7

I

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

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF PREVENTION, PESTICIDE AND TOXIC SUBSTANCES

MEMORANDUM

Date: 6/24/2009

SUBJECT: Thiophanate-methyl. Human Health Risk Assessment for the Proposed Uses on the Caneberry Subgroup, the Bushberry Subgroup, Citrus, Ginseng, Leafy *Brassica* Greens, Turnip Greens, Mushroom, Mustard, Pistachio, Sunflower, Tomato, Tomatillo, Tree Nuts, Tuberous and Corm Vegetables (PP#6E7075), Cotton (PP#6F7069), and Sweet Corn (PP#2E6478)

PC Code: 102001
Decision Nos. 367500, 367671, 367673

Petition Nos.: 2E6478, 6E7075, 6F7069
Risk Assess Type: Single Chemical Aggregate
TXR No.: None
MRID No.: None

DP Barcodes: D330476, D330976, D360951
Registration Nos.: 73545-11, 73545-13, 73545-16, 73545-18, 264-990
Regulatory Action: Section 3
Case No.: None
CAS No.: 23564-05-8
40 CFR: 180.371

FROM: Douglas Dotson, Ph.D., Chemist
Linnea Hansen, Ph.D., Toxicologist
Jerry Stokes, Chemist
Anant Parmar, Biologist
Margarita Collantes, Biologist
Risk Assessment Branch II, Health Effects Division (7509P)

THROUGH: Alan Levy, Ph.D., Toxicologist
Dennis McNeilly, Chemist
Suku Oonnithan, Ph.D., Biologist
Richard Loranger, Ph.D., Senior Scientist
Christina Swartz, Branch Chief
Risk Assessment Branch II, Health Effects Division (7509P)

TO: Susan Stanton/Barbara Madden, RM Team 5, RIMUERB
Lisa Jones/Shaja Joyner, PM Team 20, Herbicide Branch
Registration Division (7505P)

Table of Contents

EXECUTIVE SUMMARY

A human health risk assessment has been conducted to support the proposed new uses of thiophanate-methyl (dimethyl [(1,2-phenylene)bis(iminocarbonothioyl)]bis(carbamate)), on bushberries (Crop Subgroup 13-07B), juneberries, lingonberries, salal, caneberries (Crop Subgroup 13-07A), citrus, cotton, ginseng, leafy *Brassica* greens (Crop Subgroup 4-A), turnip greens, mushrooms, mustard, pistachios, sunflowers, sweet corn, tomatoes, tomatillos, tree nuts (Crop Group 14), and tuberous and corm vegetables (Crop Subgroup 1-C). Thiophanate-methyl is a systemic Group 1 fungicide currently registered for use on a variety of fruit, vegetable, nut, and field crops.

Five separate formulations are proposed for use on the various crops. Cerexagri, Inc. submitted labels for four of these formulations: Topsin M WP (a 70% wettable powder, EPA Registration Number 73545-11), Topsin 4.5FL (a 4.5 lb/gallon suspension concentrate (SC), EPA Reg. No. 73545-13), Topsin M WSB (a water soluble bag containing the 70% wettable powder product, EPA Reg. No. 73545-16), and Topsin M 70WDG (a 70% water dispersible granule, EPA Reg. No. 73545-18). A Bayer CropScience label was submitted for the fifth product: Tops 30 Flowable Fungicide (EPA Reg. No 264-990). This latter product is a seed treatment formulation proposed for use on sunflower seed and sweet corn seed.

The most recent Section 3 risk assessment performed for thiophanate-methyl was the HED chapter of the reregistration eligibility decision (RED) document completed in April, 2002 (D275774, D. Smegal, 4/25/2002). In 2007, HED evaluated new uses that were proposed for the chemical and reviewed the toxicology database (D340134, 9/12/2007).

Carbendazim (MBC, methyl 1H-benzimidazol-2-ylcarbamate) is a major metabolite and environmental degradate of thiophanate-methyl. Risk from exposure to MBC is not being addressed in this risk assessment, however. HED is preparing a separate risk assessment for this chemical. The only registered use for MBC is in paint. The only new sources of exposure to MBC are the new food uses for thiophanate-methyl, which result in food and drinking water exposure to MBC.

Toxicology

The toxicology database for thiophanate-methyl is not complete, but is considered to be adequate for evaluating the proposed new uses. A 90-day inhalation toxicity study and a developmental thyroid study in the rat are required. As a result of revisions in 40 CFR Part 158 data requirements, an immunotoxicity study in the rat must also be submitted for review.

Thiophanate-methyl has low acute toxicity via the dermal and inhalation routes of exposure (Category IV) and minimal acute toxicity via the oral route of exposure (Category III). It is not an eye or skin irritant, but it is a dermal sensitizer.

Liver and thyroid effects were observed after subchronic and chronic dosing in the rat, dog, and mouse. Hepatocellular hypertrophy and increased liver weight were seen in all species evaluated

(dog, rat, mouse) along with effects on clinical chemistry parameters. Evaluation of circulating thyroid hormones and liver enzymes in subchronic and chronic studies and additional mechanistic studies showed evidence of disruption of thyroid homeostasis, but data were not considered to be sufficient to support a rat-specific antithyroid mode of action. Effects on circulating thyroid hormones and thyroid histopathology (follicular cell hypertrophy, hyperplasia) were observed in the rat and dog chronic studies at comparable dose levels and are, therefore, considered to be relevant to human risk assessment. Other effects included decreased body weight/weight gain, mild red blood cell effects at higher exposures and, in rats, renal and testicular toxicity. Decreased food consumption was observed following a three-week dermal exposure in the rabbit.

Rat and rabbit developmental studies and a rat two-generation reproductive toxicity study showed no evidence of increased susceptibility. No developmental effects were observed in the rat. In the rabbit, supernumerary ribs were observed at a dose above the maternally toxic dose. No reproductive toxicity was observed in the rat 2-generation study. The reproductive study included additional evaluations pertinent to thyroid function. In F1 animals, there were no treatment-related effects on circulating thyroid hormones (postnatal Week 8) or on selected developmental milestones that could be affected by changes in thyroid hormone levels. Histopathological changes in F1 thyroid and liver were observed at the high dose, but were also seen at lower doses in P0 animals.

Thiophanate-methyl did not show evidence of neurotoxicity. A transient decrease in landing foot splay at all doses in the rat acute neurotoxicity study was considered to be treatment-related. However, it was an isolated effect, did not show a clear dose-response, and was not observed in the subchronic neurotoxicity study. Transient tremors in the dog chronic study were only observed postdosing in the first weeks at a dose that caused significant toxicity, and were not observed in the subchronic dog study at higher doses. A developmental neurotoxicity study is not required.

Thiophanate-methyl is classified as "likely to be carcinogenic to humans," based on evidence of carcinogenicity in the rat (thyroid follicular cell tumors) and the mouse (liver tumors). Genotoxicity studies showed evidence of aneugenicity. A cancer potency factor (Q_1*) of 1.16 x 10^{-2} $(mg/kg/day)^{-1}$ was calculated based on the incidence of liver tumors in male mice.

HED has recommended reduction of the FQPA Safety Factor to 3x for assessment of risks associated with repeated exposures (dietary, residential, and occupational). There is concern for thyroid toxicity based on thyroid effects in adult animals and, therefore, residual concerns for potential effects during early development. A developmental thyroid study is required to characterize potential thyroid effects that might occur during late gestational and early postnatal development, based on thyroid effects in adult animals and the critical role the thyroid plays in early development. However, despite residual uncertainties, concerns for increased susceptibility are reduced because the available data, which include a limited evaluation of thyroid in parental and offspring animals and thyroid-sensitive developmental milestones in offspring, do not indicate increased susceptibility. In addition, the endpoints selected for risk assessment are protective of thyroid effects observed in the submitted studies. Although thyroid

toxicity is of concern for development, it is not an endpoint of concern for acute exposure (i.e., from a single dose), as repeated exposures would be required to cause a significant disruption of thyroid hormone. Therefore, HED recommends reduction of the FQPA Safety Factor to 1x for acute dietary exposures.

An acute dietary endpoint was selected from the rabbit developmental toxicity study for females age 13 to 49 (developmental NOAEL of 20 mg/kg/day, based on supernumerary ribs, decreased fetal weight at the LOAEL of 40 mg/kg/day), but no endpoint was identified for the general population, including infants and children. The chronic dietary endpoint for all populations was selected from the dog chronic oral toxicity study. The NOAEL of 8 mg/kg/day was based on decreased body weight observed at the LOAEL of 40 mg/kg/day. Incidental oral doses (short- and intermediate-term exposure) were based on the maternal NOAEL of 10 mg/kg/day from the rabbit developmental toxicity study, with the endpoint of decreased maternal body weight and food consumption observed at the LOAEL of 20 mg/kg/day. A short- and intermediate term dermal dose of 100 mg/kg/day was selected from the rabbit 21-day dermal toxicity study, based on an endpoint of decreased food consumption and body weight gain observed at the LOAEL of 300 mg/kg/day. A short- and intermediate term inhalation dose of 10 mg/kg/day was selected from the rabbit developmental study in which maternal toxicity was observed at the LOAEL of 20 mg/kg/day. A default inhalation absorption value of 100% was assumed, as an oral study was selected for inhalation risk assessment.

Metabolic Profile

Adequate studies are available depicting the metabolism of thiophanate-methyl in rats, primary crops (apples, lima beans, sugar beets, wheat), rotational crops (carrots, lettuce, wheat), and livestock (lactating goats, laying hens). Metabolism in primary and rotational crops is comparable. Parent thiophanate-methyl and the metabolites MBC, and 2-AB are the primary compounds found in crops. Parent and MBC are the primary compounds in drinking water. In animals, the residues of concern are parent thiophanate-methyl and MBC as well as the hydroxylated derivatives of MBC (4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S). In the rat, thiophanate-methyl is rapidly absorbed, metabolized and excreted at all dose levels (>90% by 24 hrs post-dosing). The primary route of excretion was via the urine for single doses, but via the feces following repeated doses. Sixteen urinary metabolites (12 identified) were isolated, including MBC (≤3.7% of recovered radioactivity) and other sulfate-conjugated and/or hydroxylated derivatives. The major urinary metabolite was 5-hydroxy(2-methoxycarbonylamino)benzimid-azolyl sulfate (14-42%). Parent compound was the major excreted compound in feces following repeated oral or single high dose. Nine fecal metabolites (7 identified) were also isolated including MBC (≤3.7% of recovered radioactivity). The major fecal metabolite was dimethyl[(1,2-(4-hydroxyphenylene)] bis(iminocarbonothioyl)bis-(carbamate)(3.5 to 11%). Parent compound and MBC were found in plants, drinking water, ruminants, poultry, and rats. The residues of concern have been accounted for in the rat toxicity studies. Sufficient metabolism data have been submitted for the purposes of the current tolerance petitions.

HED has determined that the residues of concern in plant commodities for risk assessment are parent thiophanate-methyl, MBC, and 2-AB. The residues of concern in animal commodities for risk assessment are parent thiophanate-methyl, MBC, and the hydroxylated derivatives of MBC (4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S). Parent compound and MBC are the residues of concern for risk assessment in drinking water. For tolerance expression, the residues of concern in plant and animal commodities are parent thiophanate-methyl and MBC.

Residue Chemistry and Dietary Risk Estimates

HED evaluated the residue chemistry database for thiophanate-methyl. In general, the residue chemistry data are sufficient to evaluate the nature and magnitude of residues in the proposed commodities. An analytical method is available for enforcement of the proposed tolerances. Thiophanate-methyl and MBC are completely recovered using multiresidue methods Section 404 (method for benzimidazoles). HED has identified numerous residue chemistry data deficiencies in the submitted tolerance petitions. These data deficiencies concern directions for use, proposed tolerances, crop field trials, and processing studies.

To evaluate acute, chronic, and cancer dietary risks, HED used information in the residue chemistry database along with modeled estimates of thiophanate-methyl in drinking water to conduct dietary (food + water) exposure assessments. The dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID, Version 2.03), which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The acute, chronic, and cancer dietary exposure analyses were all based on estimates of actual percent crop treated. The acute analysis was based on crop field trial data residues and Pesticide Data Program (PDP) monitoring data for a few commodities with existing tolerances. Default and empirical processing factors were used in the assessment. Maximum percent crop treated estimates were used for commodities for which data were available. If no percent crop treated data were available, 100% crop treated was assumed. The acute analysis incorporated the 1 in 10 year peak surface drinking water estimate resulting from application of thiophanate-methyl to citrus. The resulting 99.9th percentile acute exposure estimate for females 13-49 years old is not of concern to HED (8.6% aPAD).

The chronic analysis assumed average field trial residues and average PDP residues for a few commodities. Default and empirical processing factors were used. The chronic analysis assumed average percent crop treated estimates or average projected percent crop treated estimates, when available, and incorporated modeled 1-in-10 year average surface drinking water estimates resulting from application of thiophanate-methyl to turf. The resulting chronic exposure estimates are not of concern to HED (3.6% cPAD for Children 1-2 years old, the most highly exposed population).

A refined cancer dietary analysis was conducted. The analysis used the same food residue inputs, processing factors, percent crop treated data, and projected percent crop treated data as did the chronic non-cancer assessment. The cancer analysis incorporated modeled 1-in-30 year average surface water drinking water estimates resulting from application of thiophanate-methyl to citrus. The cancer risk estimate using these food residue inputs and a worst case use pattern

assumption for water is 4.7×10^{-6}. Typically, HED is concerned when cancer risk estimates water exceeds 3×10^{-6}. As a result, cancer risk to the general U.S. population is above HED's level of concern when all registered and proposed commodities (including citrus) are included in the dietary exposure analysis. A revised cancer dietary analysis was conducted without citrus and incorporating modeled drinking water values from application of thiophanate-methyl to turf. The resulting cancer risk estimate is 3×10^{-6}. As a result, cancer risk to the general U.S. population is not of concern with the removal of the proposed citrus use. The cancer dietary exposure analysis, after the removal of citrus, is considered to be conservative. The following commodities constituted 97% of the total dietary cancer risk: drinking water, blackberries, raspberries, tomatoes, nectarines, peaches, strawberries, and blueberries. The estimated drinking water concentration (EDWC) was generated by the PRZM-EXAMS Model which utilizes conservative inputs. The drinking water exposure numbers are high-end, largely because they are based upon assumptions of heavy usage in the drainage basin associated with the drinking water intake and applications at the maximum possible labeled rates and minimum labeled intervals between applications. Field trial values were used for the food commodities listed above. Field trials are performed using maximum label rates and minimum PHIs, and provide upper-bound estimates of potential residues in foods as consumed.

All aggregate risk assessments performed for thiophanate-methyl are based on dietary exposure estimates that exclude citrus.

Tolerance Harmonization

Maximum residue limits (MRLs) for residues of thiophanate-methyl have been established by Codex Alimentarius, under carbendazim (MBC). Codex MRLs are expressed in terms of the sum of benomyl, carbendazim, and thiophanate-methyl, expressed as carbendazim, and are, therefore, not compatible with U.S. tolerances. A total of 15 MRLs have been established for carbendazim, including one for berries at 1 ppm, one for tomato at 0.5 ppm, and one for tree nuts at 0.1 ppm. Canadian MRLs have also been established for "benomyl, carbendazim, and thiophanate-methyl," expressed as carbendazim, in citrus fruits (10 ppm); blackberries, boysenberries, and raspberries (6 ppm); mushrooms (5 ppm); and tomatoes (2.5 ppm). No Mexican MRLs have been established for thiophanate-methyl; however, MRLs have been established for carbendazim and benomyl in tomato (5 ppm), almond (1 ppm), and lemon (10 ppm). All benomyl uses have been cancelled in the U.S. As the U.S. tolerance definition for thiophanate-methyl differs from the Codex, Canadian, and Mexican MRL definitions, harmonization of tolerance levels is not possible at this time.

Residential Exposure

There are no new residential uses associated with the proposed uses of thiophanate-methyl. However, HED has updated the previously-completed residential exposure assessment conducted in conjunction with the RED, in order to calculate aggregate exposure and risk. The purpose of this assessment is to revise the previous 2002 thiophanate-methyl residential turf exposure assessment performed in support of the 5/2/2002 RED for thiophanate-methyl.

The registered residential thiophanate-methyl products are formulated as liquids and granules for use on turf and golf courses. Based on application rate and label information, exposure is expected to occur for short- and intermediate-term durations.

All residential handler scenarios were previously assessed in the 2002 thiophanate-methyl RED. Residential uses which result in MOEs less than 300 are considered to be of concern. All handler scenarios resulted in MOEs greater than 300 and, thereby, are not of concern. HED considers residential cancer risk estimates greater than 3×10^{-6} to be of concern, and attempts to mitigate such exposures where feasible. Cancer risk estimates were less than 1×10^{-6} for all residential handler scenarios.

Postapplication dermal and oral exposures and risks to adults and children were determined using current approaches and policies. All non-cancer postapplication adult and children residential lawn and golf dermal scenarios resulted in MOEs greater than the level of concern (MOEs $\geq$ 300) for short- and intermediate-term exposure. All short- and intermediate-term hand-to-mouth (HTM), object-to-mouth (OTM) and soil ingestion scenarios resulted in MOEs greater than 300 and are not of concern.

To perform a cancer assessment, HED used a recently developed draft approach for refining cancer risk resulting from exposure to turf and the chemical-specific thiophanate-methyl turf transferable residue study to determine the average amount of residues available over 14 days after application to turf. Based on this approach and these assumptions, HED's calculations indicated that residential postapplication cancer risk resulting from exposure to turf is not of concern.

In evaluating non-cancer (i.e., short-term) combined residential exposure uses, HED combined all non-dietary sources of exposure. For adults, HED combined adult handler and dermal postapplication exposure, and for children, HED combined postapplication dermal and oral (hand-to-mouth) exposures. The residential combined scenarios for adults and children resulted in MOEs greater than 300 and are not of concern.

To determine cancer risk for residential exposure, HED combined all non-dietary sources of exposure. These sources consisted of adult handler and dermal postapplication exposure. Given that only granular products are available for homeowners' application to turf, all combined cancer risks are less than 3×10^{-7}.

Aggregate Exposure

There are residential uses for thiophanate-methyl on lawns, and post-application exposure can result from its use on golf courses. The exposures resulting from residential uses must be aggregated with the dietary (food and drinking water) exposures. The aggregate risk assessments that were performed were for short- and intermediate-term risk scenarios for adults and children. In addition, a cancer aggregate risk assessment was performed for the general U.S. population. For the short- and intermediate-term risk scenarios, the levels of concern (target MOEs) for the different routes of exposure are the same. As a result, the 1/MOE approach was used for

calculating the aggregate MOE. Short-term aggregate MOEs were calculated for the adult population subgroup with the highest exposure estimate (Adults 50+) and the children's population subgroup with the highest exposure estimate (Children 1-2). For adults, the aggregate risk MOE was calculated for two different scenarios: (1) lawn (handler + postapplication) + dietary (food and drinking water), and (2) golf (postapplication) + dietary (food and drinking water). For children, the aggregate MOE was calculated for one scenario only: lawn (postapplication dermal + hand-to-mouth transfer) + dietary (food and drinking water). Chronic dietary exposure values were used for the aggregate calculations in accordance with HED's typical approach for aggregate risk assessment.

Aggregate cancer risk is comprised of the risk from dietary sources (food and drinking water) and the risk from residential postapplication uses on lawns and golf courses. The combined cancer residential exposure from handler and postapplication activities was aggregated with dietary (food and water) exposure. Several scenarios were assessed because there are various application methods. The cancer risks for these scenarios were aggregated with the dietary (food and drinking water) cancer risk to arrive at the total cancer risk for dietary and residential exposures. For the aggregate dietary plus postapplication golf course cancer risk, the highest lifetime average daily dose (LADD) from the various golfing exposure scenarios was used for aggregate calculations. The aggregate cancer risk estimates are not of concern. EPA generally considers cancer risks in the range of 10^{-6} or less to be negligible. The aggregate cancer risk estimates are in the range of 10^{-6} for all scenarios. The calculated risk estimates overestimate actual cancer risk, however. Dietary sources contribute 92% of the cancer risk. Residential uses contribute the other 8%. As discussed in the dietary section, the food and drinking water residue inputs are all based on conservative assumptions of maximum label application rates and minimum retreatment and/or preharvest intervals.

Occupational Exposure

An occupational exposure and risk assessment for the proposed uses of thiophanate-methyl has been prepared (Memo, D335120, S. Wang, 2/26/2009). However, the occupational assessment is not being included in this risk assessment. As occupational exposures are not aggregated with dietary and/or residential exposures, the results of the occupational exposure assessment will not affect the conclusions made in this risk assessment. The occupational exposure memorandum will address risk to workers and conclusions concerning occupational risk mitigation.

Environmental Justice Considerations

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that

subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intakes by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups, and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, nondietary exposures based on home-use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, which comprise the Pesticide Handlers Exposure Database (PHED), have been determined to require a review of their ethical conduct, and have received that review. The studies in PHED were considered appropriate (or ethically conducted) for use in risk assessments.

Conclusions

HED concludes that the registrant has submitted adequate data for the Agency to make the safety finding with respect to the use of thiophanate-methyl on the registered and proposed uses. With the exception of the deficiencies listed in Section 9, Data Needs and Label Recommendations, the toxicology, residue chemistry, and occupational databases are adequate for the purposes of the current tolerance petitions. With the exception of the proposed use on citrus (Crop Group 10), HED was able to make the safety finding for the existing and proposed agricultural and the existing residential uses associated with thiophanate-methyl. The registrant needs to submit revised Sections B and F. The conditions of registration recommended to be placed on the various labels are discussed in Section 9. Provided that HED can make the safety finding for MBC, HED recommends in favor of the establishment of the tolerances listed in the tolerance summary table (Table B.1) of Appendix B.

Leafy *Brassica* Greens & Turnip Greens [Broccoli raab, Chinese cabbage (bok choy), collards, kale, mizuna, mustard greens, mustard spinach, rape greens, turnip greens]							
70% WP [73545-11]	Seed treatment	0.13 lb ai/100 lb of seed	NA	NA	NA	NA	Application is to be made as a water-based slurry. Use of treated seed for food, feed, or oil purposes is prohibited.
70% WP [73545-11] 4.5 lb/gal SC [73545-13] 70% WSB [73545-16] 70% WDG [73545-18]	Postemergence	0.35	3	7	1.05	7	Apply at 7-day intervals as a foliar spray. Do not apply more than 1.5 lbs of product (1.05 lbs ai)/A/season. Preharvest interval: 7 days Tank mixing with a contact fungicide for additional disease control and resistance management is recommended. Rotation with fungicides of different chemistry is recommended after no more than 2 consecutive applications of Topsin M 70 WP.
Mushroom: Agaricus spp. (button mushrooms)							
70% WP [73545-11]	Spawn treatment	1.4 lb ai/1,600 lb of spawn	NS	NS	NS	NS	Product is to be mixed with gypsum, limestone, or chalk then used to coat spawn grain before mixing into growing substrate. Treated spawn to be applied to be surface at 1,600 lb of spawn per 8,000 ft^2 of surface.
70% WP [73545-11]	Nutrient supplement mix	4.9 lb ai/ 8,000 ft^2 of bed	NS	NS	NS	NS	Product is to be mixed with nutrient supplement and applied to mushroom bed (compost) at spawning.
70% WP [73545-11]	Bed drench	0.7 lb ai/ 8,000 ft^2	2	NS	NS	7	Product is to be mixed into 150 gal of water and applied to bed surface, with the first application made just after casing or CACing and the second application made after pins have formed. Application is not to be made after harvest has started.

Mushroom: Shiitake spp.							
70% WP [73545-11]	Growing media mix	1.4 lb ai/2,000 lb of growing media	NS	NS	NS	NS	Product is to be mixed with growing media prior to bagging and pasteurization of growing media.
70% WP [73545-11]	Log spray	0.7 lb ai/ 100 gal water; 1 fl. oz solution per log	4	5	NS	20	Product is to be applied to shiitake logs during browning phase, with first application made within 5 days of bag removal.
Mushroom: Pleurotus spp. (Oyster mushroom)							
70% WP [73545-11]	Growing media mix	0.5 lb ai/2,000 lb of growing media	NS	NS	NS	NS	Product is to be mixed with growing media prior to bagging and pasteurization of growing media. Application at any other time is prohibited.
Mustard (grown for seed) [Use limited to ND, MN, and MT east of Interstate 15]							
70% WP [73545-11] 4.5 lb/gal SC [73545-13] 70% WSB [73545-16] 70% WDG [73545-18]	Postemergence at 20-50% flowering	0.7-1.4	2	NS	1.4	NS	A single application, at up to 1.4 lb ai/A, is to be made at 20-50% flowering; or two applications, at 0.7 lb ai/A/application, are to be made at 20-30% flowering and then at 40-50% flowering.
Pistachio							
70% WP [73545-11] 4.5 lb/gal SC [73545-13] 70% WSB [73545-16] 70% WDG [73545-18]	Postemergence	1.4	4 (implied)	10	5.6	14	Applications are to begin at bloom and are to be made in a minimum of 100 gal/A using ground equipment or 20 gal/A using aerial equipment.

Sunflower							
70% WP [73545-11] 4.5 lb/gal SC [73545-13] 70% WDG [73545-18]	Seed treatment	0.126 lb ai/100 lb of seed	1	NA	0.126 lb ai/100 lb of seed	NA	Application is to be made as a water-based slurry. Use of treated seed for food, feed, or oil purposes is prohibited.
TOPS 30 Flowable	Seed Treatment	0.126 lb ai/100 lb of seed	1	NA	0.126 lb ai/100 lb of seed	NA	Apply as a seed treatment using standard slurry or mist-type seed treatment equipment. Use of treated seed for food, feed, or oil purposes is prohibited.
Sweet Corn							
2.8 lb/gal SC [73545-13]	Seed Treatment	0.126 lb ai/100 lb of seed	1	NA	0.126 lb ai/100 lb of seed	NA	Seed colorant, captan, thiram, and metalaxyl may be used as treatment additives. Sweet corn is to be harvested at commercial maturity.
Tomato and Tomatillo							
70% WP [73545-11] 4.5 lb/gal SC [73545-13] 70% WSB [73545-16] 70% WDG [73545-18]]	Soil drench application at transplant	0.35	1	NA	2.8	NA	For use on field and greenhouse tomatoes.
70% WP [73545-11] 4.5 lb/gal SC [73545-13] 70% WSB [73545-16] 70% WDG [73545-18]	Postemergence	0.70	4	NS	2.8	0	

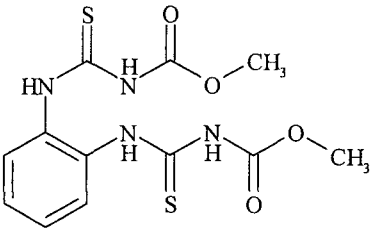
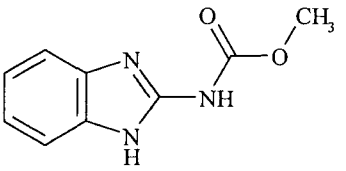
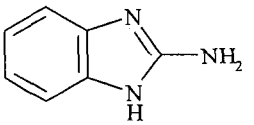
Tree Nuts Crop Group [almonds, beech nut, Brazil nut, butternut, cashew, chestnut, chinquapin, filbert, hickory nut, pecan, walnut (black & English)]							
70% WP [73545-11] 4.5 lb/gal SC [73545-13] 70% WSB [73545-16] 70% WDG [73545-18]	Postemergence	0.70	3 (implied)	NS	2.1	NS	Application after hull/shuck split is prohibited for all nuts. For almonds, applications are to begin at pink bud and continue as needed; the product may be used with a horticultural oil at pink bud. For pecans, applications are to begin when first leaves are showing and repeated at 3- to 4-week intervals until shuck split. For all other nuts, applications are to be made as needed.
Tuberous and Corm Vegetables Subgroup 1C [arracacha, arrowroot, Chinese artichoke, Jerusalem artichoke, edible canna, cassava, bitter and sweet cassava, chayote root, chufa, dasheen (taro), leren ginger, potato, sweet potato, tanier, tumeric, yam bean, true yam]							
70% WP [73545-11] 4.5 lb/gal SC [73545-13] 70% WSB [73545-16] 70% WDG [73545-18]	Dip treatment for seed pieces or transplants	1.4 lb ai/100 gal	1	NA	1.4 lb ai/100 gal	NA	Seed pieces or transplants are to be dipped or immersed in treatment solution for at least 5 minutes [solution tank is to be agitated during treatment]. Treatment is to be made once, at the time of planting; seed pieces are to be dried prior to planting. Transplants may be planted immediately after draining.

RTI = Retreatment interval.

Table 2.1.b Registered Residential Use Pattern for Thiophanate-methyl

Formulation and Product	Method of Application	Use Sites	Application Rate	Timing of Application
Granular and liquid	Hose-end sprayer, low pressure handwand, backpack and push-type granular spreader	Turf	2.72 lb a.i./acre	According to 2002 assessment, an estimation of 5 applications per season
		golf courses	5.4 lbs a.i./acre for fairways and 8.9 lb ai/acre for tees, greens and aprons	

2.2 Structure and Nomenclature

Table 2.2. Thiophanate-Methyl Nomenclature.	
Compound	
Common name	Thiophanate-methyl
IUPAC name	dimethyl 4,4'-(o-phenylene)bis(3-thioallophanate)
CAS name	dimethyl [(1,2-phenylene)bis(iminocarbonothioyl)]bis(carbamate)
CAS registry number	23564-05-8
End-use products	70% WP formulation (Topsin® M 70WP; EPA Reg. No. 73545-11); 4.5 lb/gal SC formulation (Topsin® 4.5FL; EPA Reg. No. 73545-13); 70% WP formulation (Topsin® M WSB; EPA Reg. No. 73545-16); 70% WDG formulation (Topsin® M 70 WDG; EPA Reg. No. 73545-18); 30% SC formulation (Tops® 30 Flowable Fungicide; EPA Reg. No. 264-990)
Regulated Metabolite	
Common name	MBC, carbendazim
CAS name	methyl 1H-benzimidazol-2-ylcarbamate
CAS registry number	10605-21-7
Metabolite to be included in risk assessment for plant commodities	
Common name	2-AB
Chemical name	2-aminobenzimidazole
CAS registry number	934-32-7

2.3 Physical and Chemical Properties

Table 2.3. Physicochemical Properties of Thiophanate-Methyl.		
Parameter	Value	Reference
Melting point/range	162.6°C, with decomposition	MRID 41608907: DP# 235376, 6/17/97, L. Cheng
pH	6.5 at 25°C (~21.8 ppm saturated aqueous suspension)	MRID 41608908; DP# 235376, 6/17/97, L. Cheng
Density	1.5319 at 20°C (specific gravity) 1.5292 g/L at 20°C (density) 0.439 g/cm^3 (bulk density)	MRID 40053204; DP# 235376, 6/17/97, L. Cheng
Water solubility (25°C)	21.8 ppm	MRID 41482801; DP# 235376, 6/17/97, L. Cheng
Solvent solubility (25°C)	29 g/L acetone 7.8 g/L methanol 8.4 g/L ethyl acetate 0.73 g/L dichloromethane 0.18 g/L n-octanol 0.11 g/L xylene 4.7 x 10^{-4} g/L n-hexane	MRID 41482801; DP# 235376, 6/17/97, L. Cheng
Vapor pressure	1.3 x 10^{-5} mm Hg	MRID 41482802; DP# 235376, 6/17/97, L. Cheng
Dissociation constant	pK_a = 7.28 at 25°C	MRID 41482803; DP# 235376, 6/17/97, L. Cheng
Octanol/water partition coefficient	P_{OW} = 25.1 at 25°C	MRID 40053207; DP# 235376, 6/17/97, L. Cheng
UV/visible absorption spectrum	λmax Acidic Solution: 236 nm Neutral Solution: 238 nm Basic Solution: 238 nm	MRID 46638704

3.0 HAZARD CHARACTERIZATION/ASSESSMENT

3.1 Hazard and Dose-Response Characterization

The hazard characterization for thiophanate-methyl has been revised since the 2007 assessment (TXR# 0054610, D340134, Updated Hazard Characterization for Proposed New Uses, Petition Nos. 2E6478, 6F7069, 6E7075, 9/12/2007). Changes have been made in the assessment of neurotoxic potential, acute dietary endpoint selection, FQPA factor recommendations, and toxicology data requirements in response to the registrant's rebuttal to the Agency's findings.

3.1.1. Database Summary

3.1.1.1 Studies available and considered (animal, human, general literature)

Acceptable studies on thiophanate-methyl include: acute lethality (oral, inhalation, and dermal), primary eye/skin irritation and dermal sensitization, 14-day inhalation toxicity in the rat,

subchronic and chronic oral toxicity in the rat and dog, developmental toxicity studies in the rat and rabbit, reproductive toxicity in the rat, carcinogenicity in the rat and mouse, dermal toxicity in the rabbit, genotoxicity, acute and subchronic neurotoxicity in the rat, general metabolism in the rat, and special (nonguideline) mechanistic studies on thyroid effects in the rat. Some genotoxicity and developmental toxicity studies from the open literature were also considered.

3.1.1.2 Mode of action, metabolism, toxicokinetic data

Thiophanate-methyl, a carbamate, is a systemic fungicide of the benzimidazole chemical class. Its pesticidal action derives from inhibition of fungal β-tubulin polymerization. Other members of this group include benomyl and thiophanate-ethyl, which are not currently registered in the United States. Thiophanate-methyl is also structurally related to MBC, which is registered in the United States. MBC is the active moiety for fungicidal activity. However, the toxicological profile of MBC is generally distinct (see Appendix B in TXR# 0054610, D340134, for a summary of MBC toxicity). MBC is also a metabolite and environmental degradate of thiophanate-methyl.

The mechanism of toxicity of thiophanate-methyl in mammals has not been fully characterized. Effects on the thyroid have been observed in the rat, mouse, and dog. Although the results of mechanistic studies on the mode of action for thyroid effects were determined to be consistent with disruption of thyroid-pituitary homeostasis via induction of hepatic UDPGT activity, the data were not considered adequate to demonstrate rat-specific antithyroid activity as the sole mode of action. Thyroid effects are therefore considered to be relevant to human risk assessment.

Thyroid tumors in the rat, and liver tumors in the mouse, were observed after long-term dietary exposure. Thiophanate-methyl shows some evidence of aneugenic potential in mammalian assays. At this time the data in support of an antithyroid mode of action for thyroid tumors are not considered adequate to support a solely non-genotoxic mechanism of liver or thyroid carcinogenesis.

Thiophanate-methyl is rapidly absorbed, metabolized, and excreted at both lower (14 mg/kg) and higher (170 mg/kg) dose levels, with >90% of the administered radioactivity being excreted within 24 hours of dosing. There was not significant accumulation of radioactivity in tissues, but the highest levels seen were in target organs, thyroid, liver, and kidney. Several metabolites were identified, including low levels of MBC (<4% of administered radioactivity). Excretion was primarily via the urine at the low dose, but fecal excretion increased with increasing dose or repeated low dosing. No significant differences were observed between males and females.

3.1.1.3 Sufficiency of studies/data

The toxicology database for thiophanate-methyl is considered to be incomplete at this time. A rat developmental thyroid study is required, based on evidence of thyroid disruption in adult animals of multiple species tested and residual concerns for exposure during development. A 90-day inhalation toxicity study in the rat is also required. In addition, as part of the new EPA

40CFR Part 158 data requirements, an immunotoxicity study in rats and/or mice is required (see Appendix A.1). Executive summaries for toxicology studies on thiophanate-methyl are provided in the previous assessment (Appendix A.3 of TXR# 0054610; D340134).

3.1.2 Toxicological Effects

Thiophanate-methyl has low to minimal acute toxicity via the oral (Toxicity Category III), dermal (Toxicity Category IV) and inhalation (Toxicity Category IV), routes of exposure. Although it is not an eye or skin irritant (Toxicity Category IV), it is a dermal sensitizer.

Liver and thyroid are two major target organs in several species following oral exposure to thiophanate-methyl. In the liver, hepatocellular hypertrophy and increased weight were observed in all species tested (dog, rat, mouse). Effects on clinical chemistry parameters related to liver function, such as cholesterol, serum albumin, and alkaline phosphatase, were also observed. Thyroid effects in rats, dogs, and mice included thyroid enlargement, hypertrophy, and follicular hyperplasia, with effects in the mouse being less pronounced than in the dog or rat. Studies in rats showed an increase in liver UDPGT activity along with effects on circulating thyroid hormones.

In addition to liver and thyroid effects, thiophanate-methyl also caused mild red blood cell effects at the higher dose levels in rats, dogs, and mice, following subchronic or chronic exposure. In rats, thiophanate-methyl caused toxicity to the kidney, as indicated by increased urinary protein (in males), lipofuscin pigmentation, and increased severity of nephropathy 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. Effects on the testes were seen in rat chronic studies (one study showed decreased spermatogenesis, the other, testicular hyperplasia). 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 mouse carcinogenicity study, increased heart weight (females) and incidence of atrial thrombosis were observed.

Thiophanate-methyl is a thiocarbamate, but only limited data are available in the rat on cholinesterase (ChE) inhibition. As a class of compounds, thiocarbamates do not produce consistent ChE inhibition patterns. In the rat subchronic toxicity study, serum ChE was increased in males but decreased in females. In the rat chronic toxicity/carcinogenicity study, males showed increases or decreases in serum ChE at different time points, while in females, ChE activity was slightly decreased at 6 and 12 months. Red blood cell (RBC) and brain ChE activities were not evaluated.

Dermal exposure of rabbits to thiophanate-methyl for three weeks (5 applications per week) caused decreased food consumption in females and, at a higher dose, in males. Because this decrease was seen in both sexes, and a dose-response was observed in females, it is considered to be treatment-related. Comparison to the oral rabbit developmental toxicity study provided an

estimated dermal absorption value of 7%, based on decreased food consumption in both studies. Dermal irritation was observed at the site of application in all dose groups.

A 14-day rat inhalation toxicity study on a formulation containing 5.2% thiophanate-methyl is the only inhalation information available. Local pulmonary effects were observed at the LOAEL, and decreased body weights were observed at the highest dose tested (HDT). 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 adequately characterize inhalation toxicity.

Thiophanate-methyl is classified as "likely to be carcinogenic to humans," based on rat thyroid follicular cell and mouse liver tumors. Genotoxicity studies show evidence of aneugenicity but not mutagenicity. In the rat, increased incidences of thyroid follicular cell adenomas in both sexes and carcinomas in males were observed. As noted above in Section 3.1.1.2, additional mechanistic studies on thyroid and liver effects showed changes consistent with an antithyroid mode of action for thyroid tumorigenesis. The findings were not considered to be conclusive; therefore, the thyroid tumors were included in the qualitative assessment of human cancer risk. In the mouse, an increased incidence of hepatocellular adenomas in both sexes was observed.

Thiophanate-methyl did not show evidence of neurotoxicity. Tremors in the first two weeks of the dog chronic study were observed at the high dose, but were not observed in the subchronic dog study at higher doses. In the rat acute neurotoxicity study, a transient decrease in landing foot splay followed dosing. This finding was not observed by one week post-dosing. Although decreased landing foot splay was reproducible and treatment-related, it was transient and not associated with other effects. These findings were not considered signs of neurotoxic potential.

There was no evidence of increased susceptibility (qualitative or quantitative) in the available developmental and reproduction studies. Developmental effects (decreased fetal weight, increased supernumerary ribs) were observed in the rabbit at maternally toxic doses. No developmental effects were reported in the rat at maternally toxic doses. Reproductive effects were not observed up to levels causing effects to parental animals (liver and thyroid) and offspring (decreased litter weights). Assessment of P0 parental and F1 offspring circulating thyroid hormones at postnatal week 8 and thyroid histopathology at termination in the rat reproductive toxicity study did not show evidence of increased offspring sensitivity. Several physical parameters (pinna unfolding, eye opening, incisor eruption) and neurodevelopmental functional tests (auditory, pupillary, gripping, and surface righting reflexes) also showed no treatment-related changes. Assessment of thyroid hormones and histopathology of offspring at earlier times were not evaluated.

In the 2002 HED risk assessment for the thiophanate-methyl RED, a cumulative assessment with MBC was performed. Risks were combined because MBC is a metabolite and an environmental degradate of thiophanate-methyl. Both compounds caused developmental effects and an increased incidence of liver tumors. The need to combine risks for these two pesticides was reevaluated in 2007. It was concluded that there are insufficient data demonstrating a common mode of action; therefore, a cumulative risk assessment was not performed in conjunction with

these newly proposed uses. Although MBC is a rat metabolite of thiophanate-methyl, it comprises a low percentage of total metabolites (1.1 to 3.7% of recovered radioactivity). The toxicity profiles of thiophanate-methyl and MBC show distinct effects: for example, thyroid toxicity is seen with thiophanate-methyl but not MBC; severe liver toxicity (necrosis, cirrhosis) is observed for MBC but only liver enlargement is observed for thiophanate-methyl; and developmental effects of the two compounds are distinct, with an increased incidence of malformations observed for MBC but not thiophanate-methyl.

3.1.3 Dose-response

The endpoints selected for the human health risk assessments of thiophanate-methyl are presented and discussed in greater detail in Section 3.5 of this document.

An acute dietary endpoint for females age 13 to 49 was selected from the rabbit developmental toxicity study. The developmental NOAEL of 20 mg/kg/day was based on an increased incidence of supernumerary ribs at the LOAEL of 40 mg/kg/day. The NOAEL is considered to be protective for potential developmental effects from a single exposure. An appropriate endpoint for acute dietary exposure to the general population including infants and children was not identified.
For incidental oral exposure (young children), as well as short-term occupational and non-occupational inhalation exposures, the maternal toxicity NOAEL of 10 mg/kg/day was selected as the most sensitive available point of departure (POD) relevant to humans (decreased body weight gain and food consumption).

The POD selected for occupational and non-occupational short- and intermediate-term dermal exposures was based on the NOAEL of 100 mg/kg/day from the twenty-one day dermal toxicity study in rabbits. This endpoint represents the most sensitive one relevant to humans (decreased food consumption and body weight gain) that is appropriate for these durations. The effects were observed by one week of exposure.

No long-term studies are available on dermal or inhalation exposure. The dog chronic oral study was used for all chronic exposure scenarios (dietary, occupational, and non-occupational dermal and inhalation routes of exposure). The NOAEL of 8 mg/kg/day represented the most sensitive long-term exposure POD and is based on decreased body weight and thyroid effects observed at the LOAEL of 20 mg/kg/day. It is comparable to the NOAEL of 8.8 mg/kg/day in the chronic rat study, based on similar effects.

Although a rat 14-day inhalation toxicity study was submitted, it was unacceptable and was not used for inhalation risk assessment. The rabbit maternal toxicity NOAEL of 10 mg/kg/day was selected as the POD for this short- and intermediate-term assessment, based on decreased body weight and food consumption at the LOAEL of 20 mg/kg/day in the first week of exposure. Inhalation absorption was assumed to be 100% (default).

The cancer classification of "likely to be carcinogenic to humans" is based on the findings of increased thyroid tumors in rats and liver tumors in mice. A cancer potency factor of 1.16×10^{-2}

$(mg/kg/day)^{-1}$ was assigned based on the combined increased incidence of liver adenoma and/or carcinoma and/or hepatoblastoma in the mouse.

3.1.4 FQPA

A detailed discussion of FQPA considerations is presented below in Sections 3.3 and 3.4.

The HED Hazard Assessment Science Policy Committee (HASPOC) reviewed thiophanate-methyl to determine whether the 10x FQPA Safety Factor should be retained (Memo, L. Hansen to HED HASPOC, 1/20/2009) and what data should be required to address residual uncertainties. The FQPA considerations discussed below, and the hazard characterization in this risk assessment, reflect the recommendations from this meeting.

For acute dietary exposure of females age 13 to 49, HED recommends reduction of the FQPA Safety Factor to 1x. There is high confidence in the endpoint, which is based on rat developmental toxicity. There are no residual uncertainties, and no additional data are required.

For all repeated exposure scenarios, HED recommends reduction of the FQPA Safety Factor to 3x. A developmental thyroid study is required to characterize more fully any potential thyroid effects that might occur during late gestational and early postnatal development, based on thyroid effects in adult animals and the critical role the thyroid plays in early development. However, despite residual uncertainties, concerns for increased susceptibility are reduced because the available data, which include a limited evaluation of thyroid in parental and offspring animals and thyroid-sensitive developmental milestones in offspring, do not indicate increased susceptibility, and because the doses and endpoints selected for risk assessment are protective of these effects.

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

Data on ADME of thiophanate-methyl following oral administration are available in the rat. No studies on metabolism in humans are available at this time. In the rat, thiophanate-methyl is rapidly absorbed, metabolized, and excreted at all dose levels (>90% by 24 hrs postdosing). Radioactivity did not show significant tissue accumulation, but levels were highest in the thyroid, liver, and kidney. Plasma half-life ranged from 1.6 to 2.8 hrs for single doses and 4 to 7.8 hrs for repeated doses. The primary route of excretion was via the urine for single doses, but via the feces following repeated doses. Sixteen urinary metabolites (12 identified) were isolated, including MBC (≤3.7% of recovered radioactivity) and other sulfate-conjugated and/or hydroxylated derivatives. The major urinary metabolite was 5-hydroxy(2-methoxycarbonyl-amino)benzimidazolyl sulfate (14-42%). Nine fecal metabolites (7 identified) were also isolated, including MBC (≤3.7% of recovered radioactivity). The major fecal metabolite was dimethyl[(1,2-(4-hydroxy phenylene)]bis(iminocarbonothioyl)bis(carbamate)(3.5 to 11%). Parent compound was the major excreted compound in feces following repeated oral or single high dose. Metabolism in males and females was qualitatively similar.

Thiophanate-methyl is also absorbed via other routes. Although a dermal absorption study is not available, systemic toxicity was observed in a twenty-one day dermal toxicity study in the rabbit. A comparison of oral and dermal studies in rabbits allowed an estimation of about 7% of the applied dose. Systemic toxicity was also seen in a rat fourteen-day inhalation toxicity study.

3.3 FQPA Considerations

3.3.1 Adequacy of the Toxicity Database

The toxicity database for thiophanate-methyl is not considered to be complete at this time for purposes of an FQPA assessment. Based on thyroid effects in adult animals, a developmental thyroid study is required to address residual uncertainties for potential thyroid effects during late gestational and early postnatal development. Although the available data, which include a limited evaluation of thyroid function and thyroid-sensitive developmental effects in the rat reproductive toxicity study, do not indicate increased sensitivity of offspring to thyroid toxicity, this study is required to characterize more fully any potential effects on thyroid function that occur during the early stages of development. The data gaps for the immunotoxicity and 90-day inhalation studies in the rat do not impact the FQPA assessment (see Section 3.4, below).

3.3.2 Evidence of Neurotoxicity

Effects observed in the rat acute neurotoxicity study (decreased landing foot splay) and dog chronic studies (transient tremors) have been reevaluated for their relevance to human risk assessment. These findings were considered evidence of neurotoxicity in the previous hazard characterization. The HED HASPOC reviewed the data again (Memo, L. Hansen to HED HASPOC, 1/20/2009).

In the dog chronic oral toxicity study (MRID 42311801), capsule doses were administered at 0, 8, 40, or 200 mg/kg/day. Tremors were seen within two to four hours following administration of the encapsulated dose at 200 mg/kg. All dogs were sporadically affected during the first few weeks of the study, but not at later times. Tremors were not seen in the subchronic dog study at higher doses. The HASPOC concluded that the tremors should not be considered evidence of neurotoxicity because they were seen only at a dose that was associated with significant toxicity (a large decrease in body weight gain), were not reproducible in the subchronic dog study, and were not observed in other species.

In the acute oral neurotoxicity study in the rat (MRID 48729901), a statistically significant decrease in landing foot splay was observed in both sexes on the day of gavage dosing (time of peak effect) at all doses tested ($\geq$50 mg/kg), but was not observed at later times. No other significant findings were reported. In the subchronic rat neurotoxicity study (MRID 48729902), no effects on landing foot splay or other neurobehavioral parameters were observed up to 166 mg/kg/day. Decreased landing foot splay has been reported for several other compounds, including amitraz (Moser, *Fund. Appl. Toxicol.* 17:7-16, 1991; Moser *et al.*, *Toxicol. Appl. Pharmacol.* 108:267-283, 1991), tetramisole (Mohammad *et al.*, *Neurotoxicol.* 27(2):153-157, 2006) and harmiline (Tariq *et al.*, *Brain Res.* 945(2):212-218, 2002). However, decreased

landing foot splay is observed in association with other effects related to hyperreactivity and central nervous system (CNS) stimulation, none of which occurred with thiophanate-methyl. In the absence of other findings, the HASPOC considered decreased landing foot splay to be of uncertain biological significance and recommended against using it for acute dietary risk assessment. Although treatment-related, it was transient, not associated with other neurotoxic effects, and did not show a clear dose-response effect.

3.3.3 Developmental Toxicity Studies

No developmental toxicity was observed in the rat. In a dietary developmental toxicity study, thiophanate-methyl was administered to pregnant rats from GD 6 through 19 at concentrations equivalent to daily intakes of 0, 18, 85, or 163 mg/kg/day. Maternal toxicity in the form of significantly reduced food consumption with a transient decrease in body weight gain was observed at 163 mg/kg/day. In an earlier gavage study in the rat, animals were administered thiophanate-methyl by gavage on GD6 through 19 at 0, 100, 300, or 1000 mg/kg/day. No developmental or maternal toxicity was reported, but the study was considered to be unacceptable pending submission of additional information.

In rabbits, supernumerary ribs were observed in the fetuses of does administered thiophanate-methyl by gavage (GD 6 through 28) at 40 mg/kg/day. These effects were not observed at 10 or 20 mg/kg/day. Maternal toxicity (decreased body weight gain, food consumption) was observed at 20 mg/kg/day. In an earlier gavage study in the rabbit, determined to be unacceptable because of experimental problems, animals were administered doses equivalent to 0, 2, 6 or 20 mg/kg/day. Maternal toxicity (decreased body weight and food consumption, increased abortions) was observed at 20 mg/kg/day. An increased incidence of asymmetric pelvis was observed at 6 and 20 mg/kg/day, but was not considered to be treatment-related because it was not observed in the other study at doses up to 40 mg/kg/day.

3.3.4 Reproductive Toxicity Studies

No evidence of reproductive toxicity was observed in two multigeneration reproductive toxicity studies in the rat. In a two-generation study, thiophanate-methyl was administered in the diet at concentrations equivalent to average daily intakes of 0, 13.7/15.5, 43.3/54, or 138.9/172 mg/kg/day (M/F). Liver hypertrophy and thyroid follicular cell hypertrophy/hyperplasia were observed at all dose levels in P males. Changes were slight at low dose and more pronounced at higher doses. Liver and thyroid weights were increased at the highest dose in males and females. A slight decrease in body weight was observed in high dose males. Toxicity in offspring was observed at 43 mg/kg/day based on a minimal decrease in F2b pup body weights during lactation. Examination of F1 offspring at necropsy indicated a clear increase in thyroid hypertrophy/hyperplasia in males at the high dose of 138.9 mg/kg/day. No significant effects on thyroid hormone levels were observed when F1 offspring were assayed at postnatal week 8. In addition, several developmental tests (functional tests such as papillary, auditory, gripping reflex, surface righting reflex; physical developmental markers such as pinna unfolding, incisor eruption and eye opening) examined in F1 offspring during lactation showed no changes. The data do not

indicate an increased susceptibility of offspring for thyroid toxicity, but assessments of thyroid hormones and histopathology at earlier stages of development were not evaluated.

In an earlier three-generation reproductive toxicity study, animals were tested at dietary concentrations equivalent to 2, 8, or 32 mg/kg/day. No parental toxicity was observed at the doses tested. In offspring, a slight reduction in mean litter weights (not statistically significant, but reproducible) was observed in most litter generations at 32 mg/kg/day. Although mild effects were observed in offspring in the absence of parental toxicity, it is noted that this study did not examine thyroid or liver histopathology. In addition, this study was considered to be unacceptable pending submission of additional information.

3.3.5 Additional Information from Literature Sources

A published study evaluated developmental toxicity in CD rats following gavage administration of 0, 310, or 560 mg/kg/day thiophanate-methyl from GD 10 through 14 (Maranghi, F. *et al.*, *Reproductive Toxicity* 17(5): 617-623, 2003). No maternal toxicity was reported. Developmental effects at both doses included delayed ear pinna detachment and eye opening, along with thyroid and adrenal histopathology.

HED notes that the results of this study are not consistent with the results of the battery of studies submitted by the registrant. Those studies showed maternal effects at significantly lower doses than the doses of 310 and 560 mg/kg/day in the literature study. In addition, the NOAELs chosen for risk assessment purposes are well below these levels.

3.3.6 Pre-and/or Postnatal Toxicity

3.3.6.1 Determination of Susceptibility

The available developmental and multigeneration reproductive studies on thiophanate-methyl do not show evidence of increased qualitative or quantitative susceptibility of offspring. The NOAELs for developmental and offspring toxicity are at, or above, the maternal or parental toxicity NOAELs. There were no findings of abnormal development of the nervous system in developmental toxicity studies. In the rat reproductive study, there were no significant effects on circulating thyroid hormone levels (assessed at postnatal Week 8) or on several developmental milestones that are sensitive to thyroid hormone levels (pinna unfolding, incisor eruption, eye opening; assessment of reflexes; assessed during the first three postnatal weeks) in F1 offspring. Thyroid histopathology, examined at necropsy, was observed in F1 offspring at the high dose; but in the P0 parental animals, it was observed at lower doses. Thiophanate-methyl did not show evidence of neurotoxicity.

3.3.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Postnatal Susceptibility

Although there is no evidence of increased pre- or postnatal susceptibility in the available developmental and reproductive toxicity studies, there are residual concerns for potential effects

on fetal and pup thyroid function. Maternal hypothyroidism and direct effects on the developing thyroid from pre- and/or postnatal exposure may affect the developing nervous system. Because these effects are potentially significant and permanent, a careful assessment of thyroid function during development is important. The reproductive study provided important data on thyroid and early exposure; however, circulating thyroid hormone levels were assessed in F1 offspring in the rat reproductive toxicity study only at Week 8 and not at earlier times, and histopathology was only evaluated upon necropsy. Assessment of fetal and pup thyroid function at earlier times would provide a complete characterization of thyroid function and a more reliable endpoint protective for these effects.

Concern is reduced because the database does not show evidence of increased susceptibility. If significant changes in thyroid function of fetuses or pups were occurring, effects on developmental milestones and circulating thyroid hormone levels would be anticipated. Offspring did not show increased susceptibility to thyroid toxicity and, in fact, thyroid histopathology showed more pronounced effects in the P0 generation. In addition to the thyroid, several physical and functional developmental parameters sensitive to thyroid hormone levels, including appearance of reflexes and physical milestones (pinna unfolding, eye opening, incisor eruption), did not show treatment-related changes. Although additional data are required to address the residual uncertainties, the lack of detectable effects in the available data suggests that there is not increased susceptibility. Additionally, the endpoints selected for risk assessment (e.g., 8 and 10 mg/kg/day) are considered to be protective of thyroid effects in offspring, based on the available data. They are considerably lower than the F1 offspring NOAEL of 43 mg/kg/day for thyroid histopathology. Selecting an endpoint 4x lower than the NOAEL associated with thyroid disruption, in combination with a 3x FQPA factor (retained as a UF_{DB}) should, therefore, be adequately protective of offspring, pending receipt of data on the developing thyroid.

3.3.7 Recommendation for a Developmental Neurotoxicity Study

A developmental neurotoxicity study with thyroid measures, required in the 2007 hazard assessment, is no longer recommended. Instead, a developmental thyroid study is required because the primary concern is for thyroid toxicity, based on thyroid effects in adult animals and residual concerns for potential effects during early development. Maternal hypothyroidism and direct fetal thyroid toxicity are clearly associated with neurodevelopmental deficits in children. As noted above, the reproductive toxicity study included some evaluation of thyroid function during development. While these data do not indicate increased susceptibility, there are no data examining fetal thyroid hormones and histopathology during pre- and/or early postnatal development. The developmental thyroid study is intended to characterize effects that may not have been detected by evaluations in the existing data. It is presumed that identification of a NOAEL for thyroid hormones and histopathology would provide a protective endpoint for development. The HED HASPOC supported this study requirement to address residual uncertainties (Memo, L. Hansen to HED HASPOC, 1/20/09).

3.3.8 Rationale for the UFDB (when a DNT is recommended)

The 3x FQPA Safety Factor represents a database uncertainty factor, UF_{DB}, for the developmental thyroid study (see Section 3.4, below).

3.4 FQPA Safety Factor for Infants and Children

For acute dietary exposure (Females age 13 to 49), the thiophanate-methyl risk assessment team recommends reduction of the FQPA factor to 1x, based on the following: (1) acceptable developmental (rat, rabbit) and reproductive (rat) toxicity studies show no increase in qualitative or quantitative susceptibility in fetuses and pups from *in utero* and/or postnatal exposure; (2) as discussed in Section 3.3.2, thiophanate-methyl did not show evidence of neurotoxicity; (3) no other appropriate single-dose endpoints were identified; although thyroid toxicity is of concern for development, it is not an endpoint of concern for acute (i.e., single dose) exposure, as repeated exposures would be required to cause a significant disruption of thyroid hormone levels; and (4) assessments of drinking water and dietary exposure are not expected to underestimate risk.

For all repeated exposure scenarios, the thiophanate-methyl risk assessment team recommends reduction of the FQPA Safety Factor to 3x. A developmental thyroid study is required to address residual uncertainties at early stages of development, but the factor may be reduced based on the following: (1) acceptable developmental (rat, rabbit) and reproductive (rat) toxicity studies showed no increased qualitative or quantitative susceptibility in fetuses and pups from *in utero* and/or postnatal exposure; (2) offspring in the rat reproductive study did not show increased susceptibility for thyroid histopathology compared to the P0 parental generation; (3) assessment of offspring thyroid hormones and selected thyroid hormone-sensitive developmental milestones were not affected by treatment up to 139 mg/kg/day; (4) thiophanate-methyl did not show evidence of neurotoxicity; (5) assessments of dietary and nondietary exposure are not anticipated to underestimate risk; and (6) the endpoints selected for risk assessment (8-10 mg/kg/day in oral studies) are significantly lower than the NOAEL observed for thyroid histopathology (43 mg/kg/day) and for thyroid hormone or developmental milestone effects (139 mg/kg/day) in F1 offspring. Reduction of the 10x FQPA Safety Factor to 3x is therefore adequately protective pending submission of the additional thyroid .

The data gaps for immunotoxicity and 90-day inhalation studies in the rat do not require an additional UF_{DB}. There was no evidence of immunological effects in the available studies; therefore EPA does not believe that an immunotoxicity study will provide a lower point of departure than those currently selected. Thiophanate-methyl is not from a class of chemicals known to be immunotoxic, and the available studies did not show effects consistent with immunotoxicity. Inhalation risk assessments were not relevant for residential exposure scenarios and were not performed. The 90-day inhalation study is required for assessment of occupational exposure. However, the oral endpoints selected for inhalation risk assessment assume 100% inhalation absorption relative to oral absorption, thiophanate-methyl shows low acute inhalation toxicity (Category III), and the major route of occupational exposure is expected to be via the dermal route. Based on these considerations, EPA has concluded that the doses and endpoints

selected for inhalation risk assessment (along with traditional uncertainty factors and the 3x UF_{DB} for the developmental thyroid study data gap) provide adequate protection for developmental effects in pregnant workers.

3.5 Hazard Identification and Toxicity Endpoint Selection

3.5.1 Acute Reference Dose (aRfD) – Females Age 13-49

Study Selected: Developmental toxicity (oral) - rabbit
MRID No.: 45051001
Executive Summary: In a rabbit developmental toxicity study, (MRID 45051001) thiophanate-methyl (97.28% purity) was administered to groups of 20 New Zealand White Rabbits by gavage in a 1% aqueous methyl cellulose vehicle (at a rate of 10 mL/kg) at dose levels of 0, 5, 10, 20, or 40 mg/kg/day on gestation days 6 to 28. The rabbits were sacrificed on day 29. The does were subjected to uterine examination, and the pups were subjected to external, visceral, and skeletal examination.

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

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

Classification: This study is classified as **Acceptable/Guideline** and satisfies the requirement for a series OPPTS 870.3700b developmental toxicity study in rabbits.

Dose and Endpoint for Risk Assessment: Developmental Toxicity NOAEL = 20 mg/kg/day based on supernumerary ribs and decreased fetal weight at LOAEL = 40 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factors: The developmental toxicity LOAEL of 40 mg/kg/day was selected as the most sensitive available endpoint considered to result from a

single dose that is protective of the developing fetus. The FQPA Safety Factor was reduced to 1x because of high confidence in the endpoint. Significant alterations to thyroid function are not anticipated from a single exposure because of reserves in circulating thyroid hormone levels. The route of exposure (oral) and duration of dosing are appropriate for this scenario because the effects may occur after a single dose. The NOAEL of 20 mg/kg/day is the dose for risk assessment.

3.5.2 Acute Reference Dose (aRfD) – General Population Including Infants and Children

An appropriate endpoint associated with a single dose of thiophanate-methyl was not identified for this scenario. As a result, there is no acute risk associated with thiophanate-methyl for the general U.S. population, including infants and children.

3.5.3 Chronic Reference Dose (cRfD) - All Populations Including Females Age 13-49

Study Selected: Chronic Feeding-Dog
MRID No.: 42311801
Executive Summary: In a chronic oral toxicity study (MRID 42311801), 4 beagle dogs/sex/dose group were administered thiophanate-methyl (tech., 96.55% a.i.) daily for 1 year by gelatin capsule at doses of 0, 8, 40, or 200 mg/kg/day.

At 40 mg/kg/day, decreased mean body weight/weight gain (compared to controls at termination, -7%/-19%, males and -6%/-19%, females; not statistically significant), decreased mean serum T4 levels in males at 6 months (-46%) and markedly increased TSH in 1 male at 6 and 12 months (approximately 2-fold over pretest), increased serum cholesterol in males at 6 and 12 months (+47% and +30%; latter not significant), increased absolute/relative thyroid weights (+33%/+42%, males and +28%/+10%, females; not statistically significant) and thyroid follicular epithelial cell hypertrophy (2/4 females) were observed.

At 200 mg/kg/day, tremors (mostly moderate in all dogs) were observed on day 1 in 7/8 dogs (2-4 hours after dosing), on days 7, 12, or 13, for 3 of 4 male dogs, and on days 2, 16, and 17, for one female dog. Other observations at 200 mg/kg/day included: slightly decreased Hgb, Hct and RBC in males at 6 and 12 months (-13% to -14% below controls); increased serum ALP at 6 and 12 months (+100% and +300%, males and +47% and +82%, females; not significant in females); increased cholesterol at 6 and 12 months (+51% and +42%, males; latter not significant and +93% and +76%, females); increased relative liver weights (+46%, males and +35%, females); and thyroid follicular epithelial cell hyperplasia (1 male and 1 female). Decreases in body weight/weight gain, increases in thyroid weight and follicular cell hypertrophy, and effects on thyroid hormones were more pronounced than they were at 40 mg/kg/day. Slight decreases in serum A/G ratio, Ca^{++}, K^{+} and phosphate in males were reported, but were not considered to be toxicologically significant. There were no treatment-related effects on survival, ophthalmologic parameters or urinalysis. **The LOAEL is 40 mg/kg/day, based on decreased body weight/weight gain and thyroid effects. The NOAEL is 8 mg/kg/day.**

This study is classified as acceptable/guideline (§870.4100b), and satisfies the guideline requirement for a chronic oral toxicity study in the dog.

Dose and Endpoint for Risk Assessment: NOAEL = 8 mg/kg/day based on thyroid effects and decreased body weight seen at LOAEL = 40 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factors: The NOAEL of 8 mg/kg/day is the lowest NOAEL from any oral study of the appropriate duration and the body weight decrease is the most sensitive endpoint identified in studies of chronic duration. Chronic dose and endpoint selection are further supported by comparable values observed in the two-year dietary study in the rat (MRID 42896601), in which a NOAEL of 8.8 mg/kg/day was observed, based on decreased body weight (males) and treatment-related findings in the liver, kidneys, and thyroid of both sexes at the LOAEL of 54.4 mg/kg/day (males) and 63.5 mg/kg/day (females). In addition to the standard 100x uncertainty factor for intra- and interspecies uncertainty, the FQPA/UF_{DB} was retained. There are residual concerns for thyroid effects during early development and the lack of a developmental thyroid study. The FQPA/UF_{DB} factor is reduced to 3x. Reduction is based on reduced concern because available studies, including limited data on offspring thyroid function in the rat reproductive toxicity study, did not indicate increased susceptibility, and the observed NOAELs for thyroid effects in offspring were considerably higher than the NOAEL selected for this exposure scenario. The NOAEL of 8 mg/kg/day, together with the combined 300x factor, is considered to be protective for potential thyroid effects *in utero* and to infants and young children.

3.5.4 Incidental Oral Exposure (Short- and Intermediate-Term)

Study Selected: Developmental Toxicity (rabbit)
MRID No.: 45051001
Executive Summary: See Section 3.5.1, Acute Reference Dose
Dose and Endpoint for Risk Assessment: Maternal toxicity NOAEL = 10 mg/kg/day based on decreased body weight at LOAEL = 20 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factors: The maternal toxicity LOAEL of 20 mg/kg/day represents the most sensitive endpoint (decreased body weight) available for this exposure scenario. The route of exposure (oral) and duration of this study are appropriate for incidental exposure of either short- or intermediate-term. In addition to the standard 100x uncertainty factor for intra- and interspecies uncertainty, an FQPA/UF_{DB} was retained based on residual concerns for thyroid effects during early development and lack of a developmental thyroid study. The FQPA/UF_{DB} factor is reduced to 3x. Although there are residual uncertainties for thyroid effects in early development, the concern is reduced because available data, including limited data on offspring thyroid function in the rat reproductive toxicity study, did not indicate increased susceptibility, and the NOAELs for thyroid effects in offspring are considerably greater than the NOAEL selected for this assessment. The NOAEL of 10 mg/kg/day, together with the combined 300x factor, is considered to be protective for potential thyroid effects to infants and young children.

3.5.5 Dermal Absorption

No dermal absorption studies are available for thiophanate-methyl. A dermal absorption rate of 7% was estimated based on comparison of the LOAELs of an oral developmental toxicity study and a 21-day dermal toxicity study in the same species (rabbit) for decreased food consumption. The absorption was calculated as follows:

$$\text{Dermal Absorption} = \frac{\text{Develpmental LOAEL}}{\text{Dermal LOAEL}} = \frac{20\ \text{mg/kg/day}}{300\ \text{mg/kg/day}} = 0.067 \times 100\% = 7\%$$

3.5.6 Dermal Exposure (Short- and Intermediate-Term)

Study Selected: Twenty-one day dermal toxicity study in rabbits
MRID No.: 42110801
Executive Summary: In a 21-day dermal toxicity study (MRID 42110801), five New Zealand White rabbits/sex/dose group were exposed dermally to thiophanate-methyl (technical, 96.55% a.i.) at 0, 100, 300, or 1000 mg/kg/day for six hours/day, five days per week (total 15 exposures).

Mild dermal irritation was noted at 100 mg/kg/day and higher. At 300 mg/kg/day, statistically significantly reduced food consumption in females during weeks 1 and 3 (-18% and -15% below controls, respectively) was reported. Cumulative consumption was decreased 9.1% for males and 15% for females (not statistically significant). At 1000 mg/kg/day, cumulative food consumption was decreased 20% for both males and females. The body weight gains for females were decreased by 8%, 28%, and 30% for the low, mid, and high dose groups. Male body weight gains did not show consistent decreases. The systemic toxicity LOAEL is 300 mg/kg/day, based on decreased food consumption and probable body weight decrease in females. The NOAEL is 100 mg/kg/day.

This study is classified as Acceptable/Guideline and satisfies the requirement for a 21-day dermal toxicity study in the rabbit.

Dose and Endpoint for Risk Assessment: NOAEL = 100 mg/kg/day based on dose-dependent and statistically significant decreases in food consumption in females at the LOAEL of 300 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factors: The study selected for this exposure scenario is of the appropriate duration and route (dermal) for short- or intermediate-term dermal exposure. No adjustment is needed for dermal absorption because it is a dermal study. The dose is more protective than the oral rabbit maternal toxicity NOAEL of 10 mg/kg/day with adjustment for dermal penetration because of the relatively low dermal absorption (7%) of thiophanate-methyl. In addition to the standard composite 100x uncertainty factor (intra- and interspecies), an FQPA/UF_{DB} was retained based on residual concerns for thyroid effects in early development and lack of a developmental thyroid study. The FQPA/UF_{DB} factor is reduced to

3x. Although there are residual concerns for potential thyroid effects to the fetus, concern is reduced because available data on offspring thyroid function in the rat did not indicate increased susceptibility.

3.5.7 Dermal Exposure (Long-Term)

Study Selected: Chronic Feeding-Dog
MRID No.: 42311801
Executive Summary: See Section 3.5.3, Chronic Reference Dose.
Dose and Endpoint for Risk Assessment: NOAEL = 8 mg/kg/day based on thyroid effects and decreased body weight seen at LOAEL = 40 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factors: The study selected for this exposure scenario represents the lowest NOAEL from any of the studies in the database, and is of the appropriate duration (one year). The endpoint of decreased body weight and thyroid effects observed at the LOAEL is protective of similar effects observed at higher doses in other long-term studies. An adjustment for dermal absorption of 7% is required because dosing was via the oral route.

3.5.8 Inhalation Exposure (Short- and Intermediate Term)

Study Selected: Developmental Toxicity (rabbit)
MRID No.: 45051001
Executive Summary: See Section 3.5.1, Acute Reference Dose Females age 13 to 49
Dose and Endpoint for Risk Assessment: Maternal toxicity NOAEL = 10 mg/kg/day based on decreased maternal body weight/food consumption at the LOAEL = 20 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factors: The NOAEL of 10 mg/kg/day, based on body weight decrement at the LOAEL of 20 mg/kg/day, represents the most sensitive endpoint and dose available for this exposure scenario. The duration of this study is appropriate for exposure of either short- or intermediate-term risk assessments. A default inhalation absorption rate of 100% is assumed relative to oral absorption, as an inhalation study and/or data on inhalation absorption are not available for thiophanate methyl. In addition to the standard composite 100x uncertainty factor (intra- and interspecies), an FQPA/UF_{DB} was retained based on residual concerns for potential thyroid effects during development and lack of a developmental thyroid study. The FQPA/UF_{DB} factor is reduced to 3x. Although there are residual concerns for potential thyroid effects to the fetus, concern is reduced because available studies, including limited data on offspring thyroid function in the rat reproductive toxicity study, did not indicate increased susceptibility, and the NOAELs for these effects are considerably higher than the NOAEL selected for this risk assessment. The NOAEL of 10 mg/kg/day, with the 300x factor, is considered to be protective for potential thyroid effects to the developing fetus.

3.5.9 Inhalation Exposure (Long-Term)

Study Selected: Chronic Feeding-Dog
MRID No.: 42311801
Executive Summary: See Section 3.5.3, Chronic RfD.
Dose and Endpoint for Risk Assessment: NOAEL = 8 mg/kg/day based on thyroid effects and decreased body weight at LOAEL = 40 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factors: The study duration is considered to be appropriate for long-term exposure, and the endpoint, thyroid effects and decreased body weight, are the most sensitive available for this duration. An oral study was selected because there are no chronic inhalation studies. Inhalation absorption of 100% is assumed for this scenario as a default. In addition to the standard composite 100x uncertainty factor (intra- and interspecies), an FQPA/UF_{DB} factor was retained because of residual concerns for potential thyroid effects during early development. The FQPA/UF_{DB} factor is reduced to 3x. Although there are residual concerns for potential thyroid effects to the fetus, the concern is reduced because available studies, including limited data on offspring thyroid function in the rat reproductive toxicity study, did not indicate increased susceptibility, and the dose of 8 mg/kg/day is considerably lower than the NOAELs for thyroid effects in offspring. The NOAEL of 8 mg/kg/day, with the 300x factor, is considered to be protective of the developing fetus.

3.5.10 Level of Concern for Margin of Exposure

Table 3.5.1 Summary of Levels of Concern for Risk Assessment.

Route	Short-Term (1 - 30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	300	300	300
Inhalation	300	300	300
Residential Exposure			
Dermal	300	300	NA
Inhalation	300	300	NA
Incidental Oral	300	300	NA

For all residential exposures including incidental oral exposure to young children, retention of a 3x FQPA Safety Factor is recommended. The 3x factor is based on residual concerns for thyroid effects during development, pending receipt of a developmental thyroid study. The rationale for reduction of the factor from 10x to 3x is discussed in Section 3.4.

A 3x UF_{DB} is also recommended for occupational exposure, in addition to the composite 100x factor for inter- and intraspecies differences. The 3x factor is intended to provide adequate

protection for pregnant pesticide handlers/applicators who might be exposed to thiophanate-methyl.

Dermal and inhalation exposure may be combined for short- and intermediate-term scenarios using a 1/MOE approach because the MOEs and endpoints (decreased body weight gain) are the same. Long-term exposures may be added because the endpoints were based on decreased body weight gain in the chronic dog study.

3.5.11 Recommendation for Aggregate Exposure Risk Assessments

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. For thiophanate-methyl it is appropriate to combine oral, dermal, and inhalation exposures, as all endpoints involve body weight effects.

Acute Aggregate Risk

For acute aggregate risk of thiophanate-methyl, oral exposure via the diet and drinking water must be considered together.

Short- and Intermediate-Term Aggregate Risk

For short- and intermediate-term aggregate risk, exposure from residential uses must be added to dietary exposure from food and drinking water. For adults, exposure from handler and postapplication lawn uses must be added to dietary exposure (food and drinking water). A second aggregate risk assessment should be performed for adult golfers in which postapplication exposure to treated golf course turf is combined with dietary exposure (food and drinking water). For children, post-application exposure from lawn and from incidental oral exposure via hand-to-mouth ingestion of thiophanate-methyl must be added to dietary exposure (food and drinking water).

Chronic Aggregate Noncancer Risk

For chronic aggregate noncancer risk, only oral exposures from diet (food and drinking water) should be combined. Long-term residential handler and postapplication exposures are not anticipated from currently registered uses of thiophanate-methyl.

Cancer Aggregate Risk

Thiophanate-methyl is classified as "likely to be carcinogenic in humans" based on an increased incidence of liver tumors in mice and thyroid follicular cell tumors in rats. A cancer risk assessment is therefore required, and a cancer potency factor was determined (see Section 3.5.11,

below). For aggregate cancer risk, residential handler and postapplication exposures from lawn uses must be combined with dietary (food and drinking water) exposure.

3.5.12 Classification of Carcinogenic Potential

Thiophanate-methyl is classified as "likely to be carcinogenic to humans," based on an increased incidence of liver tumors in mice and thyroid follicular cell adenomas/carcinomas in rats. There are insufficient mechanistic data to demonstrate conclusively that the mode of action is nonmutagenic. The available genotoxicity data indicate aneugenic potential; therefore a default quantification of cancer risk was performed using linear-low dose extrapolation. A cancer potency factor of 1.16×10^{-2} $(mg/kg/day)^{-1}$ was based on hepatocellular adenoma and/or carcinoma and/or hepatoblastoma combined tumor rates in male mice.

3.5.13 Summary of Toxicological Doses and Endpoints for Thiophanate-methyl for Use in Human Health Risk Assessments

Table 3.5.13.a. Summary of Toxicological Doses and Endpoints for Thiophanate-methyl for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-49 years of age)	NOAEL= 20 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	aPAD =0.2 mg/kg/day	Developmental toxicity oral (gavage) study in the rabbit (1997 study) LOAEL = 40 mg/kg/day based on supernumerary ribs in fetuses and decreased fetal body weight
Acute Dietary (General population including infants and children)	An appropriate endpoint was not selected. This risk assessment is not required.			
Chronic Dietary (All Populations)	NOAEL= 8 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 3x	cPAD = 0.027 mg/kg/day	Chronic oral (one-year capsule) toxicity study in the dog LOAEL = 40 mg/kg/day based on thyroid effects and decreased body weight.
Incidental Oral Short- and Intermediate-Term (1-30 days and 1-6 months, respectively)	NOAEL= 10 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 3x	Residential LOC for MOE = 300	Developmental toxicity oral (gavage) study in the rabbit (1997 study) LOAEL = 20 mg/kg/day based on decreased maternal body weight and food consumption.

Table 3.5.13.a. Summary of Toxicological Doses and Endpoints for Thiophanate-methyl for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short- and Intermediate-Term (1-30 days and 1-6 months, respectively)	NOAEL= 100 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 3x	Residential LOC for MOE = 300	Twenty-one day dermal toxicity study in the rabbit LOAEL = 300 mg/kg/day based on decreased food consumption and body weight gain.
Dermal Long-Term (>6 months)	NOAEL=8 mg/kg/day. (dermal absorption rate = 7% relative to oral absorption)	UF_A= 10x UF_H=10x FQPA SF= 3x	Residential LOC for MOE = 300	Chronic oral (one-year capsule) toxicity study in the dog LOAEL = 40 mg/kg/day based on thyroid effects and decreased body weight.
Inhalation Short- and Intermediate-Term (1-30 days and 1-6 months, respectively)	NOAEL=10 mg/kg/day (inhalation absorption rate = 100% relative to oral absorption)	UF_A= 10x UF_H=10x FQPA SF = 3x	Residential LOC for MOE = 300	Developmental toxicity oral (gavage) study in the rabbit (1997 study) LOAEL = 20 mg/kg/day based on decreased maternal body weight and food consumption.
Inhalation Long-Term (>6 months)	NOAEL= 8 mg/kg/day (inhalation absorption rate = 100% relative to oral absorption)	UF_A= 10 UF_H=10 FQPA SF = 3x	Residential LOC for MOE = 300	Chronic oral (one-year capsule) toxicity study in the dog LOAEL = 40 mg/kg/day based on thyroid effects and decreased body weight.
Cancer (oral, dermal, inhalation)	N/A (assessment based on linear low-dose extrapolation)	N/A (assessment based on linear low-dose extrapolation)	Q_1* = 0.0116 $(mg/kg/day)^{-1}$	78-week mouse dietary carcinogenicity study, based on increased incidence of liver adenoma/and/or carcinoma and/or hepatoblastoma combined tumor.

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 3.5.13.b. Summary of Toxicological Doses and Endpoints for Thiophanate-methyl for Use in Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short- and Intermediate-Term (1-30 days and 1-6 months, respectively)	NOAEL=100 mg/kg/day	UF_A=10x UF_H=10x UF_{DB} = 3x	Occupational LOC for MOE = 300	Twenty-one day dermal toxicity study in the rabbit LOAEL = 300 mg/kg/day, based on decreased food consumption and body weight gain.
Dermal Long-Term (>6 months)	NOAEL = 8 mg/kg/day (dermal absorption rate = 7% relative to oral absorption)	UF_A=10x UF_H=10x UF_{DB} = 3x	Occupational LOC for MOE = 300	Chronic oral (capsule) toxicity study in the dog LOAEL = 40 mg/kg/day based on thyroid effects and decreased body weight.
Inhalation Short- and Intermediate-Term (1-30 days)	NOAEL=10 mg/kg/day (inhalation absorption rate = 100% relative to oral absorption)	UF_A=10x UF_H=10x UF_{DB} = 3x	Occupational LOC for MOE = 300	Developmental toxicity oral (gavage) study in the rabbit (1997 study) LOAEL = 20 mg/kg/day based on decreased maternal body weight and food consumption.
Inhalation Long-term (1-6 months)	NOAEL=8 mg/kg/day (inhalation absorption rate = 100% relative to oral absorption)	UF_A=10x UF_H=10x UF_{DB} = 3x	Occupational LOC for MOE = 300	Chronic oral (capsule) toxicity study in the dog LOAEL = 40 mg/kg/day based on thyroid effects and decreased body weight.
Cancer (oral, dermal, inhalation)	N/A (linear low-dose extrapolation used to assess risk)	N/A	Q_1* = 0.0116 $(mg/kg/day)^{-1}$	78-week mouse dietary carcinogenicity study, based on increased incidence of liver adenoma/and/or carcinoma and/or hepatoblastoma combined tumor.

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

3.6 Endocrine disruption

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 were scientific bases for including, as part of the program, 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. When the appropriate screening and/or testing protocols being considered under the Agency's Endocrine Disrupter Screening Program (EDSP) have been developed and vetted, thiophanate-methyl may be subjected to additional screening and/or testing to characterize more fully the effects related to endocrine disruption.

4.0 DIETARY EXPOSURE/RISK CHARACTERIZATION

4.1 Pesticide Metabolism and Environmental Degradation

Reference: Thiophanate-methyl...Summary of Analytical Chemistry and Residue Data, D308747, J. Stokes, 3/19/2009

4.1.1 Metabolism in Primary Crops

No plant metabolism studies were submitted with the new use petitions. The qualitative nature of the residue in plants is adequately understood based on acceptable apple, lima bean, sugar beet, and wheat metabolism studies. HED has concluded that the residues of concern in plants include thiophanate-methyl and its metabolites MBC and 2-AB. For purposes of tolerance enforcement, the regulated residues consist of thiophanate-methyl and MBC.

Carbendazim (MBC, methyl 1H-benzimidazol-2-ylcarbamate) is a major metabolite and environmental degradate of thiophanate-methyl. Risk of exposure to MBC is not being addressed in this risk assessment, however. HED is preparing a separate risk assessment for this chemical, which is an active ingredient used in paints and coatings.

4.1.2. Metabolism in Rotational Crops

An adequate confined rotational crop study is available characterizing ^{14}C-residues in rotated lettuce, carrots, and wheat planted 30, 120, and 365 days following a soil application of [^{14}C]thiophanate-methyl at 1.4 lb ai/A (1x the maximum proposed seasonal rate). Metabolism in rotational crops was found to be similar to the metabolism in primary crops. Residues of thiophanate-methyl were <0.01 ppm in all crops. Residues of thiophanate-methyl metabolites MBC and 2-AB were found at >0.01 ppm in lettuce from the 30- and 120-day plantback intervals and in wheat from the 30- and 365-day plantback intervals, but residues of MBC and 2-AB were <0.01 ppm in carrot from the 30- and 120-day plantback intervals. HED concluded that,

although the maximum seasonal rate used in the confined rotational crop study was less than the maximum seasonal rate to rotated crops (3.15 lb ai/A for potatoes), the study indicates that limited rotational field trials are not required.

4.1.3. Metabolism in Livestock

No tolerances were proposed for livestock commodities and none are being recommended. No livestock metabolism studies were submitted with these petitions. The qualitative nature of the residue in animals is understood based upon previously submitted adequate ruminant and poultry metabolism studies. HED has concluded that the residues of concern in animal commodities include thiophanate-methyl, 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 thiophanate-methyl and MBC. For dietary risk assessment, the hydroxylated MBC metabolites will be included along with the parent and MBC. Concentrations of 4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S in animal commodities will be estimated using the ratio of these metabolites to thiophanate-methyl or MBC in livestock commodities from the metabolism studies along with residue data for thiophanate-methyl and MBC.

4.1.4 Analytical Methodology

Plant commodities

The FDA PESTDATA database (dated 06/05) indicates that thiophanate-methyl and MBC are completely recovered using multiresidue methods Section 404 (method for benzimidazoles). Cerexagri has recently submitted data indicating that, with the exception of multiresidue method Section 404, the multiresidue methods are not appropriate for the determination of thiophanate-methyl and MBC. **The multiresidue method is available for enforcement of the tolerances for plant commodities.**

Cerexagri previously proposed an HPLC/UV method (Elf Atochem Method No. BR-011-04 and revision Method No. BR-93-28) for the enforcement of tolerances for thiophanate-methyl residues in/on plant commodities. In this method, residues of thiophanate-methyl and MBC are extracted from plant matrices using acidified methanol, and the extract is neutralized, partitioned into methylene chloride, and the methylene chloride phase is concentrated. For matrices requiring further clean-up, extracts are purified using solid-phase extraction (SPE). Residues of thiophanate-methyl and MBC are determined by reverse-phase HPLC using a column switching system consisting of two reverse-phase columns using different solvent systems and a UV detector. The limit of quantitation for each analyte is 0.05 ppm in most plant commodities. When the LOQ for MBC is converted to thiophanate-methyl equivalents (using a molecular weight conversion factor of 1.79), the combined LOQ is 0.14 ppm.

Data collection methods: The methods used for data collection in this submission were similar to the proposed enforcement method. Samples of sunflower were analyzed for residues of thiophanate-methyl and its metabolite MBC using HPLC/UV Method BR-011-05. Samples of almond hulls and nutmeat were analyzed for residues of thiophanate-methyl and its metabolite

MBC using HPLC/UV Method KP-021-00. Samples of orange, grapefruit, and lemon, and orange processed commodities were analyzed for residues of thiophanate-methyl and its metabolite MBC using LC/MS/MS Method KP-201R0. LC/MS/MS Method KP-201R1 was used for the determination of thiophanate-methyl and MBC residues in/on blueberry, caneberry, mushroom, pistachio, and tomato samples. LC/MS/MS Method KP-201R2 was used for the determination of thiophanate-methyl and MBC residues in/on samples of cotton commodities (seed, gin byproducts, hulls, meal, and oil), ginseng, mustard greens, tomato commodities (fruit, paste, and puree). The methods were found to be adequate for data collection based on acceptable concurrent method recoveries.

HED needs to review the most recent version of the proposed enforcement method, HPLC/UV Method KP-024-01, in more detail and determine whether or not it needs to be sent to ACB for Agency method validation. If the registrant would still like for the HPLC/UV method to be the enforcement method, HED will perform this review. However, the registrant may also propose that one of the data collection methods based on LC/MS/MS be the tolerance enforcement method. In that case, the registrant needs to submit an ILV for the LC/MS/MS method. Regardless of which method the registrant prefers as the enforcement method, the multiresidue method is available for tolerance enforcement.

Livestock commodities

No tolerances were proposed for livestock commodities and HED is not recommending in favor of any. Based on the dietary exposure levels and the residue data from an available ruminant feeding study, the existing thiophanate-methyl tolerances on cattle, goat, horse, and sheep commodities as well as milk could be revoked because HED has determined that there is no reasonable expectation of finite residues. A 40CFR§180.6(a)(3) situation exists with respect to all animal commodities. As a result, a discussion of analytical methods for livestock commodities is not germane to these tolerance petitions.

4.1.5 Environmental Degradation

Reference: Thiophanate-methyl and degradate methyl 2-benzimidazolylcarbamate or carbendazim (MBC) for additional food uses and IR-4 crops, D335121, R. Parker, M. Barrett, 3/19/2009.

Thiophanate-methyl degrades primarily to MBC whether on foliage, in soil, or in water. While the thiophanate-methyl degradation rate is slower on foliage than in the aquatic environment, conversion to MBC is expected to be rapid under most normal agricultural conditions. The environmental fate of thiophanate-methyl in aquatic and terrestrial environments is dependent on rapid biotic and photolytic degradation to form MBC. When released in terrestrial environments, thiophanate-methyl is expected to degrade relatively rapidly by microbial metabolism (<1 to 4-day half-life) and photolysis ($t_{1/2}$ < 3 days). Based on data from studies that meet Agency guidelines, MBC is stable to aqueous photodegradation, stable to hydrolysis at pH values ranging from 5 to 7, and stable to soil photolysis. Hydrolytic stability decreases as pH increases from 5

to 7. Metabolism under aerobic and anaerobic conditions in both soil and water proceeds at a very slow rate.

It is uncertain, because of its limited persistence, whether thiophanate-methyl, in the form of the parent compound, will commonly be substantially transported away from the site of application, except perhaps in spray drift. However, the primary degradate, MBC, is substantially more persistent and more likely to be present in runoff water. MBC is not likely to volatilize from soil based on its low vapor pressure. Because of its very slow degradation and low mobility in soil (K_{oc} = 1885 L/Kg), MBC is expected to remain at, or near, its site of deposition until it is degraded. The combination of properties of MBC, along with the relatively rapid and substantial conversion of parent thiophanate-methyl into MBC, increases the likelihood of substantial transport from treated fields via runoff.

4.1.6 Comparative Metabolic Profile

Adequate studies are available depicting the metabolism of thiophanate-methyl in rats, primary crops (apples, lima beans, sugar beets, wheat), rotational crops (carrots, lettuce, wheat), and livestock (lactating goats, laying hens). Metabolism in primary and rotational crops is comparable. Parent thiophanate-methyl and the metabolites MBC and 2-AB are the primary compounds found in crops. Parent and MBC are the primary compounds in drinking water. In animals, the residues of concern are parent thiophanate-methyl and MBC as well as the hydroxylated derivatives of MBC (4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S). In the rat, thiophanate-methyl is rapidly absorbed, metabolized and excreted at all dose levels (>90% by 24 hrs post-dosing). The primary route of excretion is via the urine for single doses, but via the feces following repeated doses. Sixteen urinary metabolites (12 identified) were isolated, including MBC (≤3.7% of recovered radioactivity) and other sulfate-conjugated and/or hydroxylated derivatives. The major urinary metabolite was 5-hydroxy(2-methoxycarbonyl amino)benz-imidazolyl sulfate (14-42%). Parent compound was the major excreted compound in feces following repeated oral or single high dose. Nine fecal metabolites (7 identified) were also isolated including MBC (≤3.7% of recovered radioactivity). The major fecal metabolite was dimethyl[(1,2-(4-hydroxyphenylene)]bis(iminocarbonothioyl)bis-(carbamate)(3.5 to 11%). Parent compound and MBC were found in plants, drinking water, ruminants, poultry, and rats. These residues of concern have been accounted for in the rat toxicity studies. Sufficient metabolism data have been submitted for the purposes of the current tolerance petitions.

4.1.7 Toxicity Profile of Major Metabolites and Degradates

MBC is a metabolite of concern, as well as the major environmental degradate of thiophanate-methyl. A small percentage of the thiophanate-methyl administered to rats is metabolized to MBC and excreted via urine and feces (total 1.1 to 3.7% of recovered radioactivity). MBC itself is also registered for use as a fungicide in paints. The fungicidal activity of thiophanate-methyl and the cancelled fungicide, benomyl, is attributed to the tubulin-disrupting properties of MBC. However, many of the toxicological effects reported in studies on MBC are distinct from effects observed with thiophanate-methyl. As noted previously, a separate aggregate risk assessment is being conducted for MBC in association with the proposed uses.

4.1.8 Pesticide Metabolites and Degradates of Concern

HED has determined that the residues of concern in plant commodities for risk assessment are parent thiophanate-methyl, MBC, and 2-AB. The residues of concern in animal commodities for risk assessment are parent thiophanate-methyl, MBC, and the hydroxylated derivatives of MBC (4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S). Thiophanate-methyl and MBC are the residues of concern for risk assessment in drinking water. As explained in Section 7.0, thiophanate-methyl and MBC exhibit different toxicological effects. Therefore, separate risk assessments are being conducted for these two chemicals, with 2-AB being included in the MBC assessment. For tolerance expression, the residues of concern in plant and animal commodities are parent thiophanate-methyl and MBC. No rotational crop tolerances have been established for thiophanate-methyl. The metabolites and degradates of concern for tolerance expression and risk assessment are given in Table 4.1.8. As discussed below in Section 4.1.10, based on the dietary exposure levels and the residue data from an available ruminant feeding study, the existing thiophanate-methyl tolerances on cattle, goat, horse, and sheep commodities as well as milk could be revoked because HED has determined that there is no reasonable expectation of finite residues. As a result, the residues of concern in animal commodities are not relevant to the new use petitions.

Table 4.1.8 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Thiophanate-methyl, MBC, 2-AB	Thiophanate-methyl and MBC
	Rotational Crop	NA	NA
Livestock	Ruminant	Thiophanate-methyl, MBC, 4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S	Thiophanate-methyl and MBC
	Poultry	Thiophanate-methyl, MBC, 4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S	Thiophanate-methyl and MBC
Drinking Water		Thiophanate-methyl and MBC	Not Applicable

4.1.9 Drinking Water Residue Profile

Reference: Thiophanate-methyl and degradate methyl 2-benzimidazolylcarbamate or carbendazim (MBC) for additional food uses and IR-4 crops, D335121, R. Parker, M. Barrett, 3/19/2009.

Aquatic EDWCs for thiophanate methyl and MBC were estimated using PRZM 3.12/EXAMS 2.98 employing the standard index reservoir scenario. PRZM/EXAMS is a Tier II screening model designed to estimate pesticide concentrations found in a water body at the edge of a treated field. As such, it provides high-end values of the pesticide concentrations that might be found in sensitive drinking water sources following pesticide application. PRZM simulates pesticide application to an agricultural field and its transport to an adjacent reservoir, and

EXAMS determines the concentration in the index reservoir per crop scenario during 30 years of simulated weather. The Index Reservoir is a standard water body used by the Office of Pesticide Programs to assess drinking water exposure. It is based on a real reservoir (albeit not currently in active use as a drinking water supply), Shipman City Lake in Illinois, that is known to be vulnerable to pesticide contamination. The weather-dependent runoff events move amounts of the applied pesticide into the reservoir. These amounts can be reduced by degradation or effects of binding to soil in the field. Additionally, PRZM-EXAMS can account for spray drift, and adjusts for the area within a watershed that is planted with the modeled crop (Percent Cropped Area). Spray drift (modeled as direct deposition of the pesticide into the reservoir) is assumed to be 16% of the applied active ingredient for aerial application and 6.4% for other ground spray application. The location of the field is specific to the crop being simulated using site-specific information of soils, weather, cropping, and management factors associated with the scenario. The crop/location scenario in a specific state is intended to represent a high-end vulnerable site on which the crop is normally grown.

The maximum application rates for thiophanate-methyl and relevant environmental fate parameters for thiophanate- methyl and MBC were used in the screening model PRZM/EXAMS in estimating concentrations in surface water.

An extensive list of EDWCs was provided for thiophanate-methyl and the degradate MBC; however, the values shown in Table 4.1.9 only include EDWCs used in the dietary exposure assessment. The acute analysis incorporated the EDWC value based on the use on citrus, and the chronic analysis incorporated the EDWC value based on the use on turf, as these crops yielded the highest EDWC values. The original cancer analysis was performed using the EDWC that was based on the citrus use. Because the cancer dietary risk estimate exceeded HED's level of concern when the citrus use was included, the assessment was run without citrus. The turf EDWC value was incorporated into the cancer analysis when the proposed citrus uses were removed. Following citrus, the turf use resulted in the highest EDWC value for risk estimates for cancer.

Table 4.1.9. Summary of Estimated Drinking Water Concentrations for Thiophanate-methyl Used for Dietary Assessment

Drinking Water Source	Crop	Acute (ppb)	Chronic (ppb)	Cancer (ppb)
Thiophanate-methyl				
Surface water	Citrus	83.6	7.29	4.69
Surface water	Turf	41.0	7.54	4.27

4.1.10 Food Residue Profile

References:

1) Thiophanate-methyl...Summary of Analytical Chemistry and Residue Data, D304364, J. Stokes, 3/19/2009.

2) Thiophanate-methyl. Topsin M 4.5FL (EPA Reg. No. 73545-13). Addition of Foliar Use of FIC Formulation on Canola (PRIA R35) and Seed Treatment use on Sweet Corn (IR-4 Request; PP#2E6478). Summary of Analytical Chemistry and Residue Data, D315774, J. Stokes, 4/2/2009.

Data Collection Methods

Adequate analytical methods were used for data collection in the field trials that were performed in support of these tolerance petitions. An adequate LC/MS/MS method was used for ginseng, leafy *Brassica* greens, tomatoes, citrus, caneberries, bushberries, pistachios, cotton, mushrooms, and canola. An adequate HPLC/UV method was used for almonds, sunflower seeds, and sweet corn seed.

Storage Stability

Samples of raw agricultural and processed commodities from the crop field trial and processing studies submitted with this petition were stored frozen for up to 2 years prior to analysis. Adequate storage stability data are available indicating that thiophanate-methyl is stable in/on diverse crop commodities (apples, cucumbers, snap beans, soybeans, sugar beet roots, and wheat grain) during frozen storage for at least 5 years. These data are adequate to support the storage durations and conditions of raw agricultural crop samples from the submitted field trial and processing studies. No storage stability data are available for processed commodities.

Residues in Meat, Milk, Poultry, and Eggs

The proposed uses include the following livestock feedstuffs: almond hulls, cotton gin byproducts, dried citrus pulp, and canola meal. In addition, the use on sweet corn seed could result in residues in sweet corn forage, stover, and cannery waste. The available ruminant and poultry feeding data are adequate to cover secondary residues resulting from the livestock feedstuffs cited above as well as from feedstuffs with registered uses. The dietary burdens of thiophanate-methyl to livestock were recalculated using the most recent guidance from HED concerning revisions of feedstuff percentages in Table 1 of the OPPTS Series 860 Guidelines (Table 1 Feedstuffs, June 2008) and constructing maximum reasonably balanced livestock diets (MRBDs). Based on the dietary exposure levels and the residue data from an available ruminant feeding study, the existing thiophanate-methyl tolerances on cattle, goat, horse, and sheep commodities as well as milk could be revoked because HED has determined that there is no reasonable expectation of finite residues. A 40CFR§180.6(a)(3) situation exists with respect to all animal commodities. A tolerance of 0.15 ppm is currently in effect for milk and the fat, meat, and meat byproducts of cattle, goat, horse, and sheep. Based on the dietary exposure levels and the residue data from an available ruminant feeding study, HED recommends that the 0.15 ppm tolerance on these commodities be revoked.

Magnitude of the Residue in Ginseng

The submitted residue data for ginseng are adequate to fulfill data requirements. The number and locations of the field trials are in accordance with those specified in OPPTS Guideline 860.1500 for ginseng, and the use pattern of the field trials adequately reflects the use pattern proposed for ginseng. The available field trial data support a tolerance for the combined residues of thiophanate-methyl and MBC in/on ginseng at 0.30 ppm.

Magnitude of the Residue in Tuberous and Corm Vegetables

No crop field trial data were submitted to support the requested use of thiophanate-methyl on tuberous and corm vegetables. Field trial data for potato were submitted to support a previous tolerance request for potato, however (PP#2E6367). The results of seven adequate field trials were submitted. Three foliar applications at 1.05 lb ai/A/application were made, for a total foliar application rate of 3.15 lb ai/A/season, in conjunction with a seed piece treatment prior to planting of thiophanate-methyl (5% D) at 0.025 lb ai/100 lb. In these trials, combined thiophanate-methyl residues were <0.1 ppm (<LOQ) in/on 14 potato samples harvested 16-49 days after the final application. However, Agency guidelines recommend that the registrant submit 16 field trials for potatoes (12 tests if residues in all samples are <LOQ). As a result, HED requested that the registrant submit an additional 5 field trials (Residue Chemistry Chapter for thiophanate-methyl RED, D279270, J. Morales, 4/3/02). HED recommended that these field trials be conducted in Region 11 (2), Region 1 (1), Region 2 (1), and Region 10 (1), and that all trials include data for both the seed piece treatment and the three foliar applications. These data are still outstanding.

As the registrant requested a crop subgroup tolerance for the tuberous and corm vegetables (Subgroup 1-D), only 6 trials are required (instead of 8) to support this subgroup. HED is willing to translate the potato data from the 7 trials discussed above to support the proposed use. Thus the available data are adequate to support the proposed seed treatment use for tuberous and corm vegetables, Subgroup 1-D. The proposed 0.1 ppm tolerance will be adequate for the proposed use. As a tolerance is already established in 40CFR180.371 at 0.1 ppm for potato, HED has decided to recommend that a tolerance be established for Crop Subgroup 1-C rather than 1-D. The additional 5 field trials cited in the Residue Chemistry Chapter for the thiophanate-methyl RED (D279270, J. Morales, 4/3/02) are required as a condition of registration.

Magnitude of the Residue in Leafy *Brassica* Greens

The submitted residue data for mustard greens are not adequate to fulfill data requirements. Although the number and locations of the field trials are in accordance with those specified in OPPTS Guideline 860.1500 for mustard greens as the representative commodity of the leafy *Brassica* greens subgroup, the use pattern of the field trials did not adequately reflect the use pattern proposed for leafy *Brassica* greens. The petitioner proposed seed treatment use on leafy *Brassica* greens in addition to foliar uses, but no crop field trial data were submitted reflecting seed treatment plus foliar uses. The submitted data were for foliar treatment only. The results of

the cotton crop field trials indicate the potential for higher crop residues in the aerial portion of crops receiving seed treatment plus foliar applications, versus crops receiving foliar applications only. To support seed treatment plus foliar uses on leafy *Brassica* greens and turnip greens, a full set of geographically representative data must be submitted, reflecting seed treatment plus foliar applications at the maximum proposed application rate. Provided the petitioner amends the proposed use to remove seed treatment use, the available field trial data support a tolerance for the combined residues of thiophanate-methyl and MBC in/on leafy *Brassica* greens at 8.0 ppm. HED recently concluded that turnip greens should be moved from the leaves of root and tuber vegetables crop group (Group 2) to the *Brassica* leafy vegetables crop group (Group 5). Turnip greens will be a member of the leafy *Brassica* greens subgroup (5-B). Therefore, crop field trial data for mustard greens as the representative commodity of the leafy *Brassica* greens subgroup are sufficient to support the proposed use on turnip greens. Until the regulations have been finalized in the Federal Register, a separate tolerance must be established for turnip greens, at the same level as the leafy *Brassica* greens tolerance (8.0 ppm).

The submitted field trial data support the use of the WP, WDG, and WSB formulations for foliar applications. Leafy *Brassica* Greens must be removed from the SC label. The registrant submitted one side-by-side field trial in which the WP and SC formulations were used. The residues were comparable in the tested samples. Additional field trial data are needed, however, to support the use of the SC formulation. The registrant needs to submit the results of seven additional field trials performed with the SC formulation.

Magnitude of the Residue in Tomatoes

The submitted residue data for tomato are not adequate to fulfill data requirements for a national tolerance, as an insufficient number of crop field trials reflecting application to field-grown tomatoes was conducted. The number of field trials conducted with greenhouse-grown tomatoes is adequate. The crop field trial data submitted by Cerexagri are not adequate with respect to the number and location of trials needed to support the proposed use on tomatoes. As specified in OPPTS Guideline 860.1500 for tomato, sixteen field trials are needed to support a national tolerance for tomato. In their crop field trial submission, IR-4 stated that the use on tomato was to be restricted to east of the Rocky Mountains, however. The proposed use does not include any geographic restrictions. Restricting the use to east of the Rocky Mountains would require that a total of 5 trials be conducted on field-grown tomatoes, in Zones 1 (1 trial), 2 (1 trial), 3 (2 trials), and 5 (1 trial). In their submission, IR-4 included the results of trials with field-grown tomatoes in Zones 2 (1 trial), 3 (3 trials), 5 (1 trial) and 10 (1 trial). Provided that the petitioner restricts use on field-grown tomato and tomatillo to areas east of the Rocky Mountains, and revises the proposed use directions to reflect the use patterns used in the crop field trials submitted by IR-4 (i.e., soil drench application rate is to be 0.35 lb ai/100 gallons as opposed to 0.35 lb ai/A), HED concludes that the submitted field trial data are adequate to satisfy data requirements. The available field trial data will support a tolerance for the combined residues of thiophanate-methyl and MBC in/on tomato at 1.4 ppm. A separate tolerance is not needed for tomatillo, as a tolerance for tomato also covers tomatillo [40 CFR 180.1(h)]. If the petitioner wishes to register use of thiophanate-methyl on tomato without geographic restrictions, an additional 10 crop field trials, conducted in Zone 10, would be required.

Tomatoes and tomatillos must be removed from the SC label for two reasons: 1) the PHI is shorter than 7 days, and 2) in the side-by-side field trials, residues were higher when the SC formulation was used. Additional field trial data are needed to support the use of the SC formulation on tomatoes. A complete residue data set is needed for the SC formulation. The data set should include greenhouse use if the registrant wishes to register the SC formulation for greenhouse use.

Magnitude of the Residue in Citrus

The submitted residue data for citrus fruit are not adequate to fulfill data requirements (Memo, D304364, J. Stokes, 3/19/2009). HED is not recommending in favor of tolerances for citrus commodities because of risk concerns. As a result, a discussion of the adequacy of the submitted citrus data is not relevant to this risk assessment.

Magnitude of the Residue in Bushberries and Caneberries

The submitted residue data for caneberries are adequate to fulfill data requirements. The number and locations of field trials are in accordance with those specified in OPPTS Guideline 860.1500 for the caneberry subgroup, and the use pattern of the field trials adequately reflects the use pattern proposed for caneberries. Adequate residue decline data have been submitted for blueberry which indicate that combined residues of thiophanate-methyl and MBC do not increase in blueberry with increasing sampling intervals. These data may be translated to caneberry. The available field trial data support a tolerance for the combined residues of thiophanate-methyl and MBC in/on caneberries at 25 ppm. The data support the use of the WP, WDG, and WSB formulations only.

The submitted residue data for blueberries are adequate to fulfill data requirements for a tolerance for the bushberry subgroup. The number and locations of field trials are in accordance with those specified in OPPTS Guideline 860.1500 for the bushberry subgroup, and the use pattern of the field trials adequately reflects the use pattern proposed for bushberries. The available field trial data support a tolerance for the combined residues of thiophanate-methyl and MBC in/on bushberries at 5.0 ppm. Juneberry, lingonberry, and salal are now part of the bushberry subgroup. As a result, separate tolerances are not needed for these commodities. The data support the use of the WP, WDG, and WSB formulations only.

To support the use of the SC formulation on caneberries and bushberries, the registrant needs to submit additional field trial data. The registrant needs to submit two side-by-side field trials for bushberries and one side-by-side trial for caneberries in which the WP and SC formulations are used. If the residues in the SC trials are considerably higher than they are in the WP trials, a full set of field trial data will be required.

Magnitude of the Residue in Tree Nuts

Currently, thiophanate-methyl is registered for foliar applications to almond at 0.7-1.05 lb ai/A/application from pink bud until petal fall. Thiophanate-methyl is also registered for foliar applications to pecans at 0.7 lb ai/A/application, from the appearance of first leaves to shuck split. The maximum seasonal rate is 2.1 lb ai/A for both crops; applications to pecans are not to be made after petal fall. The proposed uses on pecans are identical to the registered uses. The proposed uses on almonds are similar; however, the proposed use extends the application timing to allow applications up until hull split. The available residue data for almond are adequate to fulfill data requirements for the tree nut group. The number and locations of field trials are in accordance with those specified in OPPTS Guideline 860.1500 for almond as a member of the tree nut crop group. Maximum residues of thiophanate-methyl and MBC were 7.0 and 1.2 ppm, respectively, and maximum combined residues (in parent equivalents) were 8.5 ppm in/on almond hulls harvested 20-55 days after foliar treatment with the 70% WP at a total rate of 4.16-4.42 lb ai/A. Residues of thiophanate-methyl and MBC were each below the LOQ (<0.05 ppm), for combined residues of <0.14 ppm, in/on all samples of almond nutmeat. Crop field trial data for pecan were submitted previously (DP# 279270, 4/3/02, J. Morales). Total residues of thiophanate-methyl and MBC (expressed as thiophanate-methyl) were <0.1 ppm (<combined LOQ) in/on pecans harvested 25-66 days after the last of eight foliar applications of thiophanate-methyl (WDG or SC formulations) at ~0.7 lb ai/A/application, for a total of 5.6 lb ai/A/season (2.7x the proposed maximum seasonal rate). Applications were made at 14- to 21-day intervals, beginning when leaves first appeared and continuing until shuck split. The available crop field trial data are adequate to support the proposed uses on the tree nut crop group. The available data support a tolerance for the combined residues of thiophanate-methyl and MBC in/on almond hulls at 20 ppm and in/on the tree nut crop group at 0.20 ppm. The WP, WSB, WDG, and SC formulations may be used on tree nuts.

Magnitude of the Residue in Pistachios

The submitted residue data for pistachio are adequate to fulfill data requirements. The number and locations of field trials are in accordance with those specified in OPPTS Guideline 860.1500 for pistachio, and the use pattern of the field trials adequately reflects the proposed use pattern for the WP formulation. Maximum residues of thiophanate-methyl and MBC were 0.698 and 0.0106 ppm, respectively, and maximum combined residues (in parent equivalents) were 0.717 ppm in/on pistachio nutmeat harvested 14-15 days after treatment with the 70% WP at 8.40-8.47 lb ai/A. The available field trial data support a tolerance for the combined residues of thiophanate-methyl and MBC in/on pistachio at 0.90 ppm. The WP, WSB, WDG, and SC formulations may be used on pistachios.

Magnitude of the Residue in Cotton

The submitted residue data for cotton are not adequate to fulfill data requirements. The petitioner has proposed to restrict use of thiophanate-methyl on cotton to AL, AR, FL, GA, LA, MS, NC, SC, TN, VA, and TX (east of Route 283 and southeast of Route 377 only). To support use on cotton in these areas (Zones 2, 3, 4, and 6), HED would require a total of 5 cotton field

trials, in Zones 2 (1 trial), 4 (3 trials), and 6 (1 trial). The number and locations of field trials conducted with the WP formulation are in accordance with those specified in OPPTS Guideline 860.1500 for cottonseed. This guideline requires that residue data reflect samples from cotton harvested using both picker (3 trials) and stripper (3 trials) equipment. However, a recent revision of Table 1 feedstuffs (Table 1 Feedstuffs (June 2008)) has reduced the number of trials to two, and both of these are from stripper cotton only. The major trend with picker cotton is disking back into the soil. If any cotton gin byproducts are harvested from picker cotton, it might be fed only to local growing beef cattle (aka stockers), dry beef cows, and beef calves. Picker cotton is generally grown in areas not containing major beef finishing feedlots. Since the proposed use is restricted to growing regions that plant and harvest only picker cotton, HED will not require additional trials for stripper cotton. However, HED will require a label restriction limiting the use of thiophanate-methyl on picker cotton only. In addition, HED will still recommend that a tolerance be established for cotton gin byproducts based upon the submitted data from the picker cotton trials. If, in the future, the registrant wants to extend the use to include stripper cotton, and not restrict the use of thiophanate-methyl geographically to the proposed zones listed above, then data from two trials of stripper cotton will be required. The petitioner has proposed use of the WP, SC, and WDG formulations of thiophanate-methyl on cotton, as both a seed treatment and for foliar applications. Insufficient crop field trial data are available to support seed treatment use; the use pattern used in the field trials was much less than the proposed seed treatment application rate. HED notes that the field trial data indicate that seed treatment on cotton will result in readily quantifiable residues in gin byproducts. Therefore, if the petitioner wishes to register seed treatment plus foliar uses on cotton, a full set of geographically representative data must be submitted, reflecting seed treatment plus foliar applications at the maximum proposed application rate for each type of application. Also, if it is the registrant's intent to register this combination seed treatment/foliar use, then HED suggests that the registrant submit a protocol for review before any trials are performed. Under certain circumstances, HED allows translation of residue data between WP, WDG, WSB, and SC formulations (ChemSAC decision 3/4/09). For cotton, the crop field trial data reflecting foliar applications of the WP formulation may be translated to support the WDG, WSB, and SC formulations. Provided the petitioner amends the proposed labels for the WP, WDG, WSB, and SC formulations to delete seed treatment uses, and adds the label restriction for use on picker cotton only, the available field trial data support tolerances for the combined residues of thiophanate-methyl and MBC in/on undelinted cotton seed at 0.05 ppm and in/on cotton gin byproducts at 8.0 ppm.

Magnitude of the Residue in Mushrooms

The submitted residue data for mushroom are adequate to fulfill data requirements. The number and locations of the field trials are in accordance with those specified in OPPTS Guideline 860.1500 for mushroom, and the use pattern of the field trials adequately reflects the use pattern proposed for agaricus, shiitake, and oyster mushrooms. In OPPTS 860.1500 it is noted that the decision to require only 3 field trials for mushrooms is due to the fact that mushrooms are generally grown indoors under relatively constant growing conditions, likely leading to little residue variability. The available field trial data support tolerances for the combined residues of

thiophanate-methyl and MBC in/on mushroom at 2.0 ppm. The WP formulation is the only one proposed for use on mushrooms.

Mustard Seed

No crop field trial data were submitted to support the proposed use on mustard grown for seed. The proposed use on mustard grown for seed is identical to the registered use on canola (including the geographic restriction to ND, MN, and MT east of Interstate 15), except that the registered use on canola is not restricted to canola grown for seed. Adequate crop field trial data have been submitted and reviewed for canola (DP# 279033, 3/15/02, J. Morales). In three crop field trials conducted on canola during 2001 in ND, residues of thiophanate-methyl and MBC were below the LOQ (<0.05 ppm each) in/on 6 canola seed samples harvested 39-57 days after a single foliar application of the 70% WP formulation at 1.4 lb. ai/A (1x the proposed maximum seasonal rate to mustard grown for seed), and were each below the LOQ in/on two samples of canola seed harvested 38 days after a single foliar application at 7.1 lb ai/A (5x).
In review of those data, it was concluded that the proposed tolerance needed to be increased to 0.20 ppm (to account for the combined LOQs expressed as thiophanate-methyl equivalents) and that a 40-day PHI was required on the label. HED concludes that the available crop field trial data for canola are adequate to support the proposed use on mustard grown for seed, provided that the proposed use is amended to include a 40-day PHI and the proposed tolerance is increased to 0.20 ppm. The WP, WSB, WDG, and SC formulations may be used on mustard seed.

Magnitude of the Residue in Sunflowers

The submitted residue data for sunflower are adequate to support the proposed seed treatment use. The treatment rates used in the field trials were 0.125 and 0.625 lb ai/100 lb of seed. However, the locations of the field trials are not in accordance with OPPTS Guideline 860.1500 for sunflower. For a use resulting in nonquantifiable residues, six sunflower field trials are required all together, 2 trials in Zone 5, 3 trials in Zone 7, and 1 trial in Zone 8. All submitted field trials were conducted in Zone 5. A geographical restriction is not necessary as residues were <LOQ following application at a 5x rate at all sites. The submitted field trials represent seed treated with the 4.5 lb/gal SC formulation and the proposed use is for the WP formulation. Field trial data for use of the SC formulation may be translated to support the WP formulation because the proposed use is for seed treatment. The available field trial data support a tolerance for the combined residues of thiophanate-methyl and MBC in/on sunflower seed at 0.20 ppm.

Magnitude of the Residue in Sweet Corn

For sweet corn, an adequate number of field trials was conducted, samples were analyzed using an adequate method, and the sample storage intervals are supported by the available storage stability data. No residue decline data are required because residues were nondetectable in/on all samples. Although the locations of crop field trials were not in exact agreement with the zones suggested in Table 5 of 860.1500, HED concludes that the geographic representation is adequate to support seed treatment use. The available data are adequate and support use of the 4.5 lb/gal SC formulation of thiophanate-methyl as a seed treatment to sweet corn at 0.125 lb ai/100 lb

seed. The available data support tolerances at the combined LOQ of 0.14 ppm, expressed as thiophanate-methyl, for sweet corn (kernel plus cob with husks removed), forage, and stover.

Processing Studies

The submitted cotton processing data are not adequate to satisfy data requirements. The cotton processing study needs to be repeated at an exaggerated rate (up to 5x the nominal field rate) in an attempt to obtain quantifiable residues in the RAC. Quantifiable residues of MBC were observed in some samples of cotton seed from the crop field trials conducted at 1x. Supporting storage stability data will be required for residues of thiophanate-methyl and MBC in the processed commodities of cotton, unless samples are stored frozen and analyzed within 30 days of collection. HED considers fulfillment of this data requirement to be a condition of registration.

Pending submission of supporting storage stability data, the submitted processing data for tomato are adequate to satisfy data requirements. Storage stability data are required for residues of thiophanate-methyl and MBC in/on tomato processed commodities (paste and puree) stored frozen for the maximum storage duration of samples from the processing studies, 18.2 months. The processing data for tomato indicate that combined residues do not concentrate in tomato paste or puree; tolerances are not required for tomato processed commodities.

If, at some point in the future, a registrant pursues a tolerance for citrus, storage stability data will be required for residues of thiophanate-methyl and MBC in/on orange processed commodities (dried pulp, juice, and oil). The processing data for orange indicate that combined residues of thiophanate-methyl and MBC do not concentrate in dried pulp or juice but do concentrate in citrus oil. Based on the HAFT residues for combined residues in/on lemon (6.54 ppm) and the average processing factor for oil (1.9x), expected residues in citrus oil would be 12.4 ppm.

Field Rotational Crops

An adequate limited field rotational crop study is available. Residues of both thiophanate-methyl and MBC were <0.01 ppm (<LOQ) in/on all samples harvested at normal maturity from the representative rotational crops planted 30, 120, or 365 days after the last of eight broadcast foliar applications of thiophanate-methyl (70% WP), totaling 4 lb ai/A/season (1.3x), to a primary crop of cucumbers. HED concluded that a 30-day plantback interval is needed for all crops without labeled uses of thiophanate-methyl. No full proposed labels were included with these petitions. A review of the most recently approved labels for the affected products (EPA Reg. No. 73545-11, EPA Reg. No. 73545-13, EPA Reg. No. 73545-16, and EPA Reg. No. 73545-18) indicates that the requested rotational crop restrictions have been added to the product labels.

4.1.11 International Residue Limits

Maximum residue limits (MRLs) for residues of thiophanate-methyl have been established by Codex Alimentarius, under carbendazim (MBC). Codex MRLs are expressed in terms of the sum of benomyl, carbendazim, and thiophanate-methyl, expressed as carbendazim. Fifteen MRLs have been established for carbendazim, including one for berries at 1 ppm, one for tomato at 0.5 ppm and one for tree nuts at 0.1 ppm. Canadian MRLs have also been established for "benomyl, carbendazim, and thiophanate-methyl" in several crops. The Canadian MRLs are expressed in terms of methyl 1-(butylcarbamoyl)benzimidazol-2-ylcarbamate (benomyl), methyl benzimidazol-2-ylcarbamate (carbendazim), and 1,2-di-(3-methoxy-carbonyl-2-thioureido)-benzene (thiophanate-methyl), expressed as carbendazim. Canadian MRLs have been established for citrus fruits at 10 ppm, blackberries, boysenberries, and raspberries at 6 ppm, mushrooms at 5 ppm, and tomatoes at 2.5 ppm. No Mexican MRLs have been established for thiophanate-methyl; however, MRLs have been established for carbendazim and benomyl in tomato at 5 ppm, almond at 1 ppm, and lemon at 10 ppm.

As the U.S. tolerance definition for thiophanate-methyl differs from the Codex, Canadian, and Mexican MRL definitions, harmonization of tolerance levels is not possible at this time.

4.2 Dietary Exposure and Risk

Reference: Thiophanate-methyl, Acute Probabilistic, Chronic, and Cancer Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessment for the Section 3 Registration Action, D360625, A. Parmar, 6/24/2009.

Acute probabilistic, chronic, and cancer dietary exposure assessments for residues of parent thiophanate-methyl were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID, Version 2.03), which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The analyses were performed to estimate the dietary exposures and risks associated with the uses of thiophanate-methyl on all registered and proposed commodities. The analyses include estimates of residues of thiophanate-methyl in drinking water.

4.2.1 Acute Dietary Exposure/Risk

A partially refined acute probabilistic dietary exposure analysis was performed for the population subgroup females 13-49 only. No acute endpoint was identified for the remaining population subgroups. The analysis was based on crop field trial data and Pesticide Data Program (PDP) monitoring data. DEEM default and empirical processing factors were used to modify the residue values. Maximum percent crop treated estimates were used for commodities for which data were available. If no percent crop treated data were available, 100% crop treated was assumed. The acute analysis incorporated the 1 in 10 year peak surface drinking water estimate from application of thiophanate-methyl to citrus. The resulting 99.9th percentile acute dietary exposure estimate for females 13-49 years old is not of concern to HED (8.6% aPAD).

4.2.2 Chronic Dietary Exposure/Risk

A refined chronic dietary analysis was conducted for this assessment. Average field trial and PDP data were used for residue values. DEEM default and empirical processing factors were used to modify the data. The chronic analysis used average percent crop treated estimates or average projected percent crop treated estimates, when available, and incorporated 1 in 10 year average surface drinking water estimates resulting from application of thiophanate-methyl to citrus. The resulting chronic exposure estimates are not of concern to HED (3.5% cPAD for Children 1-2 years old, the most highly exposed population). The dietary exposure and risk estimates for the general U.S. population and all population subgroups are given in Table 4.2.2.

Table 4.2.2. Summary of Acute and Chronic (Non-Cancer) Dietary Exposure and Risk for Thiophanate-methyl (Food and Drinking Water)

Population Subgroup	Acute Dietary (99.9th Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	N/A		0.000467	1.7%
All Infants (< 1 year old)			0.000820	3.0%
Children 1-2 years old			**0.000960**	**3.6%**
Children 3-5 years old			0.000904	3.3%
Children 6-12 years old			0.000567	2.1%
Youth 13-19 years old			0.000352	1.3%
Adults 20-49 years old			0.000369	1.4%
Adults 50+ years old			0.000482	1.8%
Females 13-49 years old	0.017107	8.6	0.000380	1.4%

4.2.3 Cancer Dietary Exposure/Risk

All Uses- A refined cancer dietary analysis was conducted for this assessment. The cancer analysis uses the same food residue inputs, processing factors, percent crop treated data, and projected percent crop treated data as the chronic non-cancer assessment. The cancer analysis incorporated 1 in 30 year average surface drinking water estimates resulting from application of thiophanate-methyl to citrus. The cancer risk estimate using these food residue inputs and a worst case use pattern assumption for water is 4.7×10^{-6}. Typically, HED is concerned when the risk estimate associated with food and drinking water exceeds 3×10^{-6}. As a result, cancer risk to the general U.S. population is above HED's level of concern with all registered and proposed uses including citrus.

Citrus Use Removed- A revised cancer dietary analysis was conducted without citrus and incorporating water values from application of thiophanate-methyl to turf (worst case non-citrus scenario). The resulting cancer risk estimate is 3×10^{-6}. As a result, cancer risk to the general U.S. population does not exceed HED's level of concern with the removal of the proposed citrus use.

Table 4.2.3. Summary of Cancer Dietary Exposure and Risk for Thiophanate-methyl

(Food and Drinking Water)

Population Subgroup	Cancer with proposed citrus use		Cancer without proposed citrus use	
	Dietary Exposure (mg/kg/day)	Risk	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	0.000407	4.7×10^{-6}	0.000260	3×10^{-6}

The cancer dietary exposure analysis overestimates exposure, however, because it is a conservative one. The following commodities contributed 97% of the total dietary cancer risk: drinking water (35%), blackberries and raspberries (27%), tomatoes (17%), nectarines and peaches (7.3%), strawberries (5.6%), and blueberries (5.3%). The EDWC was generated by the PRZM-EXAMS Model which utilizes conservative inputs. The drinking water exposure numbers are high-end for the following reasons: 1) they are based upon assumptions of heavy usage in the drainage basin associated with the drinking water intake, 2) they are based upon the assumption that applications are made at the maximum possible labeled rates, and 3) they are based upon the assumption that applications are made at the minimum labeled intervals. Field trial values were used for all of the food commodities listed above. Field trials are performed using maximum label rates and minimum PHIs. For economic reasons, farmers often do not use the maximum label rates. In addition, when field trials are performed, samples are stored frozen from collection until analysis to prevent breakdown of residues. With the exception of frozen commodities, most foods are not stored frozen from harvest until the time of consumption. For these reasons, HED is confident that the cancer dietary risk estimate overestimates dietary cancer risk to the general U.S. population.

4.3 Anticipated Residue and Percent Crop Treated (%CT) Information

References:

1) Usage Report in Support of Registration for the Fungicide Thiophanate-methyl (102001), D362434, A. Grube, 3/4/2009

2) Projected Percent Crop Treated (PPCT) with the Fungicide Thiophanate-methyl on Citrus Crops: PC Code: 102001, DP Barcode: 360131, Decision #:367673

3) Projected Percent Crop Treated (PPCT) for the Fungicide Thiophanate-methyl on Raspberries and Tomatoes, D361056, J. Carter, 3/13/2009

The residue of concern evaluated in this dietary risk assessment is parent thiophanate-methyl only. That applies to both plant and animal commodities. HED is performing a separate assessment for MBC which will include the other metabolites of concern: MBC and 2-AB in plant commodities, and MBC and its hydroxylated metabolites (4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S) in animal commodities.

Percent Crop Treated

The acute assessment is based on maximum percent crop treated estimates for commodities for which data were available. If no percent crop treated data were available, 100% crop treated was assumed. The chronic and cancer assessments are both based on the average percent crop treated estimates or average projected percent crop treated estimates, when available.

Table 4.3.a. Percent Crop Treated Data

Commodity	Max	Avg
Sugar Beet	5	5
Ginseng	100	100
Potato	2.5	1
Garlic	100	100
Onion	2.5	1
Leafy *Brassica* Greens, Crop Subgoup 5-B	100	100
Soybean	2.5	1
Bean, snap, succulent	30	15
Bean, dry	10	5
Cantaloupe	25	10
Honeydew melon, Casaba	10	10
Watermelon	20	10
Balsam pear, Chayote fruit, Chinese waxgourd	100	100
Cucumber	10	2.5
Pumpkin	5	2.5
Squash	10	5
Apple	25	15
Pear	20	5
Apricot	2.5	1
Cherry	2.5	2.5
Nectarine	100	100
Peach	10	5
Plum	2.5	2.5
Bushberry Subgroup 13-07B	100	100

Table 4.3.a. Percent Crop Treated Data		
Commodity	**Max**	**Avg**
Tree Nuts 14 (except almonds and pecans)	100	100
Almond	10	5
Pecan	2.5	1
Corn, sweet	100	100
Wheat, Triticale	2.5	1
Rapeseed	100	100
Sunflower	100	100
Banana	100	100
Cotton	100	100
Grape	2.5	1
Mushroom	100	100
Peanut	5	2.5
Strawberry	20	10

Table 4.3.b. Projected Percent Crop Treated Data Used in Chronic and Cancer Analyses Only		
Commodity	**Max**	**Avg**
Tomato Fresh: Tomato and Tomatillo	100	64
Tomato Processed: tomato paste, tomato puree, tomato dried, tomato juice	100	57
Caneberry Subgroup 13-07A (except Raspberry)	100	100
Raspberry	100	80
Citrus: citrus citron, citrus hybrids, citrus oil	100	100
Grapefruit	100	50
Kumquat	100	100
Lemon, Lime	100	12
Orange	100	39
Pummelo	100	100
Tangerine	100	34

5.0 RESIDENTIAL (Non-Occupational) EXPOSURE/RISK CHARACTERIZATION

References:
1) Revised Thiophanate-methyl Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document (RED), D279269, G. Bangs, 5/2/2002
2) Revised Residential Exposure Assessment for Use of Thiophanate-methyl on Turf, D360623, M. Collantes, 3/4/2009

No new residential uses have been proposed since the 2002 thiophanate-methyl occupational and residential exposure assessment was performed for the RED. However, for this current risk assessment, HED has performed a revised residential assessment that includes current policies, provides updated information, and incorporates mitigation proposed in the RED.

5.1 Residential Handler Exposure and Risk

Thiophanate-methyl is available for use by residential handlers as liquid and granular formulations applied by hose-end sprayer, low pressure handwand, back pack, and push-type spreader. Short-term risk estimates for residential handlers do not exceed HED's level of concern (MOEs > 300) for any scenario. Handler total MOEs range from 1,900 to 35,000. HED considers residential cancer risk estimates greater than 3×10^{-6} to be of concern. Cancer risk estimates are less than 1×10^{-6} for all scenarios and, therefore, are not of concern to HED.

Table 5.1. Thiophanate-methyl Residential Handler Short/Intermediate-Term and Cancer Risk Estimates

Scenarios	Crop Type/Use	Application Rate (lb ai/acre or lb ai/gallon)	Acreage or other Gallons	Total MOE [1]	Total LADD [2] (mg/kg/day)	Cancer Risk [3]
Applying RTU with hose-end sprayer (ORETF Data)	ornamentals	1.8	0.25 A	5,800	2.4E-06	2.8E-08
Mixing/Loading/Applying Liquids with a Low Pressure Handwand	ornamentals	0.0075	5 Gals.	1,900	7.4E-06	8.6E-08
Mixing/Loading/Applying with Backpack Spreader	ornamentals	0.0075	5 Gals.	35,000	4.1E-07	4.7E-09
Loading/Applying with a Push Type Spreader (ORETF Assessment)	turf	2.72	0.5 A	7,500 (turf)	1.8E-06	2.1E-08

1. Total MOE = Based on information provided in the Residential Exposure Assessment for the Thiophanate-methyl RED, 2002
2. LADD (life average daily dose) = total absorbed dose [(Dermal dose * 0.07) + Inhalation Dose] * average days of exposure (1)/year x (50) years of expected exposure/ (365 days/year x 70 year lifetime);
3. Cancer risk estimates = LADD * Q_1^*, where $Q_1^* = 0.0116$ $(mg/kg/day)^{-1}$

5.2 Residential Postapplication Exposure

Thiophanate-methyl postapplication residential use scenarios include toddlers playing on treated turf, adults performing yard work on treated turf, and adults playing golf on treated turf. As a result, a wide array of individuals of varying ages can potentially be exposed when they perform activities in areas that have previously been treated. For purposes of this assessment, HED revised the previous 2002 thiophanate-methyl residential turf exposure assessment (Memo, D279269, G. Bangs, 5/2/2002) to reflect a reanalysis of the postapplication dermal and oral exposure and risk for adults and children.

Data and Assumptions

Standard default assumptions within the HED Residential Standard Operating Procedures (SOPs) were used to determine potential dermal and oral postapplication exposure to thiophanate-methyl with two exceptions. In the previous 2002 review, postapplication exposure to turf was assessed using 0-day residue values and 7-day residue values from the submitted Turf Transferable Residue (TTR) study for short- and intermediate-term postapplication exposure, respectively. In this revised assessment, HED averaged the daily "predicted TTR" residue values over 14 days, which corresponds with the minimum retreatment interval specified on product labels, in order to revise dermal postapplication exposure. A summary of the predicted 14-day average TTR values and adjustments for difference in application rates are provided in Table 5.2.1. A detailed explanation of information provided in this table is available in the revised residential exposure assessment (Memo, D360623, M. Collantes, 3/4/2009).

Table 5.2.1. Turf Transferable Residue (TTR) Data

State	Application Rate[1] (lb ai/acre)	Predicted 14-day Average TTR	Adjusted 14-day TTR [1]	
			Lawn	Golf Turf [3]
Georgia	15.64	0.3038	0.05244	0.12237
Pennsylvania	18.9	0.7532	0.1076	0.25106
California	28.4	0.3507	0.0333	0.0777

1. Adjusted 14-day TTR = label application rate (2.7 lb ai/A for lawn or 6.3 lb ai/A for golf)/study application rate x predicted 14-day TTR value

In addition, for the purpose of performing cancer risk assessments, the draft approach used attempts to provide a more accurate representation of a person's average combined exposure to the actual pesticide residues over an entire year. While these two assumptions depart from the standard approach, they more closely reflect the actual use patterns and, thereby, refine the estimated exposure and risk.

5.2.1 Inhalation Postapplication Exposure

The vapor pressure of thiophanate-methyl is low (1.3×10^{-5}). Residential postapplication scenarios occur outdoors where there is sufficient air exchange. For these reasons, exposure is considered to be minimal and a quantitative postapplication inhalation exposure assessment was not performed.

5.2.2 Dermal Postapplication Exposure and Assumptions

To assess dermal postapplication exposure, HED assumes that pesticide residues are transferred to the skin of adults/toddlers who enter treated yards for recreation or other activities such as yard work and golfing.

Non-Cancer Dermal Postapplication Risk

Residential postapplication dermal exposure and risk resulting in MOEs greater than, or equal to, 300 are not of concern to HED. All adult and children residential lawn and golf dermal scenarios resulted in MOEs greater than the level of concern (MOEs $\geq$ 300) for short- and intermediate-term exposure and are not of concern to HED. Tables 5.2.2.a and 5.2.2.b provide a summary of the adult and children short- and intermediate-term dermal exposures and risks.

Table 5.2.2.a. Residential Postapplication Non-Cancer Short-term Dermal Exposure and Risk

State	Adjusted TTR [1]	CF	Short-Term Tc (cm^2/hr)	ET (hrs)	BW (kg)	Dose [2] (mg/kg/day)	MOE [3]
Adults							
Pennsylvania	0.1076	0.001	14500 - lawn	2	70	0.0445	2200
	0.251		3500 – golf	4		0.0502	2000
California	0.0333		14500 - lawn	2		0.0137	7200
	0.0778		3500 – golf	4		0.0155	6400
Georgia	0.0524		14500 - lawn	2		0.0217	4600
	0.1224		3500 – golf	4		0.0244	4100
Children							
Pennsylvania	0.1076	0.001	5200 - lawn	2	15	0.0746	1,300
California	0.0333	0.001	5200 - lawn	2	15	0.0230	4,300
Georgia	0.0524	0.001	5200 - lawn	2	15	0.0363	2,700

1. Adjusted TTR: see Table 5.2.1
2. Dermal Dose (mg/kg/day) = $\frac{\text{TTR } (\mu g/cm^2) \times 0.001 \text{ (mg/}\mu g) \times \text{TC } (cm^2/hr) \times \text{ET (hr/day)}}{\text{BW (kg)}}$
3. Short-Term Dermal MOE = $\frac{\text{NOAEL (100 mg/kg/day)}}{\text{Dermal Dose (mg/kg/day)}}$

Table 5.2.2.b. Residential Postapplication Non-Cancer Intermediate-term Dermal Exposure and Risk

State	Adjusted TTR	CF	Int. -Term Tc	ET (hrs)	BW (kg)	Dose (mg/kg/day)	MOE
Adults							
Pennsylvania	0.1076	0.001	7300 - lawn	2	70	0.022	4500
	0.251		3500 - golf	4		0.0502	2000
California	0.0333		7300 - lawn	2		0.0069	14,000
	0.0778		3500 - golf	4		0.015	6400
Georgia	0.0524		7300 - lawn	2		0.010	9000
	0.1224		3500 - golf	4		0.0244	4100
Children							
Pennsylvania	0.1076	0.001	2600 - lawn	2	15	0.037	2700
California	0.0333	0.001	2600 - lawn	2	15	0.0115	8700
Georgia	0.0524	0.001	2600 - lawn	2	15	0.018	5500

1. Adjusted Turf Transferable Residues (TTR) = see Table 5.2.1

2. Dermal Dose (mg/kg/day) = $\frac{\text{TTR } (\mu g/cm^2) \times 0.001 \text{ (mg/}\mu g) \times \text{TC } (cm^2/hr) \times \text{ET (hr/day)}}{\text{BW (kg)}}$

3. Intermediate-Term Dermal MOE = $\frac{\text{NOAEL (100 mg/kg/day)}}{\text{Dermal Dose (mg/kg/day)}}$

Cancer Dermal Postapplication Risk

HED recently developed a draft approach for refining turf cancer assessments. This draft approach assumes that residues are only available for a certain period of time after application. During the days after an application, residues of an applied pesticide can be impacted by a number of things including application rate, frequency of applications, frequency of mowing and watering events, and weather conditions. It can be assumed that, at some point in time, residues of the applied pesticide are no longer available. For the purpose of performing cancer risk assessments, this draft approach attempts to provide a more accurate representation of a person's average combined exposure to the actual pesticide residues over an entire year.

For the purposes of this cancer assessment, HED used the previously cited chemical specific TTR study and determined that residues would be available up to 14 days after application. It was assumed that a homeowner or golfer is exposed to zero residues on the other days of the year.

HED considers residential cancer risk estimates greater than 3×10^{-6} to be of concern, and attempts to mitigate such exposures where feasible. Residential postapplication exposure to turf (home, lawn, or golf course) resulted in cancer risks ranging from 4×10^{-8} to 3×10^{-7} for 5 applications per year. Based on the draft approach and assumptions, HED's cancer risk calculations for residential exposure indicate that 5 applications to turf per year applied with a 14-day retreatment interval would not result in a cancer risk of concern. A summary of the cancer risk for a 14-day retreatment interval is provided in Table 5.2.2.c.

Table 5.2.2c: Residential Postapplication Cancer Dermal Exposure and Risk: 14-day Retreatment Interval

State	Adjusted TTR (ug/cm2)	CF (mg/µg)	Tc (cm^2/hr)	ET (hrs)	BW (kg)	Dose [1] (mg/kg/day)	LADD [2] mg/kg/day	Cancer Risk [3]
5 Applications Per Season								
Pennsylvania	0.0218	0.001	7300- lwn	2	70	0.000318	1.24×10^{-6}	1×10^{-7}
	0.0508		3500- glf	4		0.000711	2.78×10^{-5}	3×10^{-7}
California	0.0068		7300- lwn	2		0.000099	3.88×10^{-6}	4.5×10^{-8}
	0.016		3500-glf	4		0.00022	8.75×10^{-6}	1×10^{-7}
Georgia	0.011		7300-lwn	2		0.000161	6.3×10^{-6}	7×10^{-8}
	0.0251		3500-glf	4		0.00035	1.37×10^{-5}	1.6×10^{-7}
3 Applications Per Season								
Pennsylvania	0.013	0.001	7300	2	70	0.00018	7.42×10^{-6}	8.6×10^{-8}
	0.0305		3500	4		0.000427	1.67×10^{-5}	2×10^{-7}
California	0.0041		7300	2		0.000060	2.35×10^{-6}	2.7×10^{-8}
	0.0096		3500	4		0.00013	5.25×10^{-6}	6×10^{-8}
Georgia	0.0065		7300	2		0.00009413	3.71×10^{-6}	$4. \times 10^{-8}$
	0.015		3500	4		0.00021	8.21×10^{-6}	9.5×10^{-8}

1 Application Per Season								
Pennsylvania	0.0044	0.001	7300	2	70	0.0000636	2.49×10^{-6}	3×10^{-8}
	0.0103		3500	4		0.00014	5.63×10^{-6}	6.5×10^{-8}
California	0.0014		7300	2		0.000020	7.82×10^{-7}	9×10^{-9}
	0.0032		3500	4		0.000044	1.74×10^{-6}	2×10^{-8}
Georgia	0.0021		7300	2		0.000030	1.2×10^{-6}	1×10^{-8}
	0.005		3500	4		0.00007	2.74×10^{-6}	3×10^{-8}

1. Dermal Dose (mg/kg/day) = $\frac{\text{TTR } (\mu g/cm^2) \times 0.001 \text{ (mg/}\mu g) \times \text{TC } (cm^2/hr) \times \text{ET (hr/day)} \times 7\% \text{ DA}}{\text{BW (70 kg)}}$

2. Life Average Daily Dose (LADD) = Daily Dose (mg/kg/day) x $\frac{20 \text{ days}}{365 \text{ days}}$ x $\frac{50 \text{ years}}{70 \text{ lifetime years}}$

3. Cancer Risk = Q*(0.0116 $(mg/kg/day)^{-1}$) x LADD (mg/kg/day)

CF: Conversion Factor, Tc: Transfer Coefficient, ET: Exposure Time, BW: Body Weight

Additional Characterization for Dermal Cancer Risk

Various residue data, input parameters, and assumptions have been used to estimate the cancer risk for homeowners and golfers. As indicated previously, turf residues may be impacted by a number of factors, such as application rates of the pesticide, frequency of applications per year, frequency of mowing and watering (irrigation) events, and weather conditions. The greatest variable is the actual frequency with which homeowners are in contact with their home lawns and golf courses. It should also be noted that the TTR study used to estimate turf residues was performed at application rates ranging from 15.64 lb ai/acre in Georgia to 28.4 lb ai/acre in California. These rates are considerably higher than the new mitigated label rates of 2.7 lb ai/A for lawns, 5.4 lb ai/A for fairways, and 8.9 lb ai/A for tees, greens, and aprons. Extrapolating data within these conditions may make risk estimates conservative. HED cannot refine cancer risk estimates without a new chemical-specific TTR study performed at the mitigated label rates.

5.2.3 Oral (Hand-to-Mouth, Object-to-Mouth, and Incidental Ingestion of Soil) Exposure

Hand-to-Mouth (HTM) Exposure and Risk

To assess oral postapplication exposure, HED assumes that pesticide residues are transferred to the skin of children playing on treated areas and are subsequently ingested as a result of hand-to-mouth transfer. Residential postapplication oral exposure estimates resulting in MOEs greater than or equal to 300 are not of concern to HED. All short- and intermediate-term hand-to-mouth (HTM) scenarios resulted in MOEs greater than the level of concern (MOEs $\geq$ 300) and, therefore, pose no risk concern to HED. Table 5.2.3.a provides a summary of the short- and intermediate-term HTM exposures.

Table 5.2.3.a. Toddler Hand-To-Mouth Exposure and Risk

TTR [1] (ug/cm^2)	SA (cm^2/event)	FQ	SE	ET (hr/day)	CF	BW (kg)	Dose [2] (mg/kg/day)	MOE [3]
Short-term								
0.839	20	20	0.5	2	0.001	15	0.0224	450
Intermediate-term								
0.839	20	9.5	0.5	2	0.001	15	0.0106	940

1. Turf Transferable Residues (TTR) = 14-day average of standard assumption for the initial fraction of residues available and assuming a 10% dissipation rate
TTR_t = AR x F x $(1\text{-}D)^0$ x CF2 x CF3 = 1.523 ug/cm^2
1.523 ug/cm^2 with 10% dissipation over 14 days = 11.75 ug/cm^2 total TTR
11.75/14 days = 0.839 ug/cm^2/day
2. Dose = $\frac{\text{Adjusted } TTR_t \text{ x SA x FQ x ET x SE x CF1}}{\text{BW}}$
3. MOE = NOAEL (10 mg/kg/day)/HTM Dose (mg/kg/day)
SA: Surface Area, FQ: Frequency, SE: Saliva Extraction, ET: Exposure Time, CF: Conversion Factor

Object-to-Mouth Exposure and Risk

For the object to mouth (OTM) scenario, HED estimates doses received by toddlers from incidental ingestion of pesticide and/or residential turfgrass that has been previously treated with pesticides. It assumes that pesticide from a treated object or turf is ingested by toddlers who play on treated areas. Residential postapplication oral exposure and risk resulting in MOEs greater than or equal to 300 are not of concern to HED. The OTM scenario resulted in an MOE greater than the level of concern (MOEs ≥ 300) and, therefore, poses no risk concern to HED. Table 5.2.3.b provides a summary of the OTM exposure and risk.

Table 5.2.3.b. Object–to-Mouth Exposure and Risk

GR [1] (ug/cm^2)	CF (mg/µg)	IgR (cm^2/day)	BW (kg)	Dose [2] (mg/kg/day)	MOE [3]
3.36	0.001	25	15	0.0056	1,800

1. GR = AR x F x $(1\text{-}D)^0$ x CF2 x CF3 = 6.09 ug/cm^2
   6.09 ug/cm^2 with 10% (0.1) over 14 days = 46.99 ug/cm^2
   46.99/14 days = 3.36 ug/cm^2/day
2. Dose = GR_0 x IgR x CF1/BW
3. OTM MOE = NOAEL (10 mg/kg/day)/OTM Dose (mg/kg/day
GR: Grass Residue, CF: Conversion Factor, IgR: Ingestion Rate for Grass, BW: Body Weight

Incidental Ingestion of Soil Exposure and Risk

This scenario assumes pesticide residues in soil are ingested by toddlers who play on treated areas as a result of normal mouthing activities. Residential postapplication oral exposure estimates resulting in MOEs greater than or equal to 300 are not of concern to HED. The soil-ingestion scenario resulted in a MOE greater than the level of concern (MOEs ≥ 300) and, therefore, poses no risk concern to HED. This assessment should be considered to be conservative in that it assumes no dissipation of soil residues would occur over the exposure period. Table 5.2.3.c provides a summary of the soil ingestion exposure and risk.

Table 5.2.3.c. Soil Ingestion Exposure and Risk

SR [1] (ug/g)	CF	IgR (mg/day)	BW (kg)	Dose [2] (mg/kg/day)	MOE [3]
20.4	0.000001	100	15	0.000136	74,000

1. SR_0 = AR(2.72) x F(1) x $(1\text{-}D)^0$ x 0.67 x $(4.54x10^8)$x (2.47×10^{-8})
2. Dose = SR_0 x IgR x CF1/BW
3. Soil Ingestion MOE = NOAEL (10 mg/kg/day)/Soil Ingestion Dose (mg/kg/day)
SR: Soil Residue, CF: Conversion Factor, IgR: Ingestion Rate of Grass, BW: Body Weight

5.3 Combined Residential Risk Estimates

5.3.1 Non-Cancer Residential Combined Exposure

In evaluating non-cancer combined residential uses of thiophanate-methyl, HED combined all non-dietary sources of exposure. HED combines risk values resulting from separate exposure scenarios when it is likely they can occur simultaneously based on the use-pattern and the behavior associated with the exposed population. For adults, adult handler (lawns only) and dermal postapplication exposure were combined. For children, postapplication dermal exposure and oral (hand to mouth only) exposure were combined. As the endpoints for all routes of exposure were based on the same toxicological effects, the following method was used to estimate the combined risks.

$$\text{Children } MOE_{Combined} = \frac{1}{\frac{1}{MOE_{Oral}} + \frac{1}{MOE_{Dermal}}}$$

Where:

MOE_{ORAL} = Oral NOAEL (10 mg/kg/day) / HTM Dose mg/kg/day or HTM MOE

MOE_{DERMAL} = Dermal NOAEL (100 mg/kg/day) / Postapplication Dermal Dose (mg/kg/day)

Similar equations were used for adults with MOEs associated with dermal and inhalation exposure.

$$\text{Adult } MOE_{combined}: = \frac{1}{\left(\frac{1}{MOE_{handler\ dermal}} + \frac{1}{MOE_{handler\ inhalation}}\right) + \frac{1}{MOE_{dermal\ postapplication}}}$$

The non-cancer residential combined scenarios for adults and children resulted in MOEs greater than the LOC (LOC = MOE ≥ 300) and, therefore, are not of concern to HED. Table 5.3.1 provides a summary of the combined MOEs for adult and children subpopulations to thiophanate-methyl.

Table 5.3.1. NON-CANCER Combined Residential Exposure and Risk – Short-term				
State in which TTR Study was performed	**Handler Dermal and Inhalation MOE**	**Postapplication Dermal MOE**	**Hand-to-Mouth MOE**	**Combined MOE**
Adult – Lawn				
Pennsylvania	1,900	2,200	NA	1,000
California		7,200		1,500
Georgia		4,600		1,300
Adult – Golf				
Pennsylvania	NA	2,000	NA	2,000
California		6,400		6,400
Georgia		4,100		4,100
Children				
Pennsylvania	NA	1,300	450	330
California		4,300	450	410
Georgia		2,700	450	390

Additional Characterization for Non-Cancer Combined Residential Exposure

The same endpoint of 100 mg/kg/day was selected for short- and intermediate-term dermal exposure. In addition, the same endpoint of 10 mg/kg/day was selected for short and intermediate-term oral exposure. The current residential SOPs provide two separate Tcs for short and intermediate-term dermal durations, along with two different frequencies for numbers of hand-to-mouth events which could occur during these two time periods. HED believes using the short-term dermal Tc and frequency of events for hand-to-mouth in assessing the combined residential exposure provides a more conservative exposure value which will be protective of all intermediate-term exposure scenarios. The intermediate-term exposures were calculated using 14-day average residue values which may not accurately represent this exposure period.

Furthermore, HED did not combine risk resulting from adult homeowner handler, postapplication, and golf exposure to treated turf. HED believes that it is unlikely that a homeowner would treat his or her lawn and play golf on a course that had just recently been treated. As a result, combining these two scenarios would result in an overestimate of exposure. In addition, as explained in the next section, HED believes the estimates of homeowner postapplication exposures are very conservative.

5.3.2 Cancer Risk for Combined Residential Exposure

HED combines risk values resulting from separate exposure scenarios when it is likely they can occur simultaneously based on the use-pattern and the behavior associated with the exposed population. To determine cancer risk for combined residential exposure to thiophanate-methyl, HED combined all non-dietary sources of exposure, which consisted of adult handler (lawns only) and dermal postapplication exposure.

HED did not determine a cancer risk for combined homeowner exposures (resulting from homeowners treating their lawn, and postapplication exposure on a treated lawn) and golfer exposures. The transfer coefficient (Tc) used in assessing postapplication exposure to homeowners from treated lawns is based on a surrogate Jazzercise study which involves high impact activities. HED believes that this Tc represents a very conservative estimation of activity compared to regular activities a homeowner performs while treating the lawn. Therefore, combining the exposure resulting from homeowner and golfer exposure to treated turf would not be appropriate.

For purposes of combining cancer handler risk scenarios with cancer postapplication scenarios for lawns, HED used the cancer risk for each handler scenario listed in Table 5.1 and combined it with the worst case cancer risk for postapplication exposure provided in Table 5.2.2c. All scenarios resulted in combined cancer risk estimates below $1x10^{-6}$, which are not of concern for residential exposure. As shown by the summary of the combined cancer risk scenarios in Table 5.3.2, all combined risks are less than or equal to 2.3×10^{-7}.

Table 5.3.2: Thiophanate-methyl Cancer Risk Estimates for Combined Residential Exposure (Lawn Only)

Scenarios	Handler Total LADD [1] (mg/kg/day)	Handler Cancer Risk [1]	Postapplication LADD [2] (mg/kg/day)	Postappplication Cancer Risk [2]	Combined LADD [3] (mg/kg/day)	Combined Cancer Risk [4]
Applying RTU with a hose-end sprayer (ORETF data) Ornamentals	2.4E-06	2.8E-08	1.24E-05	1.44E-07	1.4E-5	1.7E-7
Mixing/Loading/Applying Liquids with a Low Pressure Handwand Ornamentals	7.4E-06	8.6E-08			1.98E-5	2.3E-7
Mixing/Loading/Applying with a Backpack Sprayer Ornamentals	4.1E-07	4.7E-09			1.28E-5	1.48E-7
Loading/Applying with a Push Type Spreader (ORETF Assessment) Turf	1.8E-06	2.1E-08			1.424E-5	1.65E-7

1. Based on information provided in the Residential Exposure Assessment for the Thiophanate-methyl RED 2002 (see Table 5.1 in this assessment)
2. Based on information provided in Table 5.2.2.c above
3. Combined LADD = Handler LADD + Postapplication LADD
4. Combined Residential Cancer Risk = Combined LADD * Q_1^*, where $Q_1^* = 0.0116$ $(mg/kg/day)^{-1}$

5.4 Other (Spray Drift, etc.)

Spray drift is always a potential source of exposure to residents living in close proximity to spraying operations. This situation is particularly the case with aerial application. However, to a lesser extent, spray drift resulting from the ground application of thiophanate-methyl could also be a potential source of exposure. The Agency has been working with the Spray Drift Task Force (a membership of U.S. pesticide registrants), EPA Regional Offices, State Lead Agencies for pesticide regulation, and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, and is developing a policy on how to apply appropriately the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast, and ground hydraulic methods. After the policy is in place, the Agency might impose further refinements in spray drift management practices to reduce off-target drift risks associated with pesticide application.

6.0 AGGREGATE RISK ASSESSMENTS and RISK CHARACTERIZATION

In accordance with the FQPA, HED must consider and aggregate pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. There are residential exposure uses associated with thiophanate-methyl that must be aggregated with the dietary (food and drinking water) uses.

For most pesticide active ingredients, water monitoring data are considered inadequate to determine surface and groundwater drinking water exposure estimates, so model estimates have been used to estimate residues in drinking water. For thiophanate-methyl, the relevant PRZM/EXAMS value as a residue for water (all sources) was used in the dietary exposure assessment. The principal advantage of this approach is that the actual individual body weight and water consumption data from the CSFII are used, rather than assumed weights and consumption for broad age groups.

Because of dietary risk issues, HED is not recommending in favor of a tolerance for citrus commodities. As a result, all aggregate risk assessments performed for thiophanate-methyl are based on dietary exposure estimates that exclude citrus.

6.1 Acute Aggregate Risk

Dietary (food + water) consumption is the only source of exposure to thiophanate-methyl that is expected to result in acute exposure. Therefore, the acute aggregate exposure and risk estimates are equivalent to the acute dietary exposure and risk estimates discussed in Section 4.2.1, above. See Table 4.2.2 for the results of the analysis. Acute aggregate risk is below HED's level of concern for females 13-49, the only population subgroup for which an acute dietary endpoint

was identified. This population subgroup utilizes 8.6% of the aPAD at the 99.9th percentile of exposure.

6.2 Short-Term Aggregate Risk

There are residential uses for thiophanate-methyl on lawns and golf courses. The exposures resulting from residential uses must be aggregated with the dietary (food and drinking water) exposures (including exposures resulting from the newly proposed tolerances). The levels of concern (target MOEs) for the different routes of exposure are the same. As a result, the 1/MOE approach was used for calculating the aggregate MOE. Short-term aggregate risk MOEs were calculated for the adult population subgroup with the highest exposure estimate (Adults 50+) and the children's population subgroup with the highest exposure estimate (Children 1-2). For adults, the aggregate risk MOE was calculated for two different scenarios: (1) lawn (handler + postapplication) + dietary (food and drinking water), and (2) golf (postapplication) + dietary (food and drinking water). For children, the aggregate risk MOE was calculated for one scenario only: lawn (postapplication dermal + hand-to-mouth transfer) + dietary (food and drinking water). Chronic dietary exposure values were used for the aggregate calculations in order to provide an estimate of background exposure from food and drinking water. The equations used for the three scenarios discussed above are as follows:

Adult (lawn) Total MOE: $$MOE_{Total} = \frac{1}{\frac{1}{MOE_{handler}} + \frac{1}{MOE_{lawn\ postapp}} + \frac{1}{MOE_{dietary}}}$$

Adult (lawn) Total MOE: $$MOE_{Total} = \frac{1}{\frac{1}{1,852} + \frac{1}{2,243} + \frac{1}{20,747}} = 970$$

Adult (golf postapplication) Total MOE: $$MOE_{Total} = \frac{1}{\frac{1}{MOE_{golf\ postapp}} + \frac{1}{MOE_{dietary}}}$$

Adult (golf postapplication) Total MOE: $$MOE_{Total} = \frac{1}{\frac{1}{1,992} + \frac{1}{20,747}} = 1,800$$

Children Total MOE: $MOE_{Total} = \dfrac{1}{\dfrac{1}{MOE_{postapp}} + \dfrac{1}{MOE_{hand\text{-}to\text{-}vouth}} + \dfrac{1}{MOE_{dietary}}}$

Children Total MOE: $MOE_{Total} = \dfrac{1}{\dfrac{1}{1{,}340.5} + \dfrac{1}{446} + \dfrac{1}{10{,}417}} = 320$

The short-term aggregate risk assessment data and results are given in Table 6.2, below.

Table 6.2. Short-Term Aggregate Risk Calculations (1/MOE Approach - All LOCs Identical)

Population	Short-Term Scenario				
	LOC for Aggregate Risk	MOE Food & Water	MOE Oral[1]	MOE Dermal and/or Inhalation	Aggregate MOE (Food and Residential)
Adults 50+ (lawn)	300	20,747	NA	1020	970
Adults 50+ (golf)	300	20,747	NA	1992	1,800
Children 1-2	300	10,417	446	1340.5	320

[1]Oral MOE is for hand-to-mouth transfer

The short-term aggregate risk MOEs for thiophanate-methyl are not of concern to HED. The aggregate MOEs range from 320 to 1,800. These values are above the LOC of 300.

6.3 Intermediate-Term Aggregate Risk

As stated above, there are residential uses for thiophanate-methyl on lawns and golf courses. As with the short-term aggregate risk assessments, the exposures resulting from residential uses must be aggregated with the dietary (food and drinking water) exposures. The levels of concern (target MOEs) for the different routes of exposure are the same. As a result, the 1/MOE approach was used for calculating the aggregate MOE. Intermediate-term aggregate risk MOEs were calculated for the adult population subgroup with the highest exposure estimate (Adults 50+) and the children's population subgroup with the highest exposure estimate (Children 1-2). For adults, the aggregate risk MOE was calculated for two different scenarios: (1) lawn (handler + postapplication) + dietary (food and drinking water), and (2) golf (postapplication) + dietary (food and drinking water). For children, the aggregate risk MOE was calculated for one scenario only: lawn (postapplication dermal + hand-to-mouth transfer) + dietary (food and drinking

water). As with the short-term aggregate risk assessments, chronic dietary exposure values were used in the assessment to provide a background exposure from food and drinking water. The equations used for the three scenarios discussed above are as follows:

Adult (lawn) Total MOE: $$MOE_{Total} = \frac{1}{\frac{1}{MOE_{Handler}} + \frac{1}{MOE_{lawn\ postapp}} + \frac{1}{MOE_{dietary}}}$$

Adult (lawn) Total MOE: $$MOE_{Total} = \frac{1}{\frac{1}{1852} + \frac{1}{4456} + \frac{1}{20,747}} = 1,200$$

Adult (golf) Total MOE: $$MOE_{Total} = \frac{1}{\frac{1}{MOE_{golf}} + \frac{1}{MOE_{dietary}}}$$

Adult (golf) Total MOE: $$MOE_{Total} = \frac{1}{\frac{1}{1992} + \frac{1}{20,747}} = 1,800$$

Children Total MOE: $$MOE_{Total} = \frac{1}{\frac{1}{MOE_{postapp}} + \frac{1}{MOE_{hand\text{-}to\text{-}vouth}} + \frac{1}{MOE_{dietary}}}$$

Children Total MOE: $$MOE_{Total} = \frac{1}{\frac{1}{2681} + \frac{1}{943} + \frac{1}{10,417}} = 650$$

The intermediate-term aggregate risk assessment data and results are given in Table 6.3, below.

Table 6.3. Intermediate-Term Aggregate Risk Calculations (1/MOE Approach - All LOCs Identical)

Population	Intermediate-Term Scenario				
	LOC for Aggregate Risk	MOE Food & Water	MOE Oral[1]	MOE Dermal and/or Inhalation	Aggregate MOE (Food and Residential)
Adults 50+ (lawn)	300	20,747	NA	1315	1,200
Adults 50+ (golf)	300	20,747	NA	1992	1,800
Children 1-2	300	10,417	943	2681	650

[1]Oral MOE is for hand-to-mouth transfer

The intermediate-term aggregate risk MOEs for thiophanate-methyl are not of concern to HED. The aggregate MOEs range from 650 to 3,700. These values are above the LOC of 300.

6.4 Long-Term Aggregate Risk

Dietary (food + water) consumption is the only source of exposure to thiophanate-methyl that is expected to result in chronic exposure. Therefore, the long-term aggregate exposure and risk estimates are equivalent to the chronic dietary exposure and risk estimates discussed in Section 4.2.2, above. The most highly exposed population subgroup is Children 1-2, which utilizes 3.6% of the cPAD. The risk estimate for the general U.S. population is 1.7% of the cPAD. As with the acute assessment, the risk estimates are all below HED's level of concern (100% of the cPAD).

6.5 Cancer Aggregate Risk

Aggregate cancer risk is comprised of the risk from dietary sources (food and drinking water) and the risk from residential handler and postapplication uses on lawns and golf courses. The residential uses on lawns are combined because HED makes the assumption that people will treat their lawns and then be exposed during postapplication activities. As a result, the combined cancer residential exposure from handler and postapplication activities is aggregated with dietary (food and water) exposure. Combined cancer residential exposure values for handler and postapplication activities were given in Table 5.3.2. Several scenarios were assessed because there are various application methods. The cancer risks for these scenarios were aggregated with the dietary (food and drinking water) cancer risk to arrive at the total cancer risk for dietary and residential exposures. For the aggregate dietary plus postapplication golf course cancer risk, the highest LADD from the various scenarios was used for calculations. This scenario is the Pennsylvania golf course to which 5 applications were made.

For thiophanate-methyl, the Q_1^* approach is used for quantification of cancer risk. As a result, the residential and dietary exposure estimates can be added and the sum multiplied by the Q_1^* to arrive at the aggregate cancer risk estimates. Cancer risk is determined for the general U.S. population only. The Q_1^* value used for calculations is 0.0116 $(mg/kg/day)^{-1}$. EPA generally considers cancer risks in the range of 10^{-6} to be negligible. The aggregate cancer risks are given below in Table 6.5.

Table 6.5. Aggregate Cancer Risk Estimates: Risk is Quantified Using a Q_1^* Approach

Residential Handler Exposure Scenario	Chronic Food & Water Exposure (mg/kg/day)	Residential Exposure (Combined LADD)	Aggregate Cancer Risk (food, water and residential)
Applying RTU with a hose-end sprayer (ORETF data), Ornamentals	0.000260	0.00001400	3×10^{-6}
Mixing/Loading/Applying Liquids with a Low Pressure Handwand, Ornamentals	0.000260	0.00001980	3×10^{-6}
Mixing/Loading/Applying with a Backpack Sprayer, Ornamentals	0.000260	0.00001280	3×10^{-6}
Loading/Applying with a Push Type Spreader (ORETF Assessment), Turf	0.000260	0.00001420	3×10^{-6}
Golf Courses	0.000260	0.00002780	3×10^{-6}

The aggregate cancer risk estimates are below HED's level of concern. They are all in the range of 10^{-6} or below. The listed values overestimate actual aggregate cancer risk. Dietary sources contribute 92% of the cancer risk. Residential uses contribute the other 8%. As discussed in the dietary section, the food and drinking water residue inputs are all based on conservative assumptions of maximum label application rates and minimum retreatment and/or preharvest intervals. The following commodities contributed 97% of the total dietary cancer risk: drinking water (35%), blackberries and raspberries (27%), tomatoes (17%), nectarines and peaches (7.3%), strawberries (5.6%), and blueberries (5.3%). The EDWC was generated by the PRZM-EXAMS Model which utilizes conservative inputs. The drinking water exposure numbers are high-end for the following reasons: 1) they are based upon assumptions of heavy usage in the drainage basin associated with the drinking water intake, 2) they are based on the assumption that applications are made at the maximum possible labeled rates, and 3) they are based on the assumption that applications are made at the minimum labeled intervals. Field trial values were used for all of the food commodities listed above. Field trials are performed using maximum label rates and minimum PHIs. For economic reasons, farmers often do not use the maximum label rates. In addition, when field trials are performed, samples are stored frozen from collection until analysis to prevent breakdown of residues. With the exception of frozen commodities, most foods are not stored frozen from harvest until the time of consumption.

In light of the fact that conservative assumptions were used in determining residue levels in food and drinking water, and that conservative assumptions were also used in determining residential exposure estimates, HED is confident that the aggregate cancer risk estimates do not underestimate cancer risk to the general U.S. population.

7.0 CUMULATIVE RISK CHARACTERIZATION/ASSESSMENT

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding involving thiophanate-methyl. Thiophanate-methyl and its metabolite, MBC, are members of the benzamidazole class of carbamates. MBC is a major environmental degradate of thiophanate-methyl, and in fact, the fungicidal activity of thiophanate-methyl depends upon conversion to MBC in the environment. In the 2005 RED document for thiophanate methyl, the risk for thiophanate-methyl was combined with that of MBC because it is the primary environmental metabolite. For the present risk assessment, the toxicology database was reevaluated to determine whether it was appropriate to combine thiophanate-methyl and MBC, based on their toxicity profiles. The HED HASPOC determined that the available data do not establish sufficient commonality of effects to show a common mechanism of toxicity (Memo, L. Hansen to HED HASPOC, 6/4/2007). The toxicological profiles of thiophanate-methyl and MBC show different effects. For example, the thyroid is a major target organ of thiophanate-methyl, but not of MBC. MBC caused severe lesions to the liver, but effects from thiophanate-methyl were limited to hypertrophy. Developmental findings in the rat and rabbit were also distinct for the two compounds. *In utero* fetal exposure to thiophanate-methyl was associated with an increased incidence of supernumerary ribs in the rat, but no findings were reported in the rabbit. Fetal exposure to MBC was associated with an increase in malformations. In the rabbit, there was an increase in the incidence of skeletal alterations (fused ribs, malformed cervical vertebrae). In the rat, there was an increase in the incidence of a variety of malformations of the head, eyes, paws, and skeleton. Based on these findings, EPA has not assumed that thiophanate-methyl has a common mechanism of toxicity with MBC. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

8.0 OCCUPATIONAL EXPOSURE/RISK ASSESSMENT PATHWAY

Reference: Thiophanate-Methyl: Occupational Exposure/Risk Assessment of Thiophanate-Methyl for Crop Protection Uses on Cotton, Canola, Berries, Various Vegetable Crops, Citrus, Pistachios, Tree Nuts and Mushroom, and for Seed Treatment Uses on Cotton, Sweet Corn, Leafy Brassica Greens, and Sunflower, D335120, S. Wang, 3/24/2009.

HED has prepared an occupational exposure assessment for the proposed uses of thiophanate-methyl (Memo, D335120, S. Wang, 3/24/2009). As occupational exposures are not aggregated with dietary and/or residential exposures, the results of the occupational exposure assessment will not affect the conclusions made in this risk assessment. The occupational exposure memorandum will address risk to workers and conclusions concerning occupational risk mitigation.

9.0 DATA NEEDS AND LABEL RECOMMENDATIONS

9.1 Toxicology

A developmental thyroid study is required to address residual concerns for potential effects of thiophanate-methyl on thyroid function in early development. This study supersedes the requirement from the 2007 hazard assessment for a developmental neurotoxicity study with thyroid measures. A 90-day inhalation toxicity study is also required (Data Call-In of 2005 RED document). In addition, as part of the new Part 158 data requirements, an immunotoxicity study in the rat and/or mouse is required (See Appendix A.1). HED recommends that RD make the submission of these studies a condition of registration of the uses on the proposed commodities.

9.2 Residue Chemistry

HED has examined the residue chemistry database for thiophanate-methyl. Pending submission of a revised Section B (see requirements under Directions for Use), and a revised Section F (see requirements under Proposed Tolerances), there are no residue chemistry issues that would preclude granting a registration for the requested uses of thiophanate-methyl on bushberries, caneberries, cotton (with conditional, regional registration), ginseng, leafy *Brassica* greens (including turnip greens), mushroom, mustard grown for seed (with regional registration), pistachio, sunflower, tomato (with regional registration), sweet corn, and tree nuts, or establishment of tolerances for thiophanate-methyl on these commodities. A list of the recommended tolerances is given in Appendix B, Table B.1.

860.1200 Directions for Use

- Application equipment to be used for application as well as minimum spray volumes are needed for all use directions, except those for pistachio.

- Bushberries and caneberries must be removed from the SC label.

- For agaricus mushroom, the directions for the bed drench applications must be modified to state that applications may not be made if the nutrient supplement mix application at spawning (at 4.9 lb ai/8,000 ft^2) was made.

- For mustard grown for seed, the use directions must be amended to specify a PHI of 40 days.

- For sunflower, Section B must be modified to reflect the use pattern of the crop field trials and the application rate specified on labels for the WP, WDG, and SC formulations: seed treatment at 0.126 lb ai/100 lb of seed.

- For tomatoes and tomatillos, the proposed use directions for soil drench must be modified to reflect the use rate of the crop field trials: soil drench using a solution of 0.35 lb ai/100 gal. In addition, the maximum seasonal rate must be amended to specify that a maximum

of 2.8 lb ai/A may be applied foliarly per season, and the use directions must be amended to specify that applications to field-grown tomatoes/tomatillos may only be made to tomatoes/tomatillos grown east of the Rocky Mountains. Tomatoes and tomatillos must be removed from the SC label.

- To support the use of the SC formulation on caneberries and bushberries, the registrant needs to submit additional field trial data. The registrant needs to submit two side-by-side field trials for bushberries and one side-by-side trial for caneberries in which the WP and SC formulations are used. If the residues in the SC trials are considerably higher than they are in the WP trials, a full set of field trial data will be required.

- Because of risk issues, HED cannot recommend in favor of tolerances for citrus fruits. As a result, this proposed use must be deleted from Section B and all thiophanate-methyl labels.

- Inadequate data are available to support the proposed combined seed treatment plus foliar application use on cotton. The seed treatment uses must be deleted from the proposed labels for all formulations, or the seed treatment rate lowered to reflect the submitted field trial data.

- Label restrictions must be added to the labels limiting use of all formulations to picker cotton types only.

- Inadequate data are available to support the proposed seed treatment use on leafy *Brassica* greens and turnip greens. This proposed use must be deleted from Section B as well as from the labels for the WP, WDG, and SC formulations.

- The proposed use directions for sweet corn must be modified to include the restrictions required by the Federal Seed Act for treated seed. The requirements for coloring treated seed are described in 40CFR §153.155.

860.1380 Storage Stability

- As a condition of registration, storage stability data for thiophanate-methyl and MBC need to be submitted for the processed commodities of tomato (paste and puree). Processed samples were stored for 18.2 months prior to analysis. As a result, the storage interval in the storage stability study must be at least 18.2 months. Alternatively, data could be provided to show the stability of residues in citrus processed commodities for that time period.

860.1550 Proposed Tolerances

- The proposed tolerances should be revised to reflect the recommended tolerance levels and correct commodity definitions as specified in Appendix B.

Processed Food/Feed

- Cotton: HED recommends that conversion of conditional registration to unconditional registration for cotton be considered upon submission of the following outstanding residue chemistry data: the cotton processing study needs to be repeated at an exaggerated rate (up to 5x the nominal field rate) in an attempt to obtain quantifiable residues in the cotton seed to be processed.

860.1500 Crop Field Trials

- Cotton: If the petitioner wishes to register seed treatment plus foliar uses on cotton, a full set of geographically representative data must be submitted, reflecting seed treatment plus foliar applications at the maximum proposed application rate.

- Caneberries and Bushberries: To support the use of the SC formulation on caneberries and bushberries, the registrant needs to submit additional field trial data. The registrant needs to submit two side-by-side field trials for bushberries and one side-by-side trial for caneberries in which the WP and SC formulations are used. If the residues in the SC trials are considerably higher than they are in the WP trials, a full set of field trial data will be required.

- Leafy *Brassica* greens/turnip greens: If the petitioner wishes to register seed treatment plus foliar uses on leafy *Brassica* greens and turnip greens, a full set of geographically representative data must be submitted, reflecting seed treatment plus foliar applications at the maximum proposed application rate. The registrant needs to submit the results of seven trials performed with the SC formulation.

- Tomato: If the petitioner wishes to register use of thiophanate-methyl on tomato without geographic restrictions, an additional 10 crop field trials, conducted in Zone 10, would be required. If the registrant wishes to register use of the SC formulation on tomatoes, a full set of field trials performed with this formulation will be required.

- Tuberous and corm vegetables: If the petitioner wishes to register the proposed use of thiophanate-methyl on tuberous and corm vegetables, five additional field trials are still required as stipulated in the HED Residue Chemistry Chapter of the thiophanate-methyl RED (i.e., potato seed piece treatment followed by three foliar applications).

- Citrus: Provided risk considerations permit use on citrus in the future, residue data would be needed to support use of the SC formulation.

9.3 Residential Exposure

None

9.4 Occupational Exposure

Refer to Memo, D335120, S. Wang, 3/24/2009.

REFERENCES

Thiophanate-Methyl: HED Human Health Risk Assessment for the Reregistration Eligibility Decision (RED) Document. Chemical No. 102001, D275774, D. Smegal, 4/25/2002

Toxicology Chapter for Thiophanate Methyl and Carbendazim, TXR# 0050563, D279278, D. Smegal, 3/12/2002

Toxicology Summary of Proposed New Uses (Including Summary of Carbendazim Toxicity), TXR# 0054610, D340134, 9/12/2007

Thiophanate-methyl. Topsin ® M 70WP (EPA Reg. No. 73545-11) and Topsin M 4.5FL (EPA Reg. No. 73545-13). Addition of Uses on Bushberries, Juneberry, Lingonberry, Salal, Caneberries, Citrus, Ginseng, Leafy Brassica Greens, Turnip Greens, Mushroom, Mustard, Pistachio, Sunflower, Tomato, Tomatillo, Tree Nuts, and Tuberous and Corm Vegetables (PP#6E7075). Topsin ® M 70WP (EPA Reg. No. 73545-11), Topsin M 4.5FL (EPA Reg. No. 73545-13), Topsin ® M WSB (EPA Reg. No. 73545-16), and Topsin ® M 70 WDG (EPA Reg. No. 73545-18). Addition of Use on Cotton (PP#6F7069). Summary of Analytical Chemistry and Residue Data. D304364, J. Stokes, 3/19/2009

Thiophanate-methyl. Topsin M 4.5FL (EPA Reg. No. 73545-13). Addition of Foliar Use of FIC Formulation on Canola (PRIA R35) and Seed Treatment use on Sweet Corn (IR-4 Request; PP#2E6478). Summary of Analytical Chemistry and Residue Data., D315774, J. Stokes, 4/2/2009

Thiophanate-methyl Acute Probabilistic, Chronic, and Cancer Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessment for the Section 3 Registration Action, D360625, A. Parmar, 6/24/2009

Usage Report in Support of Registration for the Fungicide Thiophanate-methyl (102001), D362434, A. Grube, 3/4/2009

Projected Percent Crop Treated (PPCT) with the Fungicide Thiophanate-methyl on Citrus Crops: PC Code: 102001, DP Barcode: D360131, 2/25/2009

Projected Percent Crop Treated (PPCT) for the Fungicide Thiophanate-methyl on Raspberries and Tomatoes, D361056, J. Carter, 3/13/2009

Revised Residential Exposure Assessment for Use of Thiophanate-methyl on Turf, D360623, M. Collantes, 3/4/2009

Thiophanate-methyl and degradate methyl 2-benzimidazolylcarbamate or carbendazim (MBC) for additional food uses and IR-4 crops, D335121, R. Parker, M. Barrett, 3/19/2009

Revised Thiophanate-methyl: Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document, D279269, G. Bangs, 5/2/2002

Thiophanate-Methyl: Occupational Exposure/Risk Assessment of Thiophanate-Methyl for Crop Protection Uses on Cotton, Canola, Berries, Various Vegetable Crops, Citrus, Pistachios, Tree Nuts and Mushroom, and for Seed Treatment Uses on Cotton, Sweet Corn, Leafy *Brassica* Greens, and Sunflower, D335120, S. Wang, 3/24/2009

Appendix A: Thiophanate-methyl Toxicology

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for food use for thiophanate-methyl are in Table A.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	-
870.3465 90-Day Inhalation	yes	no
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5300 Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5550 Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotox. (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b 90-Day Neuro. Screening Battery (rat)	yes	yes
870.6300 Develop. Neuro	no	-
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no	-
870.7800 Immunotoxicity	yes	no
Special study – Developmental Thyroid (rat)	yes	no
Special Studies for Ocular Effects		
Acute Oral (rat)	no	-
Subchronic Oral (rat)	no	-
Six-month Oral (dog)	no	-

Appendix A.1 (continued)

Rationale for Toxicology Data Requirements.

Guideline Number: 870.7800 **Study Title: Immunotoxicity**
Rationale for Requiring the Data
The immunotoxicity study is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses). The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies not specifically conducted to assess immunotoxic endpoints are inadequate to characterize a pesticide's potential immunotoxicity. While data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies may offer useful information on potential immunotoxic effects, these endpoints alone are insufficient to predict immunotoxicity.
Practical Utility of the Data
How will the data be used? Immunotoxicity studies provide critical scientific information needed to characterize potential hazard to the human population on the immune system from pesticide exposure. Since epidemiologic data on the effects of chemical exposures on immune parameters are limited and are inadequate to characterize a pesticide's potential immunotoxicity in humans, animal studies are used as the most sensitive endpoint for risk assessment. These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997). **How could the data impact the Agency's future decision-making?** If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data. If the Agency does not have these data, a 10X database uncertainty factor may be applied for conducting a risk assessment from the available studies.

Appendix 2: Toxicity Profiles of Thiophanate-methyl

Table A.2.1: Acute Toxicity Profile of Thiophanate-methyl (tech. a.i.)				
Guideline No.	**Study Type**	**MRID #**	**Results**	**Toxicity Category**
870.1100	Acute Oral, Rat	41644301	LD_{50} >5000 mg/kg, both sexes	IV
870.1200	Acute Dermal, Rabbit	41644302	LD_{50} >2000 mg/kg, both sexes	III
870.1300	Acute Inhalation, Rat	41482804	LC_{50} = 1.7 mg/L, males 1.9 mg/L, females	III
870.2400	Primary Eye Irritation, Rabbit	40095501	Slight ocular irritant	IV
870.2500	Primary Skin Irritation, Rabbit	40095502	Not a dermal irritant	IV
870.2600	Dermal Sensitization, Guinea Pig	41482805	Is a dermal sensitizer	N/A

N/A: Not applicable to this guideline study

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Thiophanate-methyl			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day dietary toxicity (rat)	42001701 (1990) Acceptable/guideline Males 0, 13.9, 155.0, 293.2, 426.9 or 564.7 mg/kg/day Females 0, 15.7, 173.4, 323.0, 478.8 or 647.3 mg/kg/day 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	90-Day oral (capsule) toxicity (beagle dog)	41982203 (1992) Acceptable/guideline 0, 50, 200 or 800 mg/kg/day 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 (threshold) = 50 mg/kg/day, based on slight thyroid hypertrophy in 1 male and 1 female. At 200 mg/kg/day, 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 were observed. At 800/400 mg/kg/day, mortality (1 male), increased platelet count were also observed.
870.3200	21/28-Day dermal toxicity (NZW rabbit)	42110801 (1991) Acceptable/guideline 0, 100, 300 or 1000 mg/kg/day, 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	14-Day inhalation toxicity (rat)	42527601 (1992) Unacceptable/nonguide-line 0.0, 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.2.2 Subchronic, Chronic and Other Toxicity Profile for Thiophanate-methyl			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700a	Prenatal developmental in (rat)	00106090 (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 mg/kg/day (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	Prenatal developmental in (rat)	00146643 (1985) Acceptable/nonguideline 0, 18, 85, or 163 mg/kg/day (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	Prenatal developmental in (NZW rabbit)	45051001 (1997) Acceptable/guideline 0, 5, 10, 20, or 40 mg/kg/day (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
870.3700b	Prenatal developmental in (NZW rabbit)	40028801, 41056701 (1986) Unacceptable/nonguide-line 0, 2, 6 or 20 mg/kg/day (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

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Thiophanate-methyl			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3800	Reproduction and fertility effects (rat)	42899101 to -05 (1993); 43624401 (1995) Acceptable/guideline Males 0, 13.7, 43.3 or 138.9 mg/kg/day; Females 0, 15.5, 54.0 or 172.0 mg/kg/day (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 in males (females affected at mid and high dose). 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). Slight increase in TSH of P animals at Week 8. 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. Thyroid hypertrophy/hyperplasia seen at 138.9 mg/kg/day in males (F1 examined). Slight increase in TSH at Week 8 in F1 males.
870.3800	Reproduction and fertility effects (CD rat)	00117870 (1972) Unacceptable/guideline (upgradable with submission of test material purity) 0, 2, 8 or 32 mg/kg/day (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. Thyroid/liver not evaluated. Offspring NOAEL = 8 mg/kg/day Offspring LOAEL = 32 mg/kg/day, based on slightly decreased mean litter weights.
870.4100a	Chronic toxicity (rat)	See 870.4300	See 870.4300

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Thiophanate-methyl			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.4100b	Chronic toxicity (beagle dog)	42311801 (1992) Acceptable/guideline 0, 8, 40 or 200 mg/kg/day 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.
870.4200a	Carcinogenicity (rat)	See 870.4300	See 870.4300
870.4200b	Carcinogenicity (mouse)	42607701 (1992) Acceptable/guideline Males 0, 23.7, 98.6, 467.6 or 1078.8 mg/kg/day; Females 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.2.2 Subchronic, Chronic and Other Toxicity Profile for Thiophanate-methyl			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.4300	Combined chronic toxicity/carcinogenicity (rat)	42896601 (1993) Acceptable/guideline Males 0, 3.3, 8.8, 54.4 or 280.6 Females 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.
870.4300	Combined chronic toxicity/carcinogenicity (rat)	00017868 (1972) 0, 10, 40, 160 or 640 ppm (estimated at 0, 0.370, 1.54, 5.75 or 24.3 mg/kg/day, males and 0, 0.399, 1.62, 7.18 or 28.7 mg/kg/day, females) Unacceptable/guideline (not upgradable)	NOAEL = 5.75 mg/kg/day LOAEL = 24.3 mg/kg/day, based on decreased body weight/weight gain in males and females, increased thyroid epithelial cell columnar height, colloidal substance and hypertrophy in males and decreased spermatogenesis at termination in males. However, it was noted that testicular atrophy that was seen in some animals was not correlated with microscopic lesions to the testes. No evidence of carcinogenicity was observed but the overall number of surviving animals in the study was low.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Thiophanate-methyl			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
Gene Mutation 870.5100	Ames Assay (*S. typhimurium* and *E. coli* reverse gene mutation)	41608910 Acceptable/guideline 39.1 to 312.5 µg/plate without S9; 39.1 to 5000 µg/plate with S9	Not mutagenic with or without S9 activation in *S. typhimurium*
Gene Mutation 870.5100	Ames Assay (*S. Typhimurium* preincubation reverse gene mutation)	Published study (Zeiger *et al.* 1992, not submitted to Agency) Acceptable/nonguideline 0 to 10,000 µg/plate with or without rat or hamster liver S9. Tech., 95.1%	Weak equivocal response: 2-fold increases in revertant colonies of strains TA98 and TA100 at ≥3333.0µg/plate (precipitating concentration) with S9 and negative results in second assay. Negative response without S9.
Mammalian Cell *In Vitro* Cytogenetics 870.5375	*In Vitro* Mammalian Cell Cytogenetic Assay in Chinese Hamster Ovary (CHO Cells)	40980101 (1988) Acceptable/guideline 0 to 400 µg/ml culture medium without rat liver S9 and 0 to 1000 µg/mL with S9 Tech., 95% a.i.	Negative for structural chromosomal aberrations. Mitotic delay increased at 100 µg/ml without S9 and 335 µg/mL with S9. Cytotoxicity/compound insolubility observed at 400 µg/mL without S9 and 750 µg/ml with S9.
Mammalian Cell *In Vivo* Cytogenetics 870.5385	*In Vivo* Mouse Bone Marrow Micronucleus Assay	Published study (Barale, 1993, not submitted to Agency) Acceptable/nonguideline 1 mg/kg body weight, single gavage dose Tech., 95% a.i.	Borderline significant increase in polyploidy and hyperploidy. No increase in structural chromosomal aberrations.
Unscheduled DNA synthesis 870.5550	*In Vitro* Unscheduled DNA Synthesis Assay in Primary Rat Hepatocytes	40095503 (1981) Acceptable/guideline 0 to 1000 µg/mL culture medium tech., 99.8% a.i.	Negative for UDS induction at all doses tested. Cytotoxic at 1000 µg/mL.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Thiophanate-methyl			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
Other Effects (no guideline number)	*In Vitro* Cell Transformation Assay in BALB/c 3T3 Cells	Published report (Perocco *et al.*, 1997; not submitted to the Agency) Acceptable/nonguideline 0 to 200 µg/mL culture medium with rat liver S9; 0 to 25 µg/mL without S9 Tech., 99.5% a.i.	Significant and reproducible increase in morphologically transformed foci at 25 µg/mL without S9 and ≥20 µg/ml with S9. Cytotoxicity observed at ≥25 µg/mL (pronounced at ≥50 µg/mL) without S9; only weak cytotoxicity with S9 (most pronounced at 100-200 µg/mL).
870.6200a	Acute neurotoxicity screening battery (Crl:CD(SD) rat)	48729901 (2005) Acceptable/guideline Initial study 0, 500, 1000 or 2000 mg/kg (gavage) Extension study 0, 50, 125, 500 or 2000 mg/kg (gavage)	NOAEL = not established (<50 mg/kg/day) LOAEL = 50 mg/kg/day (lowest dose tested) based on decreased landing foot splay in males and females on the day of dosing at all doses tested.
870.6200b	Subchronic neurotoxicity screening battery (Crl:CD(SD) rat)	48729902 (2005) Acceptable/guideline 0, 100, 500 or 2500 ppm Males 0, 6.2, 30.3 or 149.6 mg/kg/day; Females 0, 6.8, 34.9 or 166.3 mg/kg/day Tech., 99.7% a.i.	NOAEL = 30.3 mg/kg/day LOAEL = 149.6 mg/kg/day based on decreased body weight/weight gain and decreased food consumption in females and increased liver and thyroid weights (not examined microscopically).

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Thiophanate-methyl			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.7485	Metabolism and pharmacokinetics (rat)	42474802, 42601601 (1992) Acceptable/guideline low oral radiolabeled 14 mg/kg; repeated oral unlabeled 14 mg/kg for 14 days, followed by single radiolabeled; high oral radiolabeled 170 mg/kg Tech., 97.3%-98.5% radiochemical purity ^{14}C-thiophanate-methyl	Thiophanate-methyl was rapidly absorbed, metabolized and excreted at all dose levels (>90% within 24 hrs). Radioactivity did not accumulate in tissues (highest concentrations were in thyroid, 0.04-2.49 µg/g; liver, 0.17-2.15 µg/g; kidney 0.04-0.51 µg/g). Plasma half life for low, high and repeated doses was 2.8, 2.2 and 7.8 hrs, males and 2.5, 1.6 and 4.0 hrs, females. T_{max} was achieved at 1-2, 2-3 and 4-7 hrs at single low, repeated low and single high doses, respectively. The primary route of excretion was urinary following a single low oral dose (70-72% of administered radioactivity) but was fecal after repeated low (48-49%) or single high (67-70%) doses. Excretion in CO_2 was negligible. Metabolite profiles were qualitatively similar for all groups. Twelve identified and 4 unknown urinary metabolites were identified, including methyl 2-benzimidazolylcarbamate (MBC, 0.2 to 2.2% of recovered radioactivity) and other sulfate-conjugated and/or hydroxylated derivatives of the parent compound. The major urinary metabolite was 5-hydroxy(2-methoxycarbonylamino) benzimidazolyl sulfate (14-42%). Seven identified and 2 unknown fecal metabolites were identified; the major fecal metabolite was dimethyl[1,2-(4-hydroxyphenylene)]bis (iminocarbonothioyl)bis (carbamate) (3.5-11%). MBC was also identified in feces (0.5-2.7%). After a single low dose the parent compound was almost completely metabolized (1% of dose excreted), but it was the major excreted compound in feces of the repeated low dose (21-24%) and single high dose (52-56%) groups. No significant differences in metabolism were reported between males and females.

Table A.2.3: Special thyroid and liver mechanistic studies, supplement to chronic feeding/oncogenicity study in rats (MRID 42896601b; 1996-Acceptable/Non-guideline)

Guideline	Purpose of study	Doses	Results
None	(1) Effect of short-term dietary administration of TM on liver and thyroid weights; circulating T3/T4 and TSH and serum cholesterol in male F344 rats	0 or 6000 ppm for 2 or 8 days Tech., 96.55% a.i. (all experiments in this study) Positive control groups: 500 ppm phenobarbital (liver enlargement) and 1000 ppm propylthiourea (PTU; antithyroid activity)	TM caused liver and thyroid enlargement; increased serum cholesterol and TSH; decreased T3 and T4 (decreases marginal at day 8). Phenobarbital (PB) caused liver enlargement and increased T3, T4, TSH and cholesterol at day 8. PTU caused thyroid and liver enlargement; increased TSH and cholesterol; decreased T3 and T4 (slight).
	(2) Reversibility of thyroid enlargement following termination of short-term dietary administration of TM in female F344 rats	0 or 6000 ppm for 8 days; half sacrificed on day 8 and half given basal diet for 8 additional days Positive (liver)/negative (thyroid) control group: 500 ppm Phenobarbital	Withdrawal of TM after 8 days' treatment caused reversal of the thyroid enlargement. Treatment with PB for 8 days' and subsequent withdrawal and recovery had no significant effect on thyroid weight.
	(3) Effect of T4 supplementation on thyroid and liver weights, TSH and serum cholesterol during short-term dietary administration of TM in male F344 rats	0 or 6000 ppm for 8 days; half of animals also received daily injections of 30 µg/kg L-thyroxine	Supplementation with T4 prevented thyroid enlargement and increased TSH but not liver enlargement or increased serum cholesterol.
	(4) Effect of TM on hepatic microsomal enzyme activities and protein concentration following short-term administration of TM to male F344 rats (livers collected from animals of study 1)	0 or 6000 ppm for 8 days Positive control: 500 ppm PB for 8 days	TM caused an increase in cytochromes p-450 and b5, and a pronounced increase in UDP-glucuronosyltransferase. Microsomal protein was also increased. PB caused an increase in cytochromes p-450 and b5, NADPH-cytochrome c reductase, UDP-glucuronosyltransferase and microsomal protein.
	(5) Effect of TM on porcine microsomal thyroid peroxidase activity	10^{-3} to 10^{-4}M, Guaiacol method Positive control: 10^{-4} to 10^{-6} PTU	The ED_{50} (effective dose to achieve 50% inhibition of thyroid peroxidase) for TM was 6 x 10^{-4}M and no inhibition was reported at 8 x 10^{-5} M (about 30-fold greater than PTU). The ED_{50} for PTU was 2 x 10^{-5}M and no inhibition was reported at 4 x 10^{-7}M.

Table A.2.3: Special thyroid and liver mechanistic studies, supplement to chronic feeding/oncogenicity study in rats (MRID 42896601b; 1996-Acceptable/Non-guideline)			
Guideline	**Purpose of study**	**Doses**	**Results**
	(6) Effect of TM on hepatocyte proliferation as measured by PCNA immunohistochemical staining following treatment with TM in male F344 rats and ICR mice	0 or 6000 ppm for 2 or 8 days Positive control: 500 ppm Phenobarbital	In mice, TM caused a sustained increase in PCNA staining and liver enlargement after 2 and 8 days' treatment. In rats, PCNA staining was increased at day 2 but not day 8; liver weights were increased at both times. In mice, PB caused increased PCNA staining at days 2 and 8 but less pronounced at day 8 than day 2. In rats, PCNA staining was increased at day 2 but not day 8. Liver weights were increased at both times.

Appendix B: Tolerance Summary for Thiophanate-methyl

Table B.1.	**Tolerance Summary for Thiophanate-Methyl**			
Commodity	Proposed Tolerance (ppm)	Established Tolerance[1] (ppm)	Recommended Tolerance (ppm)	Comments/ *Correct Commodity Definition*
Tolerances to be established under 40 CFR 180.371(a):				
Almond	--	0.1	Revoke	When the tolerance for the tree nut crop group is established, the tolerance for almond should be revoked.
Almond, hulls	14	0.5	20	
Brassica leafy greens subgroup	7.0	None	8.0	*Brassica, leafy greens, subgroup 5-B*
Bushberry subgroup	4.0	1.5[2]	5.0	*Bushberry subgroup 13-07B*
Caneberry subgroup	25	None	25	*Caneberry subgroup 13-07A*
Cattle, fat	None	*0.15*[3]	Revoke	There is no expectation of finite residues in animal commodities. These tolerances can be revoked.
Cattle, meat	None	*0.15*[3]	Revoke	
Cattle, meat byproducts	None	*0.15*[3]	Revoke	
Citrus group	6.0	0.5[3]	None	HED does not recommend in favor of a tolerance for this crop group because of risk issues.
Corn, Sweet	0.05	None	0.14 0.14 0.14	Separate tolerances are needed for the following commodities: *Corn, sweet, kernel plus cob with husks removed* *Corn, sweet, forage* *Corn, sweet, stover*
Ginseng	0.3	None	0.30	
Goat, fat	None	*0.15*[3]	Revoke	There is no expectation of finite residues in animal commodities. These tolerances can be revoked.
Goat, meat	None	*0.15*[3]	Revoke	
Goat, meat byproducts	None	*0.15*[3]	Revoke	
Juneberry	4.0	None	None	Juneberry and Lingonberry are now part of the Bushberry Subgroup (13-07B). Separate tolerances are not needed.
Lingonberry	4.0	None	None	
Horse, fat	None	*0.15*[3]	Revoke	There is no expectation of finite residues in animal commodities. These tolerances can be revoked.
Horse, meat	None	*0.15*[3]	Revoke	
Horse, meat byproducts	None	*0.15*[3]	Revoke	
Milk	None	*0.15*[3]	Revoke	
Mushroom	0.09	0.01[4]	2.0	
Pecan	--	0.1	Revoke	When the tolerance for the tree nut crop group is established, the tolerance for pecan should be revoked.
Pistachio	0.9	0.1	0.90	

Table B.1.	**Tolerance Summary for Thiophanate-Methyl**			
Commodity	Proposed Tolerance (ppm)	Established Tolerance[1] (ppm)	Recommended Tolerance (ppm)	Comments/ *Correct Commodity Definition*
Salal	4.0	None	None	Part of Bushberry Subgroup, separate tolerance not needed.
Sheep, fat	None	*0.15*[3]	Revoke	There is no expectation of finite residues in animal commodities. These tolerances can be revoked.
Sheep, meat	None	*0.15*[3]	Revoke	
Sheep, meat byproducts	None	*0.15*[3]	Revoke	
Sunflower	0.05	None	0.20	*Sunflower, seed*
Tomatillo	1.4	None	None	A separate tolerance is not needed for tomatillo as it is covered by the proposed tolerance for tomato.
Tree Nuts Crop Group	0.2	None	0.20	*Nut, tree, group 14*
Tuberous and Corm subgroup	0.1	None	0.1	*Vegetable, tuberous and corm, subgroup 1-C*
Turnip Greens	7.0	None	8.0	*Turnip, greens*
Tolerances to be established under 40 CFR 180.371(c):				
Cotton, undelinted seed	0.05	0.05[4]	0.05	
Cotton, gin byproducts	14.0	5.0[4]	8.0	
Mustard (grown for seed)	0.1	None	0.20	*Mustard, seed*
Tomato	1.4	None	1.4[5]	

[1] Established under §180.371(a) unless otherwise indicated.
[2] Established under §180.371(b) for blueberry.
[3] Tolerances in *italics* were not proposed by the petitioners; these are the recommended tolerances for these commodities in the 9/20/06 FR notice proposing revisions to the existing thiophanate-methyl tolerances.
[4] Established under §180.371(b).
[5] Establishment of this tolerance with regional registration is dependent upon the petitioner modifying the proposed use directions to include geographic restrictions (to conform with the use pattern of the supporting crop field trial data). Additional crop field trial data would be required before this tolerance can be established without regional registration.

13544

R172111

Chemical Name: Thiophanate-methyl

PC Code: 102001
HED File Code: 14000 Risk Reviews
Memo Date: 6/24/2009
File ID: 00000000
Accession #: 000-00-0130

HED Records Reference Center
7/7/2009