handle TM ten days for each one day that private handlers are assumed to handle it. Most private and commercial applicators were assumed to apply TM 3 and 30 days/year, respectively for 35 years for most crops. When available, EPA used the average or "typical" application rate for assessing cancer risks, since the assessment is based on a lifetime of exposure.

Handler Risk Characterization

A summary of the short- and intermediate-term risk estimates for baseline, PPE and engineering controls is presented in Table 18 for agricultural and commercial uses. Table 18 also provides a summary of the crop-specific application rates assessed for TM. As noted previously, only exposures to TM were assessed for occupational handlers. Handlers are not expected to be exposed to MBC, because MBC is formed during the environmental degradation of TM.

Non-cancer risk estimates are expressed in terms of the Margin of Exposure (MOE). MOEs for occupational handlers were derived by dividing appropriate NOAEL for TM, shown on Table 3, by the daily dermal or inhalation exposure estimate. As noted previously, the short- and intermediate-term dermal NOAEL is 100 mg/kg/day from a 21 day dermal study in rabbits that observed decreased body weight and food consumption. The short and intermediate-term NOAEL of 10 mg/kg/day from an oral developmental study in rabbits was used to evaluate inhalation exposures to TM, assuming inhalation and oral absorption are equivalent (i.e., 100% factor). The inhalation endpoint is also based on decreased body weight and food consumption, therefore, it is appropriate to combine dermal and inhalation exposure and risk estimates. TM is also classified as "likely to be carcinogenic to humans" based on the presence of liver tumors in mice following dietary exposure. The oral Q_1^* for TM is 1.16 x 10^{-2} $(mg/kg/day)^{-1}$. This cancer potency factor was used to assess dermal and inhalation exposure to handlers. Because an oral Q_1^* was selected, a 7% dermal absorption factor and 100% inhalation absorption factor (i.e., equivalent to oral absorption) were used.

For occupationally exposed workers, MOEs $\geq$100 (i.e., uncertainty factors of 10x for interspecies extrapolation and 10x for intraspecies variability) do not exceed HED's level of concern. MOEs below this level would represent a potential risk estimate of concern. As noted previously, a total dermal and inhalation MOE was calculated because the toxicity endpoint is identical for dermal and inhalation (decreased body weight and food consumption) exposures. Cancer risk estimates are presented as a probability of developing cancer. In general, the Agency is concerned whenever occupational cancer risk estimates exceed $1x10^{-4}$ and will attempt to mitigate cancer risk to workers to a lower level, preferably to 10^{-6} or less, by the addition of various exposure risk mitigation measures, where feasible.

The anticipated use patterns and current labeling indicate 23 major occupational handler exposure scenarios, which, when combined with typical ranges of application rates resulted in a total of over 190 scenarios.

Noncancer Risk Estimates: The short- and intermediate-term noncancer risk estimates for dermal and inhalation exposures of occupational handlers at baseline attire, with the addition of PPE, and with the addition of engineering controls are summarized in Table 18. Overall, nearly all MOEs were greater than 100 with either baseline attire, with maximum PPE, or when engineering controls were added, if feasible. Where data for baseline exposures were available, either from PHED, ORETF, or published literature, in general risk estimates did not exceed the level of concern at baseline attire for:

- mixing and loading dry flowable formulations,
- loading granular formulations,
- applying with any equipment, and
- flagging to support aerial applications.

For mixing and loading wettable powder formulations to support aerial or chemigation applications, engineering controls (i.e., water-soluble packaging) are required to achieve the target MOE for many crops and use patterns. For the remaining handler scenarios, in general risk estimates did not exceed the level of concern with the addition of PPE. The addition of gloves to baseline protection increased MOEs to greater than 100 for most scenarios. The MOEs were less than 100 for the highest

application rate for loader/applicators using belly grinders on ornamentals, and no feasible engineering controls are available.

Cancer Risk Estimates: Table 18 summarizes the estimated cancer risks to private and commercial occupational handlers for each of the handler scenarios with baseline attire, with the addition of PPE, and with the addition of engineering controls. At baseline, most of the exposure scenarios had estimated cancer risks less than 10^{-4}, but greater than 10^{-6}. Cancer risk estimates at baseline for private and commercial handlers range from $1.6x10^{-4}$ to $8.6x10^{-9}$, and from $1.5x10^{-3}$ to $2.6x10^{-8}$, respectively. With the addition of PPE, cancer risk estimates for all private handler scenarios and commercial handler scenarios were less than 10^{-4}. With PPE, cancer risk estimates for private and commercial handlers ranged from $1.9x10^{-8}$ to $2.5x10^{-5}$, and from $1.2x10^{-8}$ to $8.7x10^{-5}$, respectively. With the addition of engineering controls, where feasible, cancer risk estimates for all private handler scenarios were equal or less than $6.8x10^{-7}$, and estimates for commercial applicators ranged from $1.3x10^{-7}$ to $4.5x10^{-6}$. Handler scenarios with high application rates, very high acreage crops (i.e., 1200 acres per day) or hand-held application equipment generally had cancer risk estimates greater than 10^{-6}, even with addition of PPE or engineering controls. Most hand application methods (hand-directed sprays, spreaders, etc.) do not have a practical means of enclosure or other engineering control.

As noted previously, there are insufficient information and data to adequately assess seed, seedling and dip applications. HED requests data for these registered uses.

The agricultural handler assessments are believed to be reasonable representations of TM uses. There are, however, many uncertainties in these assessments. The uncertainties include but are not limited to the following:

- not all of the exposure data are of high confidence because of the lack of replicates and/or inadequate QA/QC in the studies

In particular, all hand application methods (wand, spreaders, belly grinder) are highly variable based on applicator techniques. These uncertainties are inherent in most pesticide exposure assessments. The handler assessments were based upon conservative assumptions (e.g., frequently maximum application rates, high daily acreage, 35-year exposure period) and therefore are believed to be protective of the handlers.

7.2 Postapplication

Exposure Scenarios

EPA has determined that there is potential exposure to persons entering treated sites (e.g., scouts and harvesters) after application is complete.

Postapplication Exposure Data and Assumptions

Most post-application worker exposures to TM and MBC are assumed to be of short- (1-30 days) to intermediate-term (1 to 6 months) duration, based on the available use data. Based on the slow dissipation rate of TM seen in submitted studies and multiple seasonal applications, it is possible that some workers may be exposed over a period greater than 180 days per year. This is most likely to happen in an enclosed greenhouse situation, where residues decline slowest, or less commonly, in picking field crops such as strawberries. The average number of applications based on surveys is once per season per crop, but labels allow repeated application when needed. In the agricultural fields, TM slowly breaks down (hydrolyzes) to MBC in a period of days to weeks after application based on foliar residue dissipation data. The MBC residues remain lower than TM throughout the dissipation period. All of the re-entry MOEs use TM residues alone, as the highest detected MBC residues resulted in an MOE of 350 for short/intermediate term exposure and an MOE of 100 for long-term exposure, and therefore do not exceed HED's level of concern.

Based on toxicological criteria and potential for exposure, HED has conducted a dermal exposure assessment for occupational postapplication exposure to TM. Inhalation is not expected be a significant postapplication exposure route, based on the low chemical vapor pressure and outdoor dilution effects.

Post-application dislodgeable foliar residue (DFR) data were submitted for apples, strawberries, and cut flowers in a greenhouse, as well as transferable residues from treated turf. All of these data were used in this assessment along with HED standard transfer coefficients based on EPA Science Advisory Council for Exposure guidance (Policy 3.1 8/7/00) to assess potential exposures to workers reentering treated sites. For occupational exposures, an 8-hour exposure day was assumed. For assessing short- and intermediate-term exposures associated with non-cancer risks, the maximum application rate by crop is assumed, whereas, for assessing exposures associated with cancer risks, the typical application rate, if known, for a crop is assumed.

Risk estimates for short- and intermediate-term dermal exposures are assessed based on the DFR data on day 0 or day 1, whichever is greater. Cancer risk estimates are assessed based on the average DFR data in the range of day 1 to day 14, since in general, TM can be reapplied at 14-day intervals. This means that if the restricted-entry interval were set at day 1, EPA estimates that workers would enter treated areas on days 1 through day 14, with the average exposure being the average of DFRs between days 1 and 14. If cancer risk estimates are of concern based on the average DFR between days 1 and 14, then risks are assessed using the average day 2 to day 14, day 3 to day 14, etc. This assesses the risks with increasing REIs. In some instances, risk estimates remain greater than 10^{-6} after day 14, which is the usual retreatment interval. In these cases, EPA back-calculated to ascertain what day of entry would achieve cancer risk estimates that were less than 10^{-6}. If the calculations indicate, for example, that cancer risk estimates reach 1.0×10^{-6} on day 30, that means that the *average* or *typical* day of entry is day 30 to reach that risk level. That should not be interpreted as an REI of 30 days, but rather is a range-finder calculation.

Postapplication Risk Characterization

The MOEs for postapplication workers were derived by dividing the appropriate NOAEL for TM, shown on Table 3, by the daily dermal exposure estimate. As noted previously, the short and intermediate-term dermal NOAEL of 100 mg/kg/day for TM is from a 21-day dermal study. For cancer, the oral Q_1^* for TM is 1.16×10^{-2} $(mg/kg/day)^{-1}$. These cancer estimates were used to assess dermal exposure to postapplication workers. Because the Q1* is based on an oral study, a dermal absorption factor of 7% for TM was applied to estimate the dermal cancer risks.

As noted previously, MOEs ≥100 do not exceed HED's level of concern for occupationally exposed workers. MOEs below this level would represent a potential risk concern. Only dermal exposures to TM were assessed, as post-application inhalation exposure is expected to be negligible because inhalation exposures have been shown historically to account for negligible percentage of the overall body burden and the vapor pressure of TM is low (1.3×10^{-5} mmHg). As stated above, MBC residues did not exceed the level of concern.

Postapplication Risk Estimates for TM: Table 19 presents an overall summary of occupational postapplication risk estimates by crop and worker activity. The results of the short- and intermediate-term dermal postapplication assessments indicate that the MOEs were less than 100 for grapes, citrus, almonds, cut flowers and some lawn-care activities at the current WPS-required restricted entry intervals (REIs) of 12 hours, and therefore exceed HED's level of concern. The REI represents the duration in days which must elapse before the Agency would not have a concern (MOE ≤ 100) for a worker wearing a long-sleeved shirt and long pants to enter the treated area and perform specific tasks. Overall, the days necessary to reach a target MOE ranged from 0 days to 67 days (tall flowers), although most crops had MOEs of 100 at postapplication day 1. Using translated apple DFR data, grapes required up to 28 days, citrus up to 3 days, and almonds about 2 days to attain an MOE of 100 for workers. High-contact activities on turf required 2 days to attain an MOE of 100 using a TM TTR study. Row crop reentry risk estimates using strawberry DFR data indicated 1 day was sufficient to achieve an MOE of 100 for most tasks. These risk estimates are less certain for crops which do not resemble strawberry plants in architecture and leaf surface. Cut flower risk estimates, using data for transfer coefficients and residues from TM studies, showed MOEs of 100 were not attained until 1-2 months (41 to 67 days) after application. Using 14 day average residues, cancer risk estimates for most activities on most crops were between 10^{-4} and 10^{-6}, although some high-contact activities exceeded 10^{-4}, notably those involving cut flowers.

