Proposed Re-evaluation Decision PRVD2019-07

Thiophanate-Methyl and Its Associated End-use Products

Consultation Document

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Proposed Re-evaluation Decision

Under the authority of the *Pest Control Products Act*, all registered pesticides must be regularly re-evaluated by Health Canada's Pest Management Regulatory Agency (PMRA) to ensure that they continue to meet current health and environmental safety standards and continue to have value. The re-evaluation considers data and information from pesticide manufacturers, published scientific reports, and other regulatory agencies. Health Canada applies internationally accepted risk assessment methods as well as current risk management approaches and policies.

Thiophanate-methyl is a fungicide that controls a broad spectrum of diseases on a wide variety of crops and use sites in Canada, including greenhouse non-food crops, terrestrial food crops, mushrooms, outdoor ornamentals, turf and seed treatment for food and feed (sweet corn, beans, potato seed pieces). Formulations of commercial end-use products include: wettable powder, dust or powder, wettable powder in water soluble bag, suspension or solution. Thiophanate-methyl can be applied using conventional ground application equipment, by air and as a seed treatment. A full list of products containing thiophanate-methyl can be found in Appendix I or the online Pesticide Label Search at Canada.ca.

Health Canada published a Proposed Re-evaluation Decision (PRVD2011-07) in 2011 that identified potential risks of concern for human health and the environment and the additional information required to refine the risk assessments. Subsequently in 2012, an update on the re-evaluation of thiophanate-methyl was published (REV2012-14) summarizing the main areas of focus (in other words, toxicology, occupational and dietary assessments including drinking water) that would be updated and the revised data requirements.

Health Canada has since received the required new data/information and has updated the health and environmental risk assessments to incorporate the revised registrant-supported use pattern, revised toxicology reference values and current methods/policy. Extensive comments related to the health and environmental risk assessments received during the consultation were also considered in the updated risk assessments.

This document presents the proposed regulatory decision for the re-evaluation of thiophanate-methyl, including the proposed risk mitigation measures to further protect human health and the environment, as well as the science evaluation on which the proposed decision was based. All products containing thiophanate-methyl registered in Canada are subject to this proposed re-evaluation decision. This document is subject to a 90-day public consultation period, during which the public, including the pesticide manufacturers and stakeholders, may submit written comments and additional information to the PMRA. The final re-evaluation decision will be published, taking into consideration the comments and information received.

Outcome of Science Evaluation

Based on the current use pattern of thiophanate-methyl, human health risks were shown to be acceptable for most uses with proposed risk mitigation measures. For certain other uses, health risks were identified and the cancellation of these uses is proposed.

Thiophanate-methyl and its major transformation product, carbendazim, enter the environment when thiophanate-methyl is used to control fungal pests on a variety of sites. After a review of the available scientific information, the risks of thiophanate-methyl have been shown to be acceptable to the environment when used according to the revised use pattern and label instructions.

Thiophanate-methyl is an important component of pest management programs to control economically important diseases and it is an important rotational fungicide for managing disease resistance in susceptible pathogens, as it is the only Group 1 mode of action registered on several agricultural use sites.

Proposed Regulatory Decision for Thiophanate-methyl

Under the authority of the *Pest Control Products Act* and based on the evaluation of currently available scientific information, Health Canada is proposing continued registration for uses of thiophanate-methyl that have acceptable risk with mitigation measures. Uses of thiophanate-methyl where risks to human health are not shown to be acceptable are being proposed for cancellation.

Labels of registered pesticide products include specific instructions for use that must be followed by law. Directions include risk-reduction measures to protect human and environmental health. The key risk-reduction measures being proposed to address the potential risks identified as a result of the re-evaluation of thiophanate-methyl are as follows. See details in Appendix XI.

Human Health

Proposed cancellation for the following uses:

- Aerial application using wettable powder products.
- Wettable powder products on all turf uses, white bean, sugarbeet, aspen and poplar.
- All turf uses except on golf courses and sod farms for the liquid and water-soluble packaging products.
- Greenhouse tobacco seedlings (foliar spray and foliar drench applications).
- Greenhouse cut flowers (foliar application).
- Outdoor cut flowers.
- Apples and pears in British Columbia due to the high application rate (this use in Eastern Canada has acceptable risks due to the lower application rate).
- Peach, nectarine, plum, prune, cherry.
- Commercial seed treatment of bean seeds using wettable powder products.
- On-farm dry application to bean seeds using wettable powder products.
- Potato seed piece treatment for all product formulations.

Proposed continued registration for the remaining uses with mitigation measures:

- To protect mixers/loaders and applicators, additional personal protective equipment (PPE), engineering controls, and limits on amount of product handled per day.