Postapplication Risk Estimates for MBC: A worker post-application exposure scenario was also assessed for the metabolite of TM, MBC. The same assumptions as for TM were used along with the maximum MBC DFR for each study. The highest MBC DFR value was used because of the uncertainties in the percentage of TM that degrades to MBC at any time in the environment, as well as the dissipation rate of MBC (which increases before decreasing after TM application). The risk assessment indicates that noncancer risks to postapplication workers do not exceed the level of concern (MOE >100) from exposures to MBC residues as a degradate of TM. For short/intermediate-term risks, the MOEs range from 350 to 630,000 with a target of 100, while long-term MOEs ranged from 100 to 6,000. Cancer risk estimates range from 2.6×10^{-9} to 4.4×10^{-6}. TM residues alone were used to

calculate the time required postapplication to achieve MOEs ≥100, as the highest detected MBC residues incurred an MOE of 350 for short/intermediate-term, and 100 for long-term exposures.

The occupational postapplication assessments are believed to be reasonable representations of TM uses. While some individual's exposure may exceed these estimates, the Agency believes that most workers in each group would have fewer than the 180 days of exposure that is assumed for the indicator crops. There are, however, many uncertainties in these assessments. The uncertainties include but are not limited to the following:

- not all of the exposure data are of high confidence because of the lack of replicates and/or inadequate QA/QC in the studies; and
- application timing in comparison to actual potential postapplication exposure scenarios.

These uncertainties are inherent in most pesticide exposure assessments. The conservative nature of the assessments, however, are believed to be protective of the worker. For example, conservative assumptions (e.g., maximum application rates, high daily acreages, 35-year exposure period, and first day-after-treatment residues) were used to estimate exposures and risks to workers.

Table 18
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons) (b)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
Mixer/Loader												
(1a) Mixing/ Loading Wettable Powder for Acrial/ Chemigation Application	celery, cucurbits, peanuts	0.35 NC/0.3C	350	14	2.2e-05	2.2e-04	260	1.3-06	1.3-05	Not necessary	6.4e-08	6.6e-07
	blueberries (aerial), pecans, strawberries, pears, sugar beets	0.7NC/0.5 C		6.9	6.0e-05	3.6e-04	13	3.5-06	2.1e-5		1.8e-07	1.1e-06
	wheat, soybeans	0.7NC/0.6C	1200	2.0	1.5e-04	1.5e-03	39	8.7e-6	8.7e-05	680	4.4e-07	4.5e-06
	apples, apricots, cherries, nectarines, plums/prunes	1NC/0.8C	350	4.8	5.8e-05	5.8e-04	93	3.4e-06	3.4e-05	1,600	1.7e-07	1.8e-06
	grapes, peaches, potatoes	1.05 NC/0.6C		4.6	4.3e-05	4.3e-04	88	2.5e-06	2.5e-05	1,600	1.3e-07	1.3e-06
	almonds, beans, citrus, *garlic (aerial), onions* (aerial), pistachios	1.4 NC/1C		3.5	1.2e-04	7.2e-04	66	7.0e-06	4.2e-05	1,200	3.5e-07	2.2e-06
	canola	1.4 NC/0.6 C	1200	1.0	1.5e-04	1.5e-03	19	8.7e-06	8.7e-05	340	4.4e-07	4.5e-06
	ornamentals (foliar spray) chemigation	2.3 NC/C	10	74	3.2e-05	NA	1400	1.8e-06	NA	Not necessary	9.3e-08	NA
			40	18	1.2e-04	NA	350	7.2e-06			3.7e-07	
	ornamentals (soil directed drench) chemigation	77NC/67C	5	4.4	2.3e-04	6.9e-04	84	1.3e-05	4.0e-05	1,500	6.8e-07	2.1e-06
(1b) Mixing/ Loading Wettable Powder for Groundboom Application	celery, cucurbits, peanuts	0.35NC/0.3C	80	61	4.9e-06	4.9e-05	1200	2.9e-07	2.9e-06	Not necessary	Not Necessary	1.5e-07
	blueberries, strawberries, sugar beets	0.7 NC/0.5 C		30	1.4e-05	8.2e-05	580	8e-07	4.8e-06			2.5e-07
	wheat, soybeans	0.7NC/0.6C	200	12	2.5e-05	2.5e-04	230	1.4e-06	1.4e-05		7.3e-08	7.6e-07
	grapes, potatoes	1.05NC/0.6C	80	20	9.9e-06	9.9e-05	390	5.8e-07	5.8e-06		Not necessary	3.0e-07
	beans, garlic, onions	1.4 NC/1C		15	1.6e-05	1.6e-04	290	9.6e-07	9.6e-06			5.0e-07
	canola	1.4 NC/0.6C	200	6.1	2.5e-05	2.5e-04	120	1.4e-06	1.4e-05		7.3e-08	7.6e-07
	ornamentals (foliar spray)	2.3 NC/C	10	74	7.9e-06	4.7e-05	1400	4.6e-07	2.8e-06		2.3e-08	1.5e-07
			40	18	3.2e-05	1.9e-04	350	1.8e-06	1.1e-05		9.3e-08	5.8e-07
	golf course turf (fairways)	*5.45NC/5.45 C*	*40*	7.8	7.5e-05	4.4e-04	150	4.4e-06	2.6e-05	Not necessary	2.2e-07	1.4e-06

Table 18
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons) (b)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
	golf course turf (tees and greens)	8.16NC/5.45C	10	21.0	3.7e-05	1.1e-04	400	2.2e-06	6.6e-06		1.1e-07	3.4e-07
	ornamentals (soil drench)	77NC/67C	5	4.4	2.3e-04	6.9e-04	84	1.3e-06	4.0e-05	1,500	6.8e-07	2.1e-07
(1c) Mixing/ Loading Wettable Powder for Airblast Application	pecans, pears, blueberries	0.7 NC/0.5C	40	61	6.9e-06	4.1e-05	1200	4e-07	2.4e-06	Not necessary		1.3e-07
	apples, apricots, cherries, plums/prunes, nectarines	1NC/0.8C		42	6.6e-06	6.6e-05	810	3.9e-07	3.9e-06			2.0e-07
	grapes, peaches	1.05 NC/0.6C		40	4.9e-06	4.9e-05	770	2.9e-07	2.9e-06			1.5e-07
	almonds, citrus, pistachios	1.4 NC/1C		30	1.4e-05	8.2e-05	580	8e-07	4.8e-06	Not necessary		2.5e-07
	ornamentals	2.3 NC/C	5	74	4.0e-06	2.4e-05	1400	2.3-07	1.4e-06			7.3e-08
			40	18	3.2e-05	1.9e-04	350	1.8e-06	1.1e-05	Not necessary	9.3e-08	5.8e-07
(1d)Mixing/ Loading Wettable Powders for Lawn Handgun Application	residential turf	2.72 NC/C	100	6.2	1.9e-04	5.6e-04	120	1.1e-05	3.3e-05		5.5e-07	1.7e-06
	ornamental (foliar spray)	3.8 NC/C	20	23.0	2.6e-05	1.6e-04	290	1.5e-06	9.2e-06	Not necessary	7.7e-08	4.8e-07
	golf course (tees and greens)	8.16NC/5.4C	10	21.0	3.7e-05	1.1e-04	400	2.2-06	6.6e-06		1.1e-07	3.4e-07
	ornamental (soil drench)	77NC/67C	1	22	4.6e-05	1.4e-04	420	2.7e-06	8.1e-06		1.4e-07	4.2e-07
(1e) Mixing/ Loading Wettable Powder for Dip Application	cuttings	0.007 lb ai/gal NC/C	100 gallons	2,400	4.8e-07	1.4e-06	Not necessary		8.4e-08	Not Necessary		
	bulbs, garlic	0.012 lb ai/gal NC/C	100 gallons	1,400	8.2e-07	2.5e-06			1.4e-07			
(2a) Mixing/ Loading Dry Flowable /WDG for Aerial/ Chemigation Application	celery, cucurbits, peanuts	0.35 NC/0.3C	350	780	3.9e-07	3.9e-06			2.5e-06	Not necessary		6.6e-07
	blueberries (aerial), pecans, strawberries, pears, sugar beets	0.7NC/0.5 C		390	1.1e-06	6.4e-06			4.1e-06			1.1e-06
	wheat, soybeans	0.7NC/0.6C	1200	110	2.6e-06	2.6e-05		1.7e-06	1.7e-05		4.4e-07	4.5e-06
	apples, apricots, cherries, nectarines, plums/prunes	1NC/0.8C	350	270	1.0e-06	1.0e-05	Not necessary	Not necessary	6.6e-06	Not necessary	Not necessary	1.8e-06

Table 18
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
	grapes, peaches, potatoes	1.05 NC/0.6C	(b)	260	7.7e-07	7.7e-06			4.9e-06	Not necessary		1.3e-06
	almonds, beans, citrus, garlic (aerial), onions (aerial), pistachios	1.4 NC/1C		190	2.1e-06	1.3e-05		1.4e-06	8.2e-06		3.5e-07	2.2e-06
	canola	1.4 NC/0.6 C	1200	57	2.6e-06	2.6e-05	86	1.7e-06	1.7e-05	340	4.4e-07	4.5e-06
	ornamentals (foliar spray) chemigation	2.3 NC/C	5	8,200	7.0e-08	NA	Not necessary	Not necessary	NA	Not necessary	Not necessary	NA
			40	1,000	5.6e-07	NA	Not necessary		NA		""	NA
	ornamentals (soil directed drench) chemigation	77NC/67C	5	250	4.1e-06	1.2e-05	Not necessary	2.6e-06	7.8e-06		6.8e-07	2.1e-06
(2b) Mixing/ Loading Dry Flowable/WDG for *Groundboom* Application	celery, cucurbits, peanuts	0.35NC/0.3C	80	3,400	8.8e-08	8.8e-07		Not necessary				Not necessary
	blueberries, strawberries, sugar beets	0.7 NC/0.5 C		1,700	2.4e-07	1.5e-06		Not necessary	9.4e-07	Not necessary		
	wheat, soybeans	0.7NC/0.6C	200	680	4.4e-07	4.4e-06			2.8e-06			7.6e-07
	beans, garlic, onions	1.4 NC/1C		850	2.9e-07	2.9e-06			1.9e-06			5e-07
	canola	1.4 NC/0.6C	200	340	4.4e-07	4.4e-06			2.8e-06			7.6e-07
	ornamentals (foliar spray)	2.3 NC/C	5	8,200	7.0e-08	4.2e-07	Not necessary		Not necessary	Not necessary		Not necessary
			40	1,000	5.6e-07	3.4e-06			2.2e-06			5.8e-07
	golf course turf (fairways)	5.45 NC/ C	40	440	1.3e-06	8.0e-06			5.1e-06			1.4e-06
	golf course turf (tees and greens)	8.16NC/5.45C	10	1,200	6.7e-07	2.0e-06			1.3e-06			3.4e-07
	ornamentals (soil drench)	77NC/67C	5	250	4.1e-06	1.2e-05	NN	2.6e-06	7.8e-06			**2.1e-06**
(2c) Mixing/ Loading Dry Flowable/WDG for Airblast Application	blueberries, pecans, pears	0.7 NC/0.5C	40	3,400	1.2e-08	7.3e-07	Not necessary		Not necessary	Not necessary		Not necessary
	apples, apricots, cherries, plums/prunes, nectarines	1NC/0.8C		2,400	1.2e-07	1.2e-06			7.5e-07			
	grapes, peaches	1.05 NC/0.6C		2,300	8.8e-08	8.8e-07			Not necessary			

Table 18
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
	almonds, citrus, pistachios	1.4 NC/1C	(b)	1,700	2.4e-07	1.5e-06			9.4e-07			
	ornamentals	2.3 NC/C	10	4,100	7.0e-08	4.2e-07			Not necessary			Not necessary
			40	1,000	5.6e-07	3.4e-06			2.2e-06			5.8e-07
2d) Mixing/ Loading Dry Flowable /WDG for Lawn Handgun Application	residential turf	2.72 NC/C	100	350	3.3e-06	1.0e-05	Not necessary	2.1e-06	6.4e-06	Not necessary	5.5e-07	1.7e-06
	golf course turf (fairways)	*5.45 NC/C*	*40*	*440*	*1.3e-06*	*8.0e-06*		*8.5e-7*	*5.1e-06*		NN	*1.4e-06*
	ornamental (foliar spray)	7.5 NC/6C	10	1,300	1.5e-06	8.8e-06		9.4e-07	5.6e-06	Not necessary		1.5e-06
	golf course (tees and greens)	8.16 NC/5.45C	10	1,200	6.7e-07	2.0e-06		NN	1.3e-06			3.4e-07
	ornamental (soil drench)	77NC/67C	1	1,200	8.2e-07	2.5e-06	Not necessary		1.6e-06	Not necessary		4.2e-07
(2e) Mixing/ Loading Dry Flowable/WDG for Dip Application	cuttings	0.007 lb ai/gal NC/C	100 gallons	140,000	8.6e-09	2.6e-08	Not necessary			Not necessary		Not necessary
	bulbs, garlic	0.012 lb ai/gal NC/C	100 gallons	79,000	1.5e-08	4.4e-08						
(3a) Mixing/ Loading Liquid Flowable Concentrates for Aerial/Chemigation Application	celery, cucurbits, peanuts	0.35 NC/0.3C	350	20	1.5e-05	1.5e-04	2900	1e-07	1e-06			
	blueberries (aerial), pecans, strawberries, pears, sugar beets	0.7NC/0.5 C		9.8	4.1e-05	2.4e-04	1500	2.8e-07	1.7e-06			8.2e-07
	wheat, soybeans	0.7NC/0.6C	1200	2.9	1.0e-04	1.0e-03	430	7e-07	7e-06			3.4e-06
	apples, apricots, cherries, nectarines, plums/prunes	1NC/0.8C	350	6.9	3.9e-05	3.9e-04	1000	2.7e-07	2.7e-06	Not necessary		1.3e-06
	grapes, peaches, potatoes	*1.05 NC/0.6C*		*6.5*	*2.9e-05*	*2.9e-04*	*980*	*2e-07*	*2e-06*			*9.8e-07*
	almonds, beans, citrus, garlic (aerial), onions (aerial), pistachios	1.4 NC/1C		4.9	8.1e-05	4.9e-04	740	5.7e-07	3.4e-06			1.6e-06
	canola	1.4 NC/0.6 C	1200	1.4	1.0e-04	1.0e-03	210	7e-07	7e-06	140	2.1e-06	3.4e-06
	ornamentals (foliar spray) chemigation	2.3 NC/C	5	200	2.7e-06	1.6e-05	not necessary	1.9e-08	1.1e-07	not necessary		
			40	26	2.1e-05	1.3e-04	3900	1.5e-07	9.0e-07	Not necessary		NN

Table 18
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons) (b)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
	ornamentals (soil directed drench) chemigation	77NC/67C	5	6	1.6e-04	4.7e-04	940	1.1e-06	3.3e-06			1.6e-06
(3b) Mixing/ Loading of Liquid Flowable Concentrates for Groundboom Application	celery, cucurbits, peanuts	0.35NC/0.3C	80	86	3.3e-06	3.3e-05	13000	2.3e-08	2.3e-07			
	blueberries, strawberries, sugar beets	0.7 NC/0.5 C		43	9.3e-06	5.6e-05	6400	6.5e-08	3.9e-07			
	wheat, soybeans	0.7NC/0.6C	200	17	1.4e-05	1.4e-04	2600	9.7e-08	9.7e-07			Not necessary
	grapes, potatoes	1.05NC/0.6C	80	29	6.7e-06	6.7e-05	4300	4.7e-08	4.7e-07			
	beans, garlic, onions	1.4 NC/1C		21	1.1e-05	1.1e-04	3200	7.8e-08	7.8e-07			
	canola	1.4 NC/0.6C	200	8.6	1.7e-05	1.7e-04	1300	1.2e-07	1.2e-06	Not necessary		5.6e-07
	ornamentals (foliar spray)	2.3 NC/C	5	200	2..7-06	1.6e-05	not necessary	1.9e-08	1.1e-07	Not necessary		
			40	26	2.1e-05	1.3e-04	3900	1.5e-07	9e-07			Not necessary
	golf course turf (fairways)	5.45NC/ C	40	11.0	5.1e-05	3.0e-04	1700	3.5e-07	2.1e-06			1.0e-06
	golf course turf (tees and greens)	8.16C/5.45NC	10	29.0	2.5e-05	7.6e-05	4400	1.8e-07	5.3e-07			Not necessay
	ornamentals (soil drench)	77NC/67C	5	6.2	1.6e-04	4.7e-04	940	1.1e-06	3.3e-06	Not necessary	5.0e-07	1.6e-06
(3c) Mixing/ Loading of Liquid Flowable Concentrates for Airblast Application	blueberries, pecans, pears	0.7 NC/0.5C	40	86	4.6e-06	2.8e-05	13,000	3.2e-08	1.9e-07	Not necessary		
	apples, apricots, cherries, plums/prunes, nectarines	1NC/0.8C		60	4.5e-06	4.5e-05	9000	3.1e-08	3.1e-07			
	grapes, peaches, potatoes	1.05 NC/0.8C		57	3.3e-06	3.3e-05	8600	2.3e-08	2.3e-07			
	almonds, citrus, pistachios	1.4 NC/1C		43	9.3e-06	5.6e-05	6400	6.5e-08	3.9e-07			
	ornamentals	2.3 NC/C	5	200	2.7e-06	1.6e-05	not necessary	1.9e-08	1.1e-07			
			40	26	2.1e-05	1.3e-04	3900	1.5e-07	9e-07			

Table 18
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons) (b)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
(3d) Mixing/ Loading Liquid Flowable Concentrates for Lawn Handgun Application	residential turf	2.72 NC/C	100	8.8	1.3e-04	3.8e-04	1300	8.8e-07	2.6e-06	Not necessary		1.3e-06
	golf course turf (fairways)	5.45NC/C	40	11	5.1e-05	3.0e-04	1700	3.5e-07	2.1e-06			Not necessary
	ornamental (foliar spray)	7.5 NC/6C	10	32.0	1.8e-05	1.1e-04	4800	3.9e-07	2.3e-06	Not necessary		3.5e-07
	golf course (tees and greens)	8.16NC/5.4C	10	29.0	2.5e-05	7.6e-05	4400	1.8e-07	5.3e-07	Not necessary		
	ornamental (soil drench)	77NC/67C	1	31.0	3.1e-05	9.3e-05	4700	2.2e-07	6.5e-07	Not necessary		
(3e) Mixing/ Loading Liquid Flowable Concentrates for Dip Application	cuttings	0.007 lb ai/gal NC/C	100 gallons	3,400	3.2e-07	9.7e-07	Not necessary					
	bulbs, garlic	0.012 lb ai/gal NC/C	100 gallons	2,000	5.6e-07	1.7e-06	Not necessary		1.2e-08			
(4) Loading Granular Formulations for Mechanical Ground Application	residential turf	2.72 NC/C	40	2,500	5.7e-07	1.7e-06	Not necessary		4.3e-07	Not necessary		
	golf course turf (fairways)	5.4NC/C	40	1,300	5.7e-07	3.4e-06			8.6e-07			
	golf course (tees and greens)	8.16NC/5.45C	10	3,400	2.8e-07	8.5e-07	Not necessary	Not necessary				
	ornamental	27NC/C	80	130	5.6e-06	3.4e-05		1.4e-06	8.5e-06	Not necessary	1.1e-07	6.8e-07
(5) Loading Dusts (Fenske et al., 1991(k) and Stevens and Davis, 1980 (l)	peanut seeds (gloves)	0.047	20 (l)	See PPE			7500	9.1e-08	5.5e-07	No Data		
	potato seed pieces (gloves)	1.2 (l)	30 (l)				200	3.5e-06	2.6e-05			
Applicator												
(6) Applying Sprays Aerially	celery, cucurbits, peanuts	0.35 NC/0.3C	350	See Eng. Controls						10,000	Not applicable	3e-07
	blueberries, pecans, strawberries, pears, sugar beets	0.7NC/0.5 C								5,000		5e-07
	wheat, soybeans	0.7NC/0.6C	1200							1,500		2e-06
	apples, apricots, cherries, nectarines, plums/prunes	1NC/0.8C	350							3,500		8e-07
	grapes, peaches, potatoes	1.05 NC/0.6C								3,400		6e-07

Table 18
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
	almonds, beans, citrus, onions, pistachios	1.4 NC/1C	(b)							2,500		1e-06
	canola	1.4 NC/0.6 C	1200							730		2e-06
(7) Applying with Groundboom	celery, cucurbits, peanuts	0.35 NC/0.3C	80	12,000	2.8e-08	2.8e-07	Not necessary					
	blueberries, strawberries, sugar beets	0.7NC/0.5 C		5,800	7.8e-08	4.7e-07						
	wheat, soybeans	0.7NC/0.6C	200	2,300	1.4e-07	1.4e-06	Not necessary		7.5e-07			
	grapes, potatoes	1.05NC/0.6C	8.0e+01	3,900	5.6e-08	5.6e-07						
	beans, garlic, onions	1.4 NC/1C		2,900	9.4e-08	9.4e-07	Not necessary		Not necessary	Not necessary		Not necessary
	canola	1.4 NC/0.6 C	200	1,200	1.4e-07	1.4e-06			7.5e-07			
	ornamentals (foliar spray)	2.3 NC/C	5	28,000	4.9e-08	1.4e-07			Not necessary			3.5e-07
			40	3,600	1.8e-07	1.1e-06	Not necessary	6.6e-07	5.8e-07			
	golf course turf (fairways)	5.4 NC/C	40	1,500	4.3e-07	2.6e-06	Not necessary		1.4e-06			
	golf course turf (tees and greens)	8.16 NC/5.45C	40	1,000	8.5e-07	2.6e-06			1.4e-06			
	ornamentals (soil drench)	77NC/67C	5	850	1.3e-06	3.9e-06			2.1e-06			9e-07
(8) Applying with an Airblast Sprayer	blueberries, pecans, pears	0.7NC/0.5C	40	620	6.8e-07	4.0e-06	Not necessary		2.2e-06	Not necessary		2.4e-07
	apples, apricots, cherries,plums/prunes, nectarines	1NC/0.8C		430	6.5e-07	6.5e-06			3.6e-06			3.9e-07
	grapes, peaches, potatoes	1.05NC/0.6C		410	4.9e-07	4.9e-06	Not necessary	Not necessary	2.7e-06	Not necessary	7.5e-08	2.9e-07
	almonds, citrus, pistachios	1.4NC/1 C		310	1.3e-06	8.1e-06		7.4e-07	4.4e-06		Not necessary	4.8e-07
	ornamentals	2.3NC/C	5	1,500	7.8e-07	2.3e-06	Not necessary		1.3e-06	Not necessary		1.4e-07
			40	190	3.1e-06	1.9e-05	Not necessary	1.7e-06	1e-05	Not necessary	1.8e-07	1.1e-06
(9) Applying with a Handgun Sprayer	residential turf	2.72 NC/C	5	550	2e-06	6.1e-06		7.6e-07	2.3e-06	Not feasible		

Table 18
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons) (b)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
	ornamentals: nursery plantings of large trees and landscape plantings (foliar spray)	3.8 NC/C	2	980	5.7e-07	1.7e-06	Not necessary		6.4e-07			
	ornamentals: mature trees (foliar spray)	7.5 NC/C	1	990	1.1e-06	3.4e-06	Not necessary	4.2e-07	1.3e-06			
	golf course turf (tees and greens)	8.16 NC/5.45C	10	91	8.2e-06	2.5e-05	240	3.1e-06	9.2e-06			
	ornamentals (soil drench)	77NC/67C	0.05	2000	5.0e-07	1.5e-06	Not necessary		5.6e-07			
(10) Applying Granular Formulations with a Tractor-Drawn Spreader	residential turf	2.72 NC/C	5	24,000	5.8e-08	1.8e-07	Not necessary			Not necessary		
	golf course turf (fairways)	5.45NC/C	40	1.5e+03	4.7e-07	2.8e-06	NN	1.3e-07	7.9e-07			
	golf course (tees and greens)	8.16 NC/5.45C	10	3,900	2.3e-07	7.0e-07	Not necessary					
	ornamental	27NC/C	40	300	2.3e-06	1.4e-05	Not necessary	6.5e-07	3.9e-06	Not necessary		2.7e-06
(11) Applying Dip Treatment [see mixing/loading]	cuttings	0.007 lb ai/gal NC/C	100 gallons	No Data								
	bulbs, garlic	0.012 lb ai/gal NC/C	100 gallons									
(12) Applying Dust as a Potato Seed Treatment (Stevens and Davis, 1981)	cutting/sorting (gloves)	1.2 (l)	30 (l)	No Data - See PPE			2,700	1.6e-07	5.4e-07	Not feasible/not necessary		
	planter/operator (enclosed cab)			See Eng. Controls						3,600	1.8e-07	1.1e-06
	planter/observer (no gloves)			4,400	1.5e-07	9.0e-07	Not necessary			No Data/Not necessary		
Mixer/Loader/Applicator												
(13) Mixing/ Loading/Applying Liquids using High Pressure Handwand	ornamentals (foliar spray)	0.0075 lb ai/gal NC/C	1000 gallons	See PPE			510	2.3e-06	6.9e-06	Not feasible		
(14) Mixing/ Loading/Applying WP using Low Pressure Handwand	ornamentals (soil drench and foliar spray)	0.0075 lb ai/gal NC/C	40 gallons	See PPE			2800	4.5e-07	1.3e-06			
	residential turf (j)	2.72 NC/C	0.5				610	2e-06	6.1e-06			

Table 18
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons) (b)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
	golf course turf (fairways)	5.45 NC/C	0.5				310	4.0e-06	1.2e-05			
	golf course turf (tees and greens)	8.16 NC/5.45C	0.5				200	4.0e-06	1.2e-05			
(15) Mixing/ Loading/Applying Liquid Formulations using Low Pressure Handwand	ornamentals (soil drench and foliar spray)	0.0075 lb ai/gal NC/C	40 gallons	230	4.8e-06	1.4e-05	Not necessary	2.2e-08	6.5e-08			
	turf (j)	2.72 NC/C	0.5	51.0	2.2e-05	6.5e-05	1,200	9.8e-08	3e-07			
	golf course turf (fairways)	5.45 NC/C	0.5	26.0	4.3e-05	1.3e-04	6000	2.0e-07	5.9e-07			
	golf course turf (tees and greens)	8.16 NC/5.45C	0.5	17.0	4.3e-05	1.3e-04	4000	2.0e-07	5.9e-07			
(16) Mixing/ Loading/Applying Dry Flowables using Low Pressure Handwand	ornamentals (soil drench and foliar spray)	0.0075 lb ai/gal NC/C	40 gallons	No Data						Not feasible		
	turf (j)	2.72 NC/C	0.5									
	golf course turf (fairways)	5.45 NC/C	0.5									
	golf course turf (tees and greens)	8.16 NC/5.45C	0.5									
(17) Mixing/ Loading/Applying with a Backpack Sprayer	ornamentals (soil drench and foliar spray)	0.0075 lb ai/gal NC/C	40 gallons	See PPE			13000	9.3e-08	2.8e-07	Not feasible		
	turf (j)	2.72 NC/C	0.5				2800	4.2e-07	1.3e-06			
	golf course turf (fairways)	5.45 NC/C	0.5				1400	8.4e-07	2.5e-06			
	golf course turf (tees and greens)	8.16 NC/5.45C	0.5				930	8.4e-07	2.5e-06			

Table 18
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons) (b)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
(18a) Mixing/ Loading/Applying Liquid Formulations with a Handgun Sprayer (ORETF data, MRID 44972201)	residential turf	2.72 NC/C	5	730	1.5e-06	4.6e-06	Not necessary	5.5e-07	1.7e-06	Not feasible		
	ornamentals: nursery plantings of large trees and landscape plantings (foliar spray)	3.8 NC/C	2	1,300	4.3e-07	1.3e-06	Not necessary		4.6e-07			
	golf course (fairways)	5.45 NC/C	5	370	3.1e-06	9.3e-06	NN	1.1e-06	3.3e-06			
	ornamentals: mature trees (foliar spray)	7.5 NC/C	1	1,300	8.5e-07	2.6e-06	Not necessary		9.1e-07			
	golf course turf (tees and greens)	8.16 NC/5.45C	5	240	3.1e-06	9.3e-06	NN	1.1e-06	3.3e-06			
	ornamentals (soil drench)	77NC/67C	0.05	2,600	3.8e-07	1.1e-06	Not necessary		4.1e-07			
(18b) Mixing/ Loading/ Applying Dry Flowables (WDG) with a Handgun Sprayer (ORETF data, MRID 44972201)	residential turf	2.72 NC/C	5	490	2.5e-06	7.4e-06	Not necessary	7.4e-07	2.2e-06	Not feasible		
	ornamentals: nursery plantings of large trees and landscape plantings (foliar spray)	3.8 NC/C	2	890	6.8e-07	2.1e-06	Not necessary		6.2e-07			
	golf course (fairways)	5.45 NC/C	5	250	4.9e-06	1.5e-05	NN	1.5e-06	4.5e-06			
	ornamentals: mature trees (foliar spray)	7.5 NC/C	1	900	1.4e-06	4.1e-06	Not necessary	4.1e-07	1.2e-06			
	golf course turf (tees and greens)	8.16 NC/5.45 C	5	160	4.9e-06	1.5e-05	NN	1.5e-06	4.5e-06			
	ornamentals (soil drench)	77NC/67C	0.05	1,700	6.0e-07	1.8e-06	Not necessary		5.5e-07			
(18c) Mixing/ Loading/ Applying Wettable Powders with a Handgun Sprayer (ORETF data, MRID 44972201)	residential turf	2.72 NC/C	5	320	4.1e-06	1.2e-05	Not necessary	1.2e-06	3.6e-06	Not feasible		
	ornamentals: nursery plantings of large trees and landscape plantings (foliar spray)	3.8 NC/C	2	570	1.1e-06	3.4e-06	Not necessary		1e-06			
	golf course (fairways)	5.45 NC/C	5	160	8.1e-06	2.4e-05	NN	2.4e-06	7.2e-06			

Table 18
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons) (b)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
	golf course turf (tees and greens)	8.16NC/5.45C	5	110	8.1e-06	2.4e-05		2.4e-06	7.2e-06			
	ornamentals (soil drench)	77NC/ 67C	0.05	1,100	1.0e-06	3.0e-06		3.0e-07	8.9e-07	Not Feasible		
(19) Loading/Applying Granules to Turf Using Belly Grinder	residential turf	2.72 NC/C	1	240	4.7e-06	1.4e-05	Not necessary	2.5e-06	7.6e-06			
	golf course (fairways)	5.45 NC/C		120	9.4e-06	2.8e-05		5.1e-06	1.5e-05			
	golf course turf (tees and greens)	8.16NC /5.45C		80	9.4e-06	2.8e-05	150	5.1e-06	1.5e-05			
	ornamentals	27NC/C		24	4.7e-05	1.4e-04	45	2.5e-05	7.6e-06			
(20) Loading/ Applying Granules to Turf using Push-Type Spreader (ORETF data, MRID 44972201)	residential turf	2.72 NC/C	5	170	6.5e-06	1.9e-05	Not necessary	1.6e-06	4.9e-06			
	golf course (fairways)	5.45 NC/C		600	2.0e-06	5.9e-06		5.7e-07	1.7e-06			
	golf course turf (tees and greens)	8.16NC /5.45C		400	2.0e-06	5.9e-06		5.7e-07	1.7e-06			
	ornamentals	27NC/C		120	9.8e-06	2.9e-05		2.8e-06	8.4e-06			
(21) Loading/ Applying Dust as a Seed Treatment (dry) in Planter Box (k)(Fenske et al., 1990)	peanuts	0.047	20	No Data			710 (single layer plus gloves)	7.8e-07	4.7e-06	No Data		
(22) Mixing/ Loading/Applying a Dip Treatment (see mixing/loading only)	cuttings	0.007 lb ai/gal NC/C	100 gallons	No Data								
	bulbs, garlic	0.012 lb ai/gal NC/C	100 gallons									
Flagger												
(23) Flagging Aerial Spray Applications	celery, cucurbits, peanuts	0.35NC/0.3 C	350	3,900	8.0e-08	8.0e-07	Not necessary		Not necessary	Not necessary		Not necessary
	blueberries, pecans, pears, strawberries, sugar beets	0.7NC/0.5C		2,000	2.2e-07	1.3e-06			9.2e-07			
	apples, apricots, cherries, nectarines, plums/prunes	1NC/0.8C		1,400	2.1e-07	2.1e-06			1.5e-06			7.5e-07

Table 18
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
	grapes, peaches, potatoes	1.05NC/0.6C	(b)	1,300	1.6e-07	1.6e-06			1.1e-06			5.6e-07
	almonds, beans, canola, citrus, onions, pistachios	1.4NC/1C		990	4.4e-07	2.7e-06			1.8e-06			9.4e-07

NOTE: PPE column calculated at maximum protection (double layer clothing, gloves, dust respirator); in most cases, if PPE MOE > 200, then a single layer of clothing and chemical resistant gloves will afford an MOE > 100 for thiophanate-methyl.

NA=Not applicable; NC= non-cancer; C= cancer, NN=not necessary

(a) Application rates are the maximum application rates determined from EPA registered labels. Typical application rate (used in the cancer risk estimates) were determined from EPA registered labels when a range of application rates was specified. Maximum application rate was used as a surrogate for typical rate when a range was not specified.
NC= non-cancer; C= cancer

(b) Amount handled per day values are based on HED Exposure SAC Policy # 009 "Standard Values for Daily Acres Treated in Agriculture," revised June 23, 2000; also communications with BEAD, ANLAm Cerexagri, Cleary, Scotts, and other professionals.

(c) Baseline clothing assumes long pants, long sleeved shirt, no gloves, open mixing/loading, open cab/tractor for applications, and no respirator or dust mask.

(d) PPE assumes gloves and no respirator for most cases, and in some cases assumes double layer clothing. See Occupational/Residential Chapter for inputs and calculations.

(e) Engineering Controls include: Water-Soluble Packets or Enclosed Cab Aircraft

(f) Short/Intermediate-term dermal MOE = NOAEL (100 mg/kg/day / daily dermal dose (mg/kg/day). Short/Intermediate-term inhalation MOE = NOAEL (10 mg/kg/day / daily inhalation dose (mg/-kg/day). Where daily dermal dose = dermal/inhalation unit exposure (mg/lb ai) x application rate (lb ai/acre or gallons/day) x amount handled per day (acres or gallons/day) / body weight (60 kg female >13 yrs). Short/Intermediate-term total MOE = 1 / (1/dermal MOE) + (1/inhalation MOE).

(g) Majority of private applicator treatments per year is 3, which is based on labeled number of treatments to an individual site (e.g., farm, nursery, golf course) and represents number of days per year of expected exposure. BEAD and other use data were used in determining treatment day estimates (e.g., facility or farm size / acres per day in footnote b = exposure days / year).

(h) Most commercial applicator treatments per year is 30, which is based on treatment of multiple sites or farms and represents number of days per year of expected exposure.

(i) Cancer Risk = Total LADD (mg/kg/day) x Q_1*. Where Q_1* is 0.0116 mg/kg/day^{-1}; where total LADD (mg/kg/day) = ADD (mg/kg/day) x treatment days per year (for private or commercial as appropriate) / 365 days/year x 35 years worked / 70 year lifetime; and where ADD (mg/kg/day) = absorbed daily dermal dose (mg/kg/day) + daily inhalation dose (mg/kg/day) where absorbed daily dermal dose = dermal unit exposure (mg/lb ai) x typical application rate (lb ai/acre or gallons/day) x amount handled per day (acres or gallons/day) x dermal absorption factor (7%) / body weight (70 kg adult), and inhalation dose = inhalation unit exposure (mg/lb ai) x application rate (lb ai/acre or gallons/day) x amount handled per day (acres or gallons/day) / body weight (70 kg).

(j) Turf applications based on risk mitigation rates.

(k) Unit exposure values based on a lindane study of peanut treated seed, Fenske et al., 1990.

(l) Exposure data for dust applications based on an exposure study by Stevens and Davis, 1981 (i.e., Captan treated potato seed piece and potato planting study) . The dermal exposure was adjusted to the use of thiophanate-methyl 2.5% dust at 0.025 lb/100 lb seed potatoes (TOPS 2.5D Reg No. 7501-32). It was estimated that 30 acres could be treated in an 8 hour day, based on tractor speed, capacity, and lbs seed/acre. Cancer risk was based on 3-10 planting days per year , assuming USDA estimates of farm size (i.e., 100-300 acres depending on geographic region). Exposure values from the study (mg/hr) were ÷ 4.5 lb ai/hr , in order to determine a standard unit exposure values (mg/lb ai), assuming 30 acres treated /day x 1.2 lb ai/acre ÷ 8 hrs worked/day.

Table 19: Thiophanate-methyl: Summary of Postapplication Occupational Short/Intermediate Term and Cancer Risks by Crop and Activity						
Crop Treated (Potential for Dermal Contact)	**Transfer Coefficient (cm^2/hr) (a)**	**Activities**	**REIs MOE>100 (DAT)**	**MOE at DAT 1**	**Exposure Duration (Days/ Year)**	**Cancer Risk Estimate Avg DAT 1-14 (b)**
Risk Estimates Using Apple DFR Study Data EPA MRID 44876301						
Apples, cherries, nectarines, apricots, plums/prunes	3000	Hand thinning, pruning, propping, hand harvesting	NY: 1 WA: 0	NY: 110 WA: 130	apple: 60	4.6 E-06 to 9.6E-06
					cherries: 45	2.0E-05 to 4.3E-05
Citrus		Hand thinning, pruning, harvesting	NY: 3 WA: 2	NY: 66 WA: 92	60	2.3 E-05 to 4.8 E-05
Peaches		Thinning, Hand pruning, propping, hand harvesting	NY: 1 WA: 0	NY: 110 WA: 120	45	1.0E-05 to 2.2E-05
Almonds	2500	Hand harvesting, hand pruning	NY: 2 WA: 0	NY: 96 WA: 120	60	1.5E-05 to 3.2E-05
Pecans			NY: 0 WA: 0	NY: 170 WA: 230	60	9.5E-06 to 2.0E-05
Pears	3000	Harvesting, pruning, thinning, training, tying	NY: 0 WA: 0	NY: 140 WA: 190	60	1.1E-05 to 2.4E-05
Grapes	10,000	Grape girdling and cane turning	NY: 7 WA: 28	NY: 28 WA: 39		
	5000	Hand harvesting, leaf pulling, thinning, pruning, training/tying	NY: 4 WA: 14	NY: 67 WA: 77	105	2.7E-05 to 5.6E-05
Woody Ornamentals	400	Harvesting, moving potted plants	NY: 0 WA: 0	NY: 190 WA: 270	30	4.9 E-06 to 7.4 E-06
	110	Pruning & staking container plants	NY: 0 WA: 0	NY: 700 WA: 970		
Risk Estimates Using Cut Flower DFR Study: Average of Rose & Mum Data EPA MRID 45027501.						

Table 19: Thiophanate-methyl: Summary of Postapplication Occupational Short/Intermediate Term and Cancer Risks by Crop and Activity						
Crop Treated (Potential for Dermal Contact)	**Transfer Coefficient (cm^2/hr) (a)**	**Activities**	**REIs MOE>100 (DAT)**	**MOE at DAT 1**	**Exposure Duration (Days/ Year)**	**Cancer Risk Estimate Avg DAT 1-14 (b)**
Cut Flowers	4000	Typical greenhouse activities such as pruning, thinning, harvesting, scouting, irrigating	53	14 [ST] 16 [LT]	90	3.5E-04
Herbaceous Ornamentals	400	Harvesting, moving potted plants	0	130	90	3.5 E-05
	175	Pinching, pruning potted herbaceous plants	0	300		
Risk Estimates Using Strawberry DFR Study Data EPA MRID 44866201						
Strawberries & Blueberries	1500	Hand harvest, pinch, prune, train	0	240	180	7.8E-06
	400	Irrigate, scout, weed	0	910		
Wheat	1500	Irrigate, scout	0	240	15	7.8E-07
Cucurbits	2500	hand harvest, prune, leaf pulling	0	290	60	3.5E-06
	1500	Hand weed, scout, irrigate	0	490		
Sugar beets	1500	Irrigate, scout	0	240	30	1.0E-06
Soybeans	1500	Irrigate, scout	0	240	45	1.9E-06
Beans	2500	Hand harvest	1	110	45	6.5E-06
	1500	Irrigate, scout	0	120		
Potatoes	2500	Hand harvest	0	100	45	2.6E-06

Table 19: Thiophanate-methyl: Summary of Postapplication Occupational Short/Intermediate Term and Cancer Risks by Crop and Activity						
Crop Treated (Potential for Dermal Contact)	**Transfer Coefficient (cm^2/hr) (a)**	**Activities**	**REIs MOE>100 (DAT)**	**MOE at DAT 1**	**Exposure Duration (Days/ Year)**	**Cancer Risk Estimate Avg DAT 1-14 (b)**
Potatoes	1500	Irrigate, scout mature plants	0	170		
Risk Estimates Using Turf TTR Study Data EPA MRID 45000701						
Turf: Golf course	16,500	Transplant, hand weed	Irrig: 2	Irrig: 98		
	500	Seed, scout, mech. weed, aerate, fertilize, irrigate, mow	0	4100	45	1.6E-07

(a) Standard HED values for transfer coefficients based on best available data, including ARTF and ORETF studies and Thiophanate-methyl study by Brouwer, et al., for greenhouse flowers.

(b) Cancer risks estimated for typical application rate and days of activity per year

8.0 INCIDENTS

A review of incident data sources found that relatively few incidents were reported for TM. A detailed summary of these incidents is provided in the attached memorandum from J. Blondell and M. Spann to J. Evans, August 15, 1997. The majority of significant symptoms were respiratory or eye irritation, particularly when handling dry formulations. Eleven of 37 California incident reports were judged related to TM alone, and the majority of the five systemic illnesses occurred due to a crew of workers sprinkling TM from coffee cans onto potato seed pieces. Symptoms included shortness of breath, chest pains, burning eyes, dizziness, and fatigue. The Incident Data System cited 2 incidents in 1994, both of which were reportedly a result of spray drift. One case reported respiratory irritation, the other eye irritation, with no follow up information. TM was not included on the list of the top 200 chemicals for which the National Pesticide Telecommunications Network (NPTN) received calls from 1984-1991.

9.0 DEFICIENCIES / DATA NEEDS (CONFIRMATORY DATA)

Additional data requirements have been identified in the attached Science Chapters and are summarized here.

Toxicology Data for OPPTS Guideline:

At this time, the toxicology database for TM is incomplete. The Hazard Identification Assessment Review Committee (HIARC, meeting of April 8, 1999, and September 26, 2000) requested that rat acute and subchronic neurotoxicity screening studies be submitted and that a developmental neurotoxicity study be placed in 'reserve' status pending the results of these studies and a developmental neurotoxicity study with MBC. The HIARC also requested a 90 day rat inhalation study because an unacceptable 14-day inhalation study showed possible respiratory effects from TM exposure at lower concentrations than those associated with developmental effects and because occupational exposures are potentially long-term in green houses.

Toxicology data for carbendazim (Methyl 2-Benzimidazole Carbamate) or MBC, the primary environmental breakdown product of TM and benomyl, are also considered in this assessment, and are incomplete. The HIARC requested two toxicity studies with MBC, a 21 day dermal toxicity study in rats and a developmental neurotoxicity study in rats. In addition, the 2-generation rat reproduction and subchronic studies for MBC fail to meet the Subdivision F Guidelines.

Product and Residue Chemistry Data for OPPTS Guidelines

The following confirmatory data requirements remain outstanding as discussed in the Revised Product and Residue Chemistry Chapter (J. Morales, April 3, 2002; D279270) or are now required:

Product Chemistry:

830.1620 - Starting Materials and Manufacturing Process
830.1670 - Discussion of Formation of Impurities
830.6313 - Stability
830.7050 - UV/Visible Absorption

Residue Chemistry:

860.1200 - Directions for Use
860.1340 - Residue Analytical Methods
860.1360 - Multiresidue Method Testing
860.1380 - Storage Stability Data
860.1500 - Magnitude of the Residue in Plants
860.1520 - Magnitude of the Residue in Processed Food/Feed
860.1900 - Field Accumulation in Rotational Crops

Occupational Exposure Data for OPPTS Guidelines

There are insufficient information and data to adequately assess seed and dip applications. HED requests data to support these registered uses.

10.0 REFERENCES

Nakai, M.,. Hess, R.A., Moore, B.J., Guttroff, R.F., Strader, L.F., and, Linder, R.E. 1992. "Acute and Long-term Effects of a Single Dose of the Fungicide Carbendazim (Methyl 2-Benzimidazole Carbamate) on the Male Reproductive System in the Rat." Journal of Andrology. 13(6):507-517.

Outdoor Residential Pesticide use and Usage Survey and National Gardening Association Survey. 1999. Submitted by the Outdoor Residential Exposure Task Force. D. Johnson, Steward Agricultural Research Services, Inc. R. Thomson, DOANE Marketing Research, Inc. B. Butterfield, National Gardening Association. November 12. Volume 8 and 9 of 17.

US Environmental Protection Agency, 1999. Guidance for Conducting Health Risk Assessment of Chemical Mixtures - External Scientific Peer Review Draft, NCEA-C-0148, April 1999, http://www.epa.gov/ncea/mixtures.htm

Wood et al. 1982. Chronic feeding study in CD-1 mice (2 yrs). MRID # 256028, and 256029

APPENDIX A
SUMMARY OF TOXICOLOGICAL DATA FOR THIOPHANATE-METHYL AND MBC

Table A-1: toxicity studies for thiophanate-methyl		
GUIDELINE/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day)**
870.3100 [82-1(a)] 90-Day Dietary Toxicity Study in Rats	MRID No. 42001701 Date: 1990 Acceptable-guideline♂ 0, 13.9, 155.0, 293.2, 426.9 or 564.7 ♀ 0, 15.7, 173.4, 323.0, 478.8 or 647.3 Tech., 96.55% a.i.	NOAEL = 15.7 mg/kg/day LOAEL = 155.0 mg/kg/day, based on anemia, increased serum cholesterol and calcium (males), increased liver and thyroid weights, increased kidney (males) weight and increased incidence of thyroid hyperplasia/hypertrophy, liver swelling and lipofuscin deposition, and glomerulonephrosis (males) were observed. At higher dose levels, effects included increased serum cholinesterase (males), increased thymus weight (females), increased incidence of glomerulonephritis (females) and fatty degeneration of the adrenal cortex were also reported.
870.3150 [82-1(b)] 90-Day Oral (Capsule) Toxicity Study in Beagle Dogs	MRID No. 41982203 Date: 1992 Acceptable-guideline 0, 50, 200 or 800 in gelatin capsules (HDT lowered to 400 on day 50 due to excessive toxicity) Tech., 96.55% a.i.	NOAEL = 50 mg/kg/day LOAEL = 200 mg/kg/day, based on thin/dehydrated appearance, tarry stools, decreased body weight/weight gain, decreased food consumption, slight anemia, increased serum cholesterol, decreased serum T3/T4 (females), increased liver and thyroid weights, thyroid follicular cell hypertrophy and hyperplasia, hypoplasia/atrophy of the prostate, thymic involution/atrophy (males) and depletion of spleen lymphoid cells. At 800/400 mg/kg/day, mortality (1 male), increased platelet count were also observed.
870.3200 [82-2] 21-Day Dermal Toxicity Study in New Zealand White Rabbits	MRID No. 42110801 Date: 1991 Acceptable-guideline 0, 100, 300 or 1000, moistened with water (5 days/week, 6 hrs/day) Tech., 96.55% a.i.	Systemic toxicity NOAEL = 100 mg/kg/day Systemic toxicity LOAEL = 300 mg/kg/day, based on decreased food consumption in females. At 1000 mg/kg/day, consumption also decreased in males. Slight dermal irritation was observed at all dose levels.
870.3465 [82-4] 14-Day Inhalation Toxicity Study in HSD:(SD) Rats	MRID No. 42527601 Date: 1992 Unacceptable-nonguideline0.0, 0.00514, 0.0151 or 0.247 mg/L Tech., 5.2% a.i. (Tops® 5 formulation)	NOAEL = 0.00514 mg/L LOAEL = 0.0151 mg/L, based on increased incidence of alveolar macrophages, pneumonocyte hyperplasia of the lung and nonsuppurative alveolitis. At 0.247 mg/L, decreased body weight gain (females) and increased incidence of lung microgranulomas (both sexes) were also observed.

Table A-1: toxicity studies for thiophanate-methyl		
GUIDELINE/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day)**
870.4100 [83-1b] 1-Year Oral (Capsule) Study in Beagle Dogs	MRID No. 42311801 Date: 1992 Acceptable-guideline 0, 8, 40 or 200 in gelatin capsules Tech., 96.55% a.i.	NOAEL = 8 mg/kg/day LOAEL = 40 mg/kg/day, based on decreased body weight/weight gain, markedly increased serum TSH (1 male) and decreased T4 (males), increased serum cholesterol (males), increased abs/rel thyroid weights (both sexes) and thyroid follicular cell hypertrophy (females). At 200 mg/kg/day, tremors in all dogs 2-4 hrs postdosing (most on day 1; sporadically through day 17), slight anemia, increased serum alkaline phosphatase and cholesterol, increased relative liver weight, thyroid follicular cell hypertrophy in males and hyperplasia (both sexes) were also observed.
870.4200b [83-2b] 18-Month Dietary Carcinogenicity Study in CD-1 Mice	MRID No. 42607701 Date: 1992 Acceptable-guideline ♂ 0, 23.7, 98.6, 467.6 or 1078.8 mg/kg/day; ♀ 0, 28.7, 123.3, 557.9 or 1329.4 mg/kg/day Tech., 95.93% and 96.55% a.i.	Systemic toxicity NOAEL = 23.7 mg/kg/day Systemic toxicity LOAEL = 123.3 mg/kg/day, based on hepatocellular hypertrophy in females. At ≥98.6 mg/kg/day, decreased body weights,, sporadic effects on circulating T4 and TSH, increased thyroid and liver weights, increased heart weight (females), increased hepatocellular hypertrophy and increased atrial thrombosis were also observed. At the HDT, mortality was increased in both sexes. Increased incidence of hepatocellular adenomas in males at ≥467.6 mg/kg/day (control to high dose, 9%, 17%, 15%, 42% and 57%) and in females at ≥123.3 mg/kg/day (0%, 0%, 8%, 24% and 56%). Both sexes showed significant increasing trends and pair wise increases at the highest two dose levels.

Table A-1: toxicity studies for thiophanate-methyl		
GUIDELINE/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day)**
870.4300 [83-5] 24-Month Dietary Chronic Toxicity/ Carcinogenicity Study in F-344 Rats	MRID No. 42896601 Date: 1993 Acceptable-guideline ♂ 0, 3.3, 8.8, 54.4 or 280.6 ♀ 0, 3.8, 10.2, 63.5 or 334.7 Tech., 96.55% a.i.	NOAEL = 8.8 mg/kg/day LOAEL = 54.4 mg/kg/day, based on decreased body weight/weight gain (males; marginal in females), decreased food efficiency (males; marginal in females), sporadic effects on circulating T3/T4 and TSH, increased serum cholesterol and creatinine, decreased serum cholinesterase in females, increased liver, thyroid and kidney weights, liver hypertrophy and lipofuscin accumulation, thyroid hypertrophy and hyperplasia and lipofuscin accumulation in the kidney. At≥280.6 mg/kg/day, excessive mortality in males (2/50 survivors at termination), decreased body weight/weight gain in females, mild anemia, increased urinary protein, hyperparathyroidism (primarily in males), systemic calcification, increased severity of nephropathy and increased severity of liver and thyroid effects were also observed. The HDT was considered excessive in males. Increased incidence of thyroid follicular cell adenoma in males (control to high dose, 2%, 0%, 0%, 6% and 27%) and females (0%, 0%, 0%, 2% and 4%). Significantly increased trend in both sexes; pair wise incidence in males at high dose. Follicular cell carcinomas also observed in high dose males at high dose (11% vs. 0% all other doses; significant trend and pair wise comparison). Combined incidence significantly increased at high dose (2%, 0%, 0%, 6% and 32%) with positive increasing trend.
870.4100 [83-1a] 24-Month Dietary Chronic Toxicity Study in SD Rats	MRID No. 00057651, 00117868 Date: 1971/1972 Unacceptable-guideline ♂ 0, 0.37, 1.54, 5.75 or 24.3 ♀ 0, 0.399, 1.62, 7.18 or 28.7 Tech., >94% a.i.	NOAEL = 5.75 mg/kg/day LOAEL = 24.3 mg/kg/day based on decreased body weight and body weight gain in both sexes and increased incidence of thyroid and testicular microscopic effects in males.

Table A-1: toxicity studies for thiophanate-methyl		
GUIDELINE/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day)**
870.3700a [83-3(a)] Developmental toxicity study in Crl: COBS CD rats (gavage)	MRID No. 00106090 Date: 1981 Unacceptable-guideline (upgradable with submission of dosing solution analyses, maternal clinical sign and food consumption data, and individual litter data) 0, 100, 300 or 1000 (gavage in 5% aq. gum arabic) tech., 97.2% a.i.	Maternal NOAEL = 300 mg/kg/day* Maternal LOAEL = 1000 mg/kg/day*, based on decreased body weight gain. Developmental NOAEL ≥1000 mg/kg/day* Developmental LOAEL >1000 mg/kg/day* * All endpoints tentative pending submission of additional information to upgrade study
870..3700a [83-3(a)] Developmental toxicity study in Crl: COBS CD rats (diet)	MRID No. 00146643 Date: 1985 Acceptable-nonguideline 0, 18, 85, or 163 (0, 250, 1200 or 2500 ppm in diet) tech., 95.3% a.i.	Maternal NOAEL = 18 mg/kg/day Maternal LOAEL = 85 mg/kg/day, based on decreased food consumption. Developmental NOAEL ≥163 mg/kg/day (HDT) Developmental LOAEL none established
870.3700b [83-3(b)] Developmental Toxicity Study in New Zealand White Rabbits	MRID No. 40028801, 41056701 Date: 1986 unacceptable-nonguideline 0, 2, 6 or 20 (gavage in 1% aq. methyl cellulose) tech., 96.2% a.i.	Maternal NOAEL = 6 mg/kg/day Maternal LOAEL = 20 mg/kg/day, based on transiently decreased body weight gain, increased abortion/total litter loss Developmental NOAEL≥ 20 mg/kg/day Developmental LOAEL = none
870.3700b [83-3(b)] Developmental Toxicity Study in New Zealand White Rabbits	MRID No. 45051001 Date: 1997 Acceptable-guideline 0, 5, 10, 20, or 40 (gavage in 1% aq. methyl cellulose) tech., 97.28% a.i.	Maternal NOAEL = 10 mg/kg/day Maternal LOAEL = 20 mg/kg/day, based on decreased body weight gain and food consumption Developmental NOAEL= 20 mg/kg/day Developmental LOAEL = 40 mg/kg/day, based on increased supernumerary ribs and decreased fetal weight

Table A-1: toxicity studies for thiophanate-methyl		
GUIDELINE/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day)**
870.3800 [83-4] Two-Generation Reproductive toxicity Study in Crl:CD(SD)BR Rats	MRID Nos. 42899101 to -05; 43624401 Date: 1993 (addendum 1995) Acceptable-guideline ♂ 0, 13.7, 43.3 or 138.9; ♀ 0, 15.5, 54.0 or 172.0 (in diet) tech., 95.9% a.i.	Parental systemic NOAEL <13.7 mg/kg/day Parental systemic LOAEL = 13.7 mg/kg/day, based on hepatocellular hypertrophy and thyroid hypertrophy/hyperplasia. At ≥43.3 mg/kg/day, slightly decreased body weight gains in males and at 138.9 mg/kg/day, increased liver and thyroid weights (both sexes). Reproductive NOAEL ≥ 138.9 mg/kg/day (HDT) Reproductive LOAEL > 138.9 mg/kg/day Offspring NOAEL = 13.7 mg/kg/day Offspring LOAEL = 43.3 mg/kg/day, based on slightly reduced body weights of the F2b offspring during lactation.
870.3800 [83-4] Three-Generation Reproductive Toxicity Study in CD Rats	MRID No. 00117870 Date: 1972 Unacceptable-guideline (upgradable with submission of test material purity) 0, 2, 8 or 32 (estimated from ppm in diet) purity a.i. not stated	Parental systemic/reproductive NOAEL ≥32 mg/kg/day Parental systemic/reproductive LOAEL >32 mg/kg/day Offspring NOAEL = 8 mg/kg/day Offspring LOAEL = 32 mg/kg/day, based on slightly decreased mean litter weights.

NOAEL = No Observable Adverse Effect Level
LOAEL = Lowest Observable Adverse Effect Level
NA = Not applicable

Table A-2. Toxicity Studies for MBC		
GDLN/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day) (1)**
870.3150 (82-1(b)) Subchronic Feeding in Dogs (90 days)	00099130 Sherman et al. 1970 Unacceptable guideline M: 0, 2.7, 14.4, or 40.7 F: 0, 2.7, 11.3, or 35 (0, 100, 500 or 1500/2500 ppm)	**53% a.i. carbendazim** NOAEL: 11.3 (F), 14.4 (M) LOAEL: 35 (F), 40.7 (M) based on histopathology changes in liver (1/4 males and 1/4 females) and testes (1/4 males) and increased alkaline phosphatase, cholesterol and SGPT. Liver effects included hepatic cirrhosis (hepatic cell necrosis, tubular collapse, and increased fibrous connective tissue around triads). Decreased testes weight in 3/4 males in the high dose.
870.4100 870.4200 (83-1& 2) Chronic feeding/ carcinogenicity study in CD rats (2 yrs)	00088333, 00068982, Accession #: 2328700, 232871 Sherman et al. 1972, Lee 1978 Minimum 0, 5, 25, 250 or 125/500 (430) [0, 100, 500, 5000 or 2500/10000 (8557) ppm]	**53% a.i. carbendazim** NOAEL:25 LOAEL: 250 based on statistically significant decreases in red blood cell parameters (hematocrit, hemoglobin an red blood cells) in females and histological lesions in the liver (cholangiohepatitis and pericholangitis) in males and females. No evidence of carcinogenicity. Deficiencies: Only 36 rats/sex/dose tested (only 20 rats/sex were in 250 mg/kg/day dose group). Lack of complete clinical chemistry data and histopathology examination. At 24 months, only liver evaluated in 5 and 25 mg/kg/day groups and only liver, kidney and testes evaluated in 250 mg/kg/day group.
870.4100b (83-1b) Chronic feeding study in beagle dogs (2 yrs)	00088333 Accession #: 232870-0, 232871 (Sherman et al. 1972) Acceptable guideline 0, 2.5, 12.5, or 37.5/62.5 (0, 100, 500 and 1500/2500 ppm) (Doses adjusted for % a.i.)	**53% a.i. carbendazim** NOAEL: 2.5 LOAEL: 12.5 based on swollen, vacuolated hepatic cells, hepatic cirrhosis and chronic hepatitis and biochemical alterations indicative of liver damage (i.e., increased cholesterol, total protein, SGPT and alkaline phosphatase levels, and decreased A/G ratio). At 37.5/62.5 mg/kg/day, anorexia, distended abdomens and poor nutritional condition were reported.
870.4100b (83-1b) Chronic feeding study in beagle dogs (1 yr)	00164304 Accession # 265664 (Stadler et al. 1986) Acceptable guideline F:0, 2.93, 6.43 or 16.54 mg/kg M: 0, 3.2, 7.19, 17.07 (0, 100, 200, or 500 ppm)	**98.8% a.i. carbendazim** NOAEL: 6.43 (200 ppm) LOAEL: 16.54 (500 ppm) based on possible transient increase in cholesterol (males and females) consistent with previous dog feeding studies.

Table A-2. Toxicity Studies for MBC		
GDLN/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day) (1)**
870.4200b (83-2b), 83-1 Chronic feeding study in CD-1 mice (2 yrs)	00096513, 00154676 256028, and 256029 Wood et al. 1982, Schneider, Wood and Hall 1982 Core Grade: acceptable guideline. The study was designed to specifically evaluate the liver carcinogenicity potential of MBC 0, 75, 225, 1125 (females) or 1125/563 (males) (0, 500, 1500 or 7500 (females) or 7500/3750 (males) ppm)	**99.3% a.i. carbendazim** NOAEL (non-cancer systemic): 75 LOAEL (non-cancer systemic): 225 based on liver toxicity (hepatocellular necrosis and swelling), body weight decrease and lymphoid depletion. In both sexes, there was an increased incidence of liver tumors. In males, hepatocellular carcinomas were noted at 225 mg/kg/day, while females exhibited carcinomas and adenomas at all dose levels. Note: The 7500 ppm was reduced to 3750 ppm at 66 weeks in males due to increased mortality.
870.4200b (83-2b) Chronic feeding/ carcinogenicity study in NMRKf mice (2 years)	00154679 Accession # 2560302 (Donaubauer et al. 1982) Unacceptable guideline 0; 5.8-7.1; 17.1 -21.2; 34.4 - 41.9 or 522 - 648 (0, 50, 150, 300 or 1000/5000 ppm).	**99% a.i. carbendazim** NOAEL (non-cancer systemic): 34.4 - 41.9 LOAEL (non-cancer systemic): 522 - 648 based on increases the incidences of hepatic cell hypertrophy, clear cell foci and hepatocellular necrosis. No increased incidence of carcinogenicity was noted. Deficiencies: incomplete examination of most recommended tissues, blood and urine were not collected for analysis.
870.4200b (83-2) Chronic feeding/ carcinogenicity study in Swiss mice (80 weeks)	00153420 Accession # 256029 (Beems et al. 1976) Unacceptable guideline 0, 22.5, 45 or 750 (0, 150, 300 or 5000 ppm)	**99% a.i. carbendazim** NOAEL:45 LOAEL:750 based on hepatic alterations which included increased relative liver weights in both sexes, increased number of foci of cellular alterations in the liver in females, neoplastic nodules in females and hepatoblastomas in males Deficiencies: Brief methods, there were no historical data or microscopic or gross pathology reports for individual animals, and there was no assurance that the diets were analyzed for compound homogeneity and stability. In addition, there were no hematology or clinical chemistry analysis, nor urinalysis. Only organs or lesions suspected of being tumors and livers (2 sections) were examined histologically.
870.3700a (83-3a) Developmental Study in Crl:CE BR rats (gavage)	40438001 Alvarez 1987 Acceptable guideline 0, 10, 20, 90 gestation day 7-16	**98.8% a.i. carbendazim** Maternal NOAEL: 20 Maternal LOAEL:90 (increased absolute liver weight) Developmental NOAEL:10 Developmental LOAEL: 20 based on decreased fetal body weight and increases in skeletal variations and a threshold for malformations.

Table A-2. Toxicity Studies for MBC		
GDLN/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day) (1)**
870.3700b (83-3b) Developmental Study in New Zealand White Rabbits (gavage)	Accession # 260571 (Christian et al. 1985) Acceptable guideline 0, 10, 20 or 125 gestation day 7-19	**98.7% a.i. carbendazim** Maternal NOAEL: 20 Maternal LOAEL:125 (abortions and decreased body weight) Developmental NOAEL:10 Developmental LOAEL: 20 mg/kg/day based on decreased implantations and litter size, and increased resorptions. Malformations (fused ribs, and malformed cervical vertebrae) were noted at 125 mg/kg/day
870.3800 (83-4) Reproductive Study in ChR-CD rats (diet)	00088333 Sherman et al. 1972 Unacceptable guideline 0, 5, 25, 250 or 125/500 (0, 100, 500, 5000 or 2500/10,000 ppm)	**50 or 70% a.i. carbendazim** Reproductive NOAEL:25 Reproductive LOAEL: 250 based on toxic signs of decreased pup weight noted at weaning. Deficiencies: Litter (or fetal) weights were not measured at birth, therefore it is impossible to attribute weight decrease in 5000 and 2500/10000 ppm groups to prenatal or lactation period. Only 16 dams (20 dams for 5000 ppm), resulting in 10-16 litters per group were available, rather than the 20 litters recommended in the guideline. There was no special attention for the testes, a known target organ, including organ weights measurements.
NA Single dose (gavage) rat study	Nakai et al. (1982) Literature Study 0, 50, 100, 200, 400 or 800 mg/kg	NOAEL: none observed LOAEL: 50 based on premature release of immature germ cells 2 days post exposure, and atrophy of a few seminiferous tubules and significant decrease in seminiferous tubule diameter 70 days post exposure.

(1) Unless specified, mg ai MBC/kg/day.
NOAEL = No Observable Adverse Effect Level
LOAEL = Lowest Observable Adverse Effect Level

APPENDIX B
TOLERANCE REASSESSMENT

Table 1. Tolerance Reassessment Summary for Thiophanate-methyl			
Commodity	Current Tolerance (ppm)	Tolerance [a] Reassessment (ppm)	Comment/*Correct Commodity Definition*
Tolerances listed under 40 CFR §180.371(a):			
Almonds	0.2	0.1	Residue data indicate the tolerance for residues in/on *almond* and *almond, hulls* can be lowered.
Almond, hulls	1.0	0.5	
Apples	7.0	2.0	The available residue data indicate that the tolerance can be reduced. *Apple*
Apple, dried pomace	40.0	Revoke	Dried apple pomace is no longer a regulated commodity.
Apricots	15.0	TBD[b]	Residue data are required. *Apricot*
Bananas	2.0	2.0	*Banana*
Bananas, pulp	0.2	Revoke	Banana pulp is not a regulated commodity
Beans, dry	2.0	0.2	The available data indicate the tolerance can be lowered. *Bean, dry, seed*
Beans, forage	50.0	Revoke	With the exception of cowpea forage and hay, bean forage and hay are no longer considered significant livestock feed items.
Beans, hay	50.0		
Beans, snap	2.0	2.0	The available lima and snap bean residue data support a 2.0 ppm tolerance for residues in/on *beans, succulent.*
Beets, sugar, roots	0.2	TBD	An additional field trail in CA is required. However, the available data indicates that the established tolerance of 0.2 ppm for residues in/on sugar beet roots is adequate, and that the current tolerance of 15 ppm for residues in/on sugar beet tops is too high.
Beets, sugar, tops	15.0		
Cattle, fat	0.1 (N)	0.15	The available ruminant feeding study indicates that tolerances of 0.15 ppm are appropriate for meat and fat and that a single tolerance of 0.15 ppm should be established for residues in *cattle, mbyp.*
Cattle, kidney	0.2	Delete	
Cattle, liver	2.5	Delete	
Cattle, mbyp	0.1 (N)	0.15	
Cattle, meat	0.1 (N)	0.15	
Celery	3.0	Revoke	Data are required to support the use on celery.
Cherries	15.0	20.0	The available residue data indicate that the tolerance should be increased. *Cherry*
Cucumbers	1.0	Delete	Individual tolerances for cucumbers, melons, pumpkins, and squash should be deleted and a crop group tolerance should be established for *cucurbit vegetables* (Crop Group 9)
Eggs	0.1 (N)	Revoke	40 CFR § 180.6 (a)(3)

Table 1. Tolerance Reassessment Summary for Thiophanate-methyl

Commodity	Current Tolerance (ppm)	Tolerance [a] Reassessment (ppm)	Comment/*Correct Commodity Definition*
Goat, fat	0.1 (N)	0.15	The available ruminant feeding study indicates that tolerances of 0.15 ppm are appropriate and that a single tolerance for residues in *goat, mbyp* should be established.
Goat, kidney	0.2	Delete	
Goat, liver	2.5	Delete	
Goat, mbyp	0.1 (N)	0.15	
Goat, meat	0.1 (N)	0.15	
Hogs, fat	0.1 (N)	Revoke	Based upon the maximum theoretical dietary burden for swine and data from the ruminant feeding study, a Category 3 [40 CFR §180.6(a)(3)] situation exists for thiophanate-methyl residues in hog commodities.
Hogs, liver	1.0		
Hogs, mbyp (exc. liver)	0.1 (N)		
Hogs, meat	0.1 (N)		
Horses, fat	0.1 (N)	0.15	The available ruminant feeding study indicates that tolerances of 0.15 ppm are appropriate for meat and fat and that a single tolerance should be established for residues in *horse, mbyp*.
Horses, liver	1.0	Delete	
Horses, mbyp	0.1 (N)	0.15	
Horses, meat	0.1 (N)	0.15	
Melons	1.0	Delete	Individual tolerances for cucumbers, melons, pumpkins, and squash should be deleted and a crop group tolerance should be established for *cucurbit vegetables* (Crop Group 9)
Milk	1.0	0.15	Data from the ruminant feeding study indicates that the tolerance can be lowered.
Nectarines	15.0	Delete	In accordance with 40 CFR §180.1 (h) residues in/on nectarines are covered by the tolerance for residues in/on *peaches*.
Onions, dry	3.0	0.5	The available data indicate that the tolerance can be lowered. *Onion, dry bulb*
Onions, green	3.0	TBD	Residue data are required.
Peaches	15.0	3.0	Residue data indicate that the tolerance can be lowered *Peach.*
Peanuts	0.2 (N)	0.1	Residue data indicate that the tolerance can be lowered. *Peanut*
Peanuts, forage	15.0	Revoke	Commodity is no longer considered a significant livestock feed item.
Peanuts, hay	15.0	5.0	Residue data indicate that the tolerance can be lowered. *Peanut, hay*
Peanuts, hulls	2.0	Revoke	Commodity is no longer considered a significant livestock feed item.
Pecans	0.2	0.1	Residue data indicate that the tolerance can be lowered. *Pecan*

Table 1. Tolerance Reassessment Summary for Thiophanate-methyl			
Commodity	Current Tolerance (ppm)	Tolerance [a] Reassessment (ppm)	Comment/*Correct Commodity Definition*
Plums	15.0	0.5	Available residue data indicate that the tolerance can be lowered. *Plum*
Potatoes (seed treatment)	0.05	0.1	Additional data are required. However, the available data indicate that the tolerance should be increased. *Potato*
Poultry, fat	0.1 (N)	Revoke	40 CFR § 180.6 (a)(3)
Poultry, liver	0.2 (N)		
Poultry, mbyp (exc. liver)	0.1 (N)		
Poultry, meat	0.1 (N)		
Prunes	15.0	Revoke	The tolerance for residues in/on plums covers residues in prunes as residues do not concentrate in prunes processed from treated plums.
Pumpkins	1.0	Delete	Individual tolerances for cucumbers, melons, pumpkins, and squash should be deleted and a crop group tolerance should be established for *cucurbit vegetables* (Crop Group 9).
Sheep, fat	0.1 (N)	0.15	The available ruminant feeding study indicates that tolerances of 0.15 ppm are appropriate for meat and fat and that a single tolerance of 0.15 ppm should be established for residues in *sheep, mbyp.*
Sheep, kidney	0.2	Revoke	
Sheep, liver	2.5	Revoke	
Sheep, mbyp	0.1 (N)	0.15	
Sheep, meat	0.1 (N)	0.15	
Soybeans	0.2	0.2	*Soybean, seed*
Squash	1.0	Delete	Individual tolerances for cucumbers, melons, pumpkins, and squash should be deleted and a crop group tolerance should be established for *cucurbit vegetables* (Crop Group 9).
Strawberries	5.0	7.0	Residue data indicate that the tolerance should be increased. *Strawberry*
Sugarcane (seed piece treat Pre-H)	0.1 (N)	Revoke	Sugarcane registration was canceled by the registrant.
Wheat, grain	0.05	0.1	The tolerance should be increased as the LOQ for the combined residue is 0.1 ppm. *Wheat, grain*
Wheat, hay	0.1	TBD	Additional data are required, available data indicates that tolerance will need to be increased.
Wheat, straw	0.1		

Table 1. Tolerance Reassessment Summary for Thiophanate-methyl			
Commodity	Current Tolerance (ppm)	Tolerance [a] Reassessment (ppm)	Comment/*Correct Commodity Definition*
Tolerances to be established under 40 CFR §180.371(a)			
Vegetable, cucurbit, group	–	1.0	Individual tolerances for cucumbers, melons, pumpkins, and squash should be deleted and a crop group tolerance for cucurbit vegetables (Crop Group 9: cucumber, gherkin, watermelon, pumpkin, melons, and squash) should be established at 1.0 ppm.
Grapes	–	5.0	The available residue data would support a 5.0 ppm tolerance. *Grape.*
Pears	–	3.0	The available residue data would support a 3.0 ppm tolerance. *Pear*
Pistachio	–	0.1	Residue data on almonds will be translated to support a 0.1 ppm tolerance in/on *pistachio.*
Soybean, hulls	-	1.5	Based upon HAFT residues of 0.2 ppm in/on soybeans and the observed 6.5x concentration factor for hulls. A separate tolerance is required for soybean, hulls.
Soybean, aspirated grain factions	-	TBD	Residue data are required.
Tolerances to be established under 40 CFR §180.371(b)			
Blueberry	–	1.5	The available data are adequate to support a temporary Section 18 Emergency Exemption tolerance in MI of 1.5 ppm with a 7-day PHI.
Citrus Fruits	–	0.5	The available data are adequate to support a temporary Section 18 Emergency Exemption tolerance in FL of 0.5 ppm.
Tolerances to be established under 40 CFR §180.371(c)			
Canola, seeds	–	0.2	The available data are adequate to support a tolerance on *canola seed* with a regional registration in MN, MT (East of Interstate 15), and ND.

[a] Reassessed tolerances are tentative pending submission of supporting storage stability data.

[b] TBD = To be determined. Tolerance cannot be determined at this time because additional data are required.

13544

043967

Chemical:	**Thiophanate-methyl**
PC Code:	**102001**
HED File Code	**14000 Risk Reviews**
Memo Date:	**04/25/2002**
File ID:	**DPD275774**
Accession Number:	**412-02-0282**

HED Records Reference Center
06/05/2002