- To protect workers entering treated areas, revise or establish restricted-entry intervals (REIs), limit number of applications per season, limit greenhouse cut flower applications to soil drench only.

Environment

- Precautionary label statements to inform the user that thiophanate-methyl is toxic to bees, earthworms, birds, small and medium sized mammals, and aquatic organisms.
- Label statements to advise users to avoid application during periods of bloom for crops that are attractive to pollinators.
- A label statement to inform the user to not discharge thiophanate-methyl-contaminated effluent from greenhouses and mushroom houses into aquatic environments.
- Precautionary label statements informing users of ways to reduce the potential for runoff.
- The use of spray buffer zones to protect non-target aquatic habitats.

International Context

Thiophanate-methyl is currently acceptable for use in other Organisation for Economic Co-operation and Development (OECD) member countries, including Norway, Switzerland, Australia, European Union member countries, New Zealand, and the United States.

No decision by an OECD member country to prohibit all uses of thiophanate-methyl for health or environmental reasons has been identified.

Next Steps

The public, including the registrants and stakeholders, are encouraged to submit comments and/or additional information that could be used to refine risk assessments during the 90-day public consultation period[1] upon publication of this proposed re-evaluation decision.

All comments and information received during the 90-day public consultation period will be taken into consideration in preparation of the re-evaluation decision document[2], which could result in revised risk mitigation measures. The re-evaluation decision document will include the final re-evaluation decision, the reasons for it and a summary of comments received on the proposed re-evaluation decision with Health Canada's responses.

1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Additional Scientific Information

No additional data are required at this time.

- For the use on apples and pears, Health Canada is seeking comments from British Columbia stakeholders on the agronomic feasibility to adopt the Eastern Canada use pattern (lower rate of thiophanate-methyl in tank-mix with captan), as the higher rates in British Columbia are proposed for cancellation.
- For the uses where changes to the use pattern are proposed as mitigation measures, Health Canada is asking stakeholders if these measures are considered to be agronomically feasible for the management of the pest in the production of the crop across Canada. Stakeholders are asked to provide comment regarding the feasibility of the proposed new buffer zones, including those for aerial application and turf.

Science Evaluation

1.0 Introduction

2.0 Technical Grade Active Ingredient

A description of the technical grade active ingredient, its properties, and the registered uses of thiophanate-methyl in Canada were described in PRVD2011-07, Thiophanate-methyl.

2.1 Description of Registered Thiophanate-Methyl Uses

All registered uses of thiophanate-methyl were supported by the registrant at the time of re-evaluation initiation. However, following the publication of REV2007-12 and PRVD2011-07, the registrant proposed modifications to the registered use pattern, including a reduction in the number of applications, changes to application intervals, limiting the amount of active ingredient that can be applied in a season, and removal of the label claim for powdery mildew on turf. All uses for which thiophanate-methyl is presently registered, as well as changes in the registered use pattern proposed by the registrant, were considered in the health and environmental risk assessments of thiophanate-methyl and are listed in Appendix II.

3.0 Human Health Assessment

A detailed review of the thiophanate-methyl toxicology database was previously conducted by Health Canada and published in PRVD2011-07. Outstanding data requirements identified in PRVD2011-07 were subsequently revised in REV2012-14, and included a request for an extended-one generation reproductive toxicity study (EOGRTS) for carbendazim, a metabolite and environmental degradate of thiophanate-methyl, and a developmental thyroid toxicity study for thiophanate-methyl. The latter requirement was dependent on the results of the carbendazim EOGRTS. Data submitted and considered in this assessment included the requested EOGRTS with carbendazim, a pathology re-read of the two-year carbendazim dietary oncogenicity study in CD-1 mice, as well as acute and subchronic neurotoxicity studies with thiophanate-methyl. Review of the carbendazim EOGRTS indicated that the information was sufficient to fulfill the data gap for thiophanate-methyl, provided an uncertainty factor was applied (Refer to Section 3.1.1). As such, the thiophanate-methyl developmental thyroid toxicity study is no longer required.

The toxicology reference values and the cancer risk assessment for thiophanate-methyl and carbendazim, were revised to reflect the evaluation of additional data and submitted comments, and application of current PMRA science policies, including the application of the *Pest Control Products Act* factor (PCPA factor).

3.1 Toxicology Summary

A detailed review of the toxicology database for thiophanate-methyl and carbendazim was previously conducted and published in REV2007-12 and PRVD2011-07. A summary of those reviews, as well as results from the EOGRTS, acute and subchronic neurotoxicity studies, and the pathology re-read of the two-year carbendazim dietary oncogenicity study in CD-1 mice are provided herein. The scientific quality of the data for thiophanate-methyl and carbendazim is acceptable and the database is considered adequate to characterize the potential health hazards associated with thiophanate-methyl and carbendazim.

As described in PRVD2011-07, both thiophanate-methyl and carbendazim undergo rapid systemic absorption and distribution following oral gavage exposure, with greater than 80% excretion via the urine and feces within 24 hours. Tissue retention was minimal, with the liver and kidney showing the highest tissue concentrations for both compounds, in addition to the thyroid for thiophanate-methyl. Thiophanate-methyl is metabolized by hydroxylation and hydrolysis to carbendazim, which is further metabolized to 5-methoxycarbendazim sulfate, the major urinary metabolite. The major carbendazim metabolite is 5-hydroxy-2-benzimidazole carbamate (5-HBC).

Thiophanate-methyl and carbendazim were of low acute oral and dermal toxicity in various laboratory animal species, and of slight (thiophanate-methyl) or low (carbendazim) inhalation toxicity in rats. Thiophanate-methyl was minimally irritating to the rabbit eye, non-irritating to the rabbit skin and a potential skin sensitizer in guinea pigs in a Maximization test. Carbendazim was non- to mildly irritating to the eyes of rabbits, and skin of rabbits and guinea pigs, and non-sensitizing in guinea pigs in both the Buehler and Maximization tests.

In short- and long-term oral toxicity studies, the liver was the primary target for both compounds. Thiophanate-methyl produced additional effects in the thyroid and kidney, and carbendazim also induced testicular toxicity. The dog was the most sensitive species to thiophanate-methyl-induced thyroid hormone effects.

In a repeat-dose dermal toxicity study in rats with thiophanate-methyl, increased skin irritation was noted at the site of application. Evidence of systemic toxicity, consisting of decreased bodyweight, bodyweight gain and food consumption, was also noted in both sexes in this dermal study. Short-term dermal toxicity studies conducted with carbendazim in rabbits revealed dermal irritation but no systemic toxicity. In a 28-day dermal toxicity study with carbendazim in rats, no signs of dermal irritation were observed, but systemic effects, in the form of testicular toxicity and non-adverse increases in liver weight, were observed. The testicular effects included seminiferous tubule degeneration, sperm granulomas, and increased abnormal sperm, as well as reduced sperm concentration, production and motility. Slight reductions in red blood cell parameters were noted in females as well as slight increases in forelimb and/or hindlimb grip strength in both sexes.

Carbendazim and thiophanate-methyl were not mutagenic, but are well known aneugens, with carbendazim inducing aneugenic effects at lower doses than thiophanate-methyl.

In a rat two-year dietary chronic toxicity/oncogenicity study in rats, thiophanate-methyl induced thyroid follicular cell tumours in male rats. Mechanistic studies were provided to support a non-genotoxic mode of action (MOA) for the observed thyroid tumours in rats. The proposed MOA involves perturbation of thyroid hormone homeostasis via reduction of circulating thyroid hormone as a result of microsomal enzyme induction in the liver and/or inhibition of thyroid hormone synthesis. In the submitted mechanistic studies, thiophanate-methyl inhibited porcine thyroid peroxidase activity in vitro, and induced activities of hepatic cytochrome P-450 enzymes and uridine diphosphoglucuronosyl transferase (UDP-GT) in rats in vivo. Enhanced biliary excretion of T_4 due to the induction of hepatic UDP-GT and/or decreased synthesis of thyroid hormones due to inhibition of thyroid peroxidase can both result in reductions in thyroid hormone levels. As supporting evidence, thyroid follicular cell hyperplasia, increased thyroid weight and thyroid hormone imbalances were observed in rats, mice and dogs in the available toxicity studies. In addition, co-treatment of rats with thiophanate-methyl and T_4 blocked the thiophanate-methyl-induced thyroid enlargement and elevation in serum thyroid stimulating hormone (TSH). Species differences in the metabolism of thyroid hormones and the T_3/T_4 – TSH feedback mechanism between rats and humans have been well documented, with humans being less sensitive than rats.[3] As a result of constant stimulation of the thyroid gland and the continuous increase of TSH levels, rats develop thyroid tumours, while in humans, this is not observed, even after long-term clinical treatment with high doses of drugs that enhance elimination of thyroid hormones. Thus, thyroid tumours in rats resulting from chronic stimulation of the thyroid by TSH, is not considered relevant for the human health risk assessment.

Both thiophanate-methyl and carbendazim induced liver tumours in male and female mice in long-term dietary studies. Mechanistic studies were provided to support a phenobarbital-like MOA for thiophanate-methyl induced liver tumours. The available mechanistic studies failed to demonstrate liver cytochrome-P-450 enzyme induction by thiophanate-methyl in mice and were therefore considered insufficient to support a threshold-based MOA for thiophanate-methyl-induced liver tumours. The proposed MOA for carbendazim-induced liver tumours invoke its aneugenic potential; however, the data supporting this hypothesis are lacking in a number of areas: there are no studies on mouse tubulin binding, no in vivo assays of aneuploidy in the liver, and no clear data on cell proliferation relative to dose and time (McCarroll et al., 2002). Therefore, a linear low-dose extrapolation approach for the cancer risk assessment was deemed appropriate.

In a supplementary 22-month oncogenicity study using a different strain of mice, dietary administration of carbendazim resulted in an increased incidence of ovarian granulosa cell tumours and luteomas. However, this study was considered unacceptable for determining a no observed adverse effect level (NOAEL)/lowest observed adverse effect level (LOAEL) due to incomplete analysis of tissues. No MOA data were provided for these tumours.

The cancer potency estimate (q_1*) for thiophanate-methyl and carbendazim published in PRVD2011-07 were updated as follows: The q_1* calculations for the cancer risk assessments were undertaken using the USEPA's Benchmark Dose Tools software and used Benchmark Dose

[3] Bartsch, Ruediger, et al. "Human relevance of follicular thyroid tumors in rodents caused by non-genotoxic substances." *Regulatory Toxicology and Pharmacology* 98 (2018) 199-208.

Modelling to estimate the lower limit of the dose (BMDL) where an extra 10% increase in cancer would be induced. For thiophanate-methyl, a q_1* of 7.96×10^{-3} (mg/kg bw/day)$^{-1}$ was derived using data from the 18-month dietary oncogenicity study in CD-1 mice and is based on the combined incidence of hepatocellular adenomas, carcinomas and hepatoblastomas in males. For carbendazim, a pathology re-read of the two-year carbendazim oncogenicity study in CD-1 mice was also considered. In this re-examination of the liver pathology, the total number of liver tumours did not differ substantially from the initial results, although a slight decline in the number of carcinomas was observed. Using the BMDL approach, a q_1* of 1.09×10^{-3} (mg/kg bw/day)$^{-1}$ was derived using data from the both the original study and the pathology re-examination.

In all species tested resorptions, craniofacial and/or rib malformations were observed in carbendazim-treated animals in the absence of maternal toxicity, indicating fetal sensitivity. More severe effects occurred as a result of gavage dosing compared to dietary administration, although fetal sensitivity was noted with both types of administration. Thiophanate-methyl is metabolised to carbendazim, yet the developmental effects induced by thiophanate-methyl were less severe than those induced by carbendazim. Multiple supernumery ribs in rabbit fetuses were noted at maternally toxic dose levels of thiophanate-methyl. Neurodevelopmental concerns regarding thiophanate-methyl stem from the fact that short- and long-term exposures to thiophanate-methyl caused decrements in circulating thyroid hormones in rats, mice and dogs. Submitted MOA data indicate that thiophanate-methyl reduces both the synthesis of thyroid hormone (thyroid peroxidase inhibition) and enhances clearance of thyroid hormone, resulting in reduced thyroid hormone levels. Although adult humans are less sensitive to thyroid hormone changes than rats, these MOAs are relevant to humans with respect to reduction of circulating thyroid hormone levels and fetal/neonatal development. Adequate circulating levels of thyroid hormones are critical for normal development of the mammalian fetal and neonatal brain and persistent decreases in thyroid hormone levels increase the potential for neurodevelopmental deficits in the young.

No reproductive toxicity was observed with either compound in guideline studies; however, a number of published and unpublished studies on carbendazim reported sperm and testicular changes (inhibition of spermatogenesis and sperm reduction, germinal epithelium degeneration, lower testis weight) with high-dose, short-term gavage and dietary dosing.

Potential evidence of neurotoxicity at high dose levels was noted in a one-year study in dogs, based on tremors occurring within two to four hours of dosing, and in a two-generation reproduction study in which post-weanling male pups showed reduced performance in an open-field test. Potential signs of neurotoxicity for carbendazim were limited to mild, transient effects that occurred at high-dose levels only, with no histological evidence of neuropathy. In a review of the additional rat acute gavage neurotoxicity study with thiophanate-methyl, decreased landing foot splay was observed in both sexes in all treatment groups on the day of dosing. Decreased motor activity in treated females was observed in the main study, but not in the subsequent follow-up study. Although the decrease in motor activity in the main study was dose-dependent, given the lack of reproducibility of this finding in the extension study, the altered motor activity observed in females could not be definitively linked to treatment and was therefore considered equivocal. In the rat thiophanate-methyl short-term neurotoxicity study, no evidence of selective

neurotoxicity was observed. Treatment-related systemic toxic effects included decreased bodyweight and food consumption in females, as well as increased liver and thyroid weight in both sexes at the highest dose level.

In the rat dietary EOGRTS with carbendazim, reproductive toxicity was observed in high-dose males only, and consisted of decreased testes weight, testicular atrophy and decreased testosterone levels in the parental generation, as well as decreased testes weight in both weanling and adult F_1 males. Evidence of systemic toxicity to parental animals was noted at the two highest dose levels. Thyroid hypertrophy, increased TSH and total serum T_4, increased thyroid follicular cell height, and decreased colloid area were observed in females from the parental generation, as well as in some F_1 and F_2 animals post-weaning. The coincidental increase in T_4 and TSH was unexpected; however, it was considered that the increase in total serum T_4 did not necessarily reflect a change in free T_4 and that TSH levels were a better surrogate marker of the thyroid hormone status of the animals. Overall, although the thyroid effects were not consistent across sexes, ages and generation, the increase in TSH in combination with the histopathological changes noted in the thyroid were suggestive that adult animals tended toward hypothyroidism following carbendazim exposure.

In offspring, decreased bodyweight was observed in F_1 male pups from postnatal day (PND) 14 onwards at the two highest dose levels. The reduction in bodyweight in F_1 males was more pronounced shortly after weaning and, at the high-dose level, persisted to termination (PND 70). In accordance with the OECD Guidance Document 117,[4] a second generation in the EOGRTS was triggered by the decrease in F_1 male pup bodyweight in the absence of maternal bodyweight decrements during the lactation period. No effect on pup bodyweight was observed in the second generation.

Additional effects in offspring included a dose-dependent decrease in serum T_4 levels in pooled samples from F_1 PND 4 animals from the mid- and high-dose groups. The decrease in serum T_4 levels was not accompanied by changes in TSH levels; however, this was attributed to the immature hypothalamic-pituitary-thyroid axis known to be present in rats in the early postnatal period. In F_1 offspring sacrificed at PND 70, changes in brain morphometric measurements consisting of decreased thickness of the caudate putamen in males and decreased parietal cortex in females were observed at the high dose level. Developmental effects in the EOGRTS included skeletal variations comprised of unossified/incompletely ossified caudal arches and xiphoid, increased incidence of rudimentary ribs and left-sided umbilical artery. All of the aforementioned systemic and developmental effects in offspring occurred at dose levels that were also toxic to parental animals.

[4] Guidance Document on the Current Implementation of Internal Triggers in Test Guideline 443 for an Extended One Generation Reproductive Toxicity Study, in the United States and Canada. 2011

The toxicology reference values used in the human health risk assessment of thiophanate-methyl are summarized in Appendix III, Table 1. As carbendazim is a transformation product and mammalian metabolite of thiophanate-methyl, relevant reference values for risk assessment purposes are summarized in Table 2. Results of the toxicology studies conducted on laboratory animals with thiophanate-methyl and carbendazim are summarized in Tables 3 and 4, respectively

3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to toxicity to infants and children, the standard complement of studies, including developmental toxicity studies in rats and rabbits, and a two-generation reproductive toxicity study in rats were available for thiophanate-methyl. Additionally, a supplemental three-generation reproductive toxicity study in rats and a developmental toxicity study in mice were also available. For carbendazim, several developmental toxicity studies in rats, rabbits and hamsters were available, as well as two multi-generation reproductive toxicity studies, and an EOGRTS, in rats. While the reproductive toxicity studies with thiophanate-methyl were done according to acceptable guidelines at the time they were conducted, certain endpoints required by more recent guidelines, such as sperm parameter assessments and developmental landmarks, were not examined in these studies. However, these endpoints were examined in a more recent study (EOGRTS) conducted with carbendazim. The thiophanate-methyl toxicology database suggests that short- and long-term exposure causes decrements in circulating thyroid hormones in rats, mice and dogs. The effect of carbendazim on thyroid hormones was not thoroughly examined in the carbendazim database; however, data from the EOGRTS were suggestive of thyroid effects. Adequate circulating levels of thyroid hormones are critical for normal development of the mammalian fetal and neonatal brain and a persistent decrease in thyroid hormone levels increases the potential for neurodevelopmental deficits in the young.

With respect to concerns regarding prenatal and postnatal toxicity for thiophanate-methyl, in a two-generation reproduction study in rats, decreased pup bodyweight was noted in the presence of hepatocyte and thyroid follicular cell hypertrophy in parental animals. In prenatal developmental toxicity studies conducted with thiophanate-methyl, the developmental effects noted were less severe than those induced by carbendazim. In the rabbit developmental toxicity study, decreased fetal weight and multiple supernumerary ribs were noted at maternally toxic doses. No developmental effects were noted in the rat developmental toxicity study. However, developmental concerns for thiophanate-methyl remain due to the decrements in circulating thyroid hormones noted following short- and long-term exposure in rats, mice and dogs. Submitted MOA data indicate that thiophanate-methyl reduces both the synthesis of thyroid hormone (peroxidase inhibition) and enhances clearance of thyroid hormone, resulting in reduced thyroid hormone levels. Although adult humans are less sensitive than rats to thyroid hormone

changes, these MOAs are still relevant to humans with respect to reduction of circulating thyroid hormone levels and fetal/neonatal development. Although the EOGRTS with carbendazim was submitted to address this concern, some uncertainties remain due to methodological limitations in the conduct of the EOGRTS (see below).

A request for a developmental thyroid toxicity study was addressed by the availability of an EOGRTS conducted with carbendazim. As such, all of the required studies relevant to assessing risk of the young to thiophanate-methyl were available. The fetal effects observed were minor (decreased bodyweight) and occurred only in the presence of maternal toxicity. Therefore, for thiophanate methyl, the PCPA factor was reduced to onefold for all exposure scenarios. However, a threefold database uncertainty factor was applied as a result of residual uncertainties relating to potential sensitivity of the young with regard to potential thyroid effects in the late gestational and early postnatal period, due to the lack of learning and memory assessment in the carbendazim EOGRTS.

With respect to concerns regarding prenatal and postnatal toxicity for carbendazim, the developmental toxicity studies conducted with carbendazim provided indications of increased sensitivity of rat, rabbit and hamster fetuses following in utero exposure. Malformations, including hydrocephaly, microphthalmia, anophthalmia, malformed scapulae, exencephaly, hemivertebrae, and fused ribs and vertebrae, as well as increased resorptions, were observed in rat fetuses in one study in the presence of mild maternal toxicity (increased liver weight and reduced bodyweight gain). In another rat study, malformations in fetuses included anasarca, exencephaly, meningocele, abbreviated tail, microphthalmia, hydrocephalus, and cleft vertebrae, which occurred in the absence of effects on maternal animals. In the rabbit and hamster, increased resorptions occurred in the absence of maternal toxicity, while malformations, such as malformed cervical vertebrae and interrelated malformations of the ribs and proximate thoracic vertebrae in the rabbit, and exencephaly and fused ribs in the hamster, were observed in the presence of mild maternal toxicity (decreased bodyweight or bodyweight gain).

The malformations in rat developmental toxicity studies and the resorptions noted in rabbit and hamster developmental toxicity studies were considered serious endpoints and occurred in the absence of maternal toxicity. Therefore, for carbendazim, the 10-fold PCPA factor was retained for scenarios in which these endpoints were used to establish the point of departure for assessing risk to women of reproductive age. For exposure scenarios involving other sub-populations including children, the concerns regarding prenatal toxicity observed in the carbendazim developmental toxicity studies are not applicable and no postnatal toxicity concerns were identified in the available studies. However, residual uncertainties regarding the effect of carbendazim on thyroid hormone homeostasis and the postnatal toxicity of carbendazim remain due to limitations in the EOGRTS, specifically the lack of learning and memory assessment. As a result, in lieu of a PCPA factor for postnatal toxicity, a threefold database uncertainty factor was applied to address the uncertainties relating to potential sensitivity of the young.

3.2 Dietary Exposure and Risk Assessment

In a dietary exposure assessment, Health Canada determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet. Exposure to thiophanate-methyl and carbendazim from potentially treated imports was also included in the assessment.

Carbendazim is not registered in Canada for use on food crops; however, thiophanate-methyl degrades to carbendazim, and both are identified as residues of concern. Since different toxicological reference values were identified for each chemical, separate dietary exposure and risk estimates were conducted. Carbendazim may be produced by other fungicides (for example, benomyl). For the current dietary assessment, all residues of carbendazim were considered, since it was not possible to distinguish the source of the carbendazim residues.

Dietary exposure assessments are age-specific and incorporate the different eating habits of the population at various stages of life (infants, children, adolescents, adults and seniors). For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

Health Canada considers limiting use of a pesticide when exposure exceeds 100% of the reference value. The PMRA's Science Policy Notice SPN2003-03, *Assessing Exposure from Pesticide in Foods, A User's Guide*, presents detailed acute and chronic risk assessments procedures.

Residue estimates used in the dietary risk assessment may be conservatively based on the maximum residue limits (MRLs) or the field trial data representing the residues that may remain on food after treatment at the maximum label rate. Surveillance data representative of the national food supply may also be used to derive a more accurate estimate of residues that may remain on food when it is purchased. These include the Canadian Food Inspection Agency's (CFIA's) National Chemical Residue Monitoring Program and the United States Department of Agriculture Pesticide Data Program (PDP). Surveillance residue data suitable for the purpose of the thiophanate-methyl and carbendazim dietary risk evaluations were available from these programs.

The assessment of the residue chemistry and metabolism studies for the previous evaluations of thiophanate-methyl (REV2007-12 and PRVD2011-07) relied extensively upon the data submitted to, and reviewed by, the USEPA in their Reregistration Eligibility Decision (RED 2005). In REV2007-12 and PRVD2011-07, the PMRA requested the same data as requested by the USEPA for the reregistration of thiophanate-methyl. The registrant has submitted these studies which were reviewed for the current evaluation and were found to be adequate for the purposes of the re-evaluation of (thiophanate-methyl) TPM.

In addition, in PRVD2011-07, the PMRA requested relevant field trial data cited in the USEPA RED. These data were reviewed for the application to register the liquid formulation of thiophanate-methyl in 2014 and also meet the requirements for the re-evaluation of thiophanate-methyl.

Sufficient information was available to adequately assess the dietary risk from exposure to thiophanate-methyl and carbendazim. Acute, chronic and cancer dietary exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™, Version 4.02, 05-10-c) program which incorporates consumption data from the National Health and Nutrition Examination Survey, What We Eat in America 2005-2010 available through the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS). Further details on the consumption data are available in Science Policy Note SPN2014-01: *General Exposure Factor Inputs for Dietary, Occupational and Residential Exposure Assessments*. Information on the residue chemistry of thiophanate-methyl is available in Re-Evaluation Note REV2007-12: Preliminary Risk and Value Assessments of Thiophanate-Methyl. The dietary risk estimates are presented in Appendix IV.

3.2.1 Determination of Acute Reference Dose (ARfD)

Thiophanate-methyl

To estimate acute dietary risk (1 day) for the general population, including infants and children, the acute neurotoxicity study with a LOAEL of 50 mg/kg bw was selected for the risk assessment. At 50 mg/kg bw, the lowest dose tested, decreased landing foot splay was noted in both sexes. These effects were the result of a single exposure and are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. A threefold uncertainty factor for the use of a LOAEL and a threefold database uncertainty factor due to residual uncertainties with regards to potential sensitivity of the young were also applied. The PCPA factor was reduced to onefold. Thus, the composite assessment factor (CAF) is 1000.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{LOAEL}}{\text{CAF}} = \frac{\text{50 mg/kg bw}}{1000} = 0.05 \text{ mg/kg bw of thiophanate-methyl}$$

Carbendazim

Females 13–49 Years of Age:

To estimate acute dietary risk (1 day), the results from both the rat and rabbit developmental toxicity studies were considered co-critical. The NOAELs for these studies were identical and both studies identified critical endpoints of concern. The NOAEL of 10 mg/kg bw/day was based on an increased incidence of fetal malformations in the rat developmental toxicity study and increased resorptions in the rabbit developmental toxicity study. In both the rat and rabbit developmental toxicity studies, fetal effects were observed in the absence of maternal toxicity. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies

variability were applied. The 10-fold PCPA factor was retained. The fetal malformations induced by carbendazim are well characterized and the uncertainties relating to potential sensitivity of the young were considered to be subsumed by the 10-fold PCPA factor. Thus, the CAF is 1000.

$$\text{ARfD}_{(\text{females 13–49 years of age})} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{\text{10 mg/kg bw/day}}{1000} = 0.01 \text{ mg/kg bw of carbendazim}$$

Males 13+ Years of Age:

To estimate acute dietary risk (1 day) for males, a LOAEL of 50 mg/kg bw was selected from a published acute oral study of testicular effects in rats. At 50 mg/kg bw, the lowest dose tested, an absence of immature germ cells with round spermatids (stage I and II), and elongated spermatids sloughed from stage VII epithelium were noted on day two post-treatment. These effects were the result of a single exposure and are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, in addition to a threefold database uncertainty factor due to the lack of learning and memory assessment in the EOGRTS and residual uncertainties regarding potential sensitivity of the young, were applied. An uncertainty factor for the use of a LOAEL was subsumed by the database uncertainty factor, given that the observed effects on sperm were well documented. The PCPA factor was reduced to onefold. Thus, the CAF is 300.

The ARfD is calculated according to the following formula:

$$\text{ARfD}_{(\text{males 13+ years of age})} = \frac{\text{LOAEL}}{\text{CAF}} = \frac{\text{50 mg/kg bw}}{300} = 0.16 \text{ mg/kg bw of carbendazim}$$

3.2.2 Acute Dietary Exposure and Risk Assessment

The acute dietary risk was calculated considering the highest ingestion of residues of thiophanate-methyl or carbendazim that would be likely on any one day, and using food and drinking water consumption and food and drinking water residue values. The expected intake of residues is compared to the ARfD, which is the dose at which an individual could be exposed on any given day and expect no adverse health effects. When the estimated exposure is less than the ARfD, the acute dietary risk is shown to be acceptable.

The acute assessment was conducted using maximum residue values from CFIA and PDP food monitoring data for thiophanate-methyl and carbendazim for all commodities except soybean, sugarbeet, tree nuts (Crop Group 14), peanut and spices. American tolerances were used for tree nuts, sugarbeets and peanuts and CODEX MRLs were used for soybean and spices. Animal residues were not anticipated, as the only feed item use is sweet corn; however, since this is a seed treatment use, no significant residue accumulation is expected. In addition, the following inputs were used: 100% crop treated for all commodities; chemical-specific processing factors for apple juice, dried prunes, soybean oil and potato flour; DEEM default processing factors for other crops where applicable; and acute drinking water estimated environmental concentrations (EECs) for residues of thiophanate-methyl and carbendazim obtained from water modelling [see Section 3.3].

For thiophanate-methyl, the acute dietary exposure from food and drinking water for the general population and all population subgroups ranged from 8% to 31% of the ARfD, with infants less than one year of age being the most exposed subpopulation. Therefore, acute dietary risk is shown to be acceptable for thiophanate-methyl.

For carbendazim, acute risk assessments were required for males and females of reproductive age only. The acute dietary exposure (from food and drinking water) was 5% of the ARfD for males and 84% of the ARfD for females. Therefore, acute dietary risk is shown to be acceptable for carbendazim.

3.2.3 Determination of Acceptable Daily Intake (ADI)

Thiophanate-methyl

To estimate the risk from chronic dietary exposure to thiophanate-methyl, the results from both the one-year oral (capsule) dog toxicity study and a two-year chronic rat dietary toxicity study were considered co-critical. The NOAELs for these studies were similar and both studies revealed critical endpoints of concern. The NOAEL of 8 mg/kg bw/day in the one-year oral (capsule) dog toxicity study was based on increased thyroid weight, thyroid follicular cell hypertrophy, decreased serum thyroxine, body weight effects and cholesterol changes. In the 2two-year dietary chronic toxicity/oncogenicity study in rats, a NOAEL of 8.8 mg/kg bw/day was based on decreased bodyweight/bodyweight gain, increased thyroid weight, increased incidences of thyroid follicular cell hyperplasia/hypertrophy in males and females, effects on thyroid hormones (decreased T_4, T_3; increased TSH) in males, increased liver weight, increased incidences of centrilobular hepatocellular hypertrophy, and lipofuscin deposition in males and females. These studies provided the lowest NOAELs in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The PCPA factor was reduced to onefold and a threefold database uncertainty factor was applied to address residual uncertainties with regard to potential sensitivity of the young. Thus, the CAF is 300.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{8 \text{ mg/kg bw/day}}{300} = 0.027 \text{ mg/kg bw/day of thiophanate-methyl}$$

The ADI provides a margin of >1400 to the dose at which decreased pup bodyweight and increased supernumerary ribs occurred in thiophanate-methyl treated rabbits in the developmental toxicity study.

Carbendazim

General Population Excluding Females 13–49 Years of Age:

To estimate the risk from chronic dietary exposure to carbendazim, a NOAEL of 9 mg/kg bw/day from a two-year chronic dietary toxicity study in dogs was selected, based on reduced bodyweight gain, increased alkaline phosphatase, reduced clotting time, and testicular effects

(atrophic tubules, inflammatory cell infiltration). Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied, as well as a threefold database uncertainty factor to address residual uncertainties with regard to potential sensitivity of the young. The PCPA factor was reduced to onefold. Thus, the CAF is 300.

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{9 \text{ mg/kg bw/day}}{300} = 0.03 \text{ mg/kg bw/day of carbendazim}$$

The ADI provides a margin of >1600 to the dose at which sperm effects were noted in a published acute oral study of testicular effects in carbendazim treated rats, as well as several short-term oral and dermal rat toxicity studies.

Females 13–49 Years of Age:

To estimate the risk from chronic dietary exposure, the results from both the rat and rabbit developmental toxicity studies were considered co-critical. The NOAELs for these studies were identical and both studies revealed critical endpoints of concern. A NOAEL of 10 mg/kg bw/day was based on an increased incidence of fetal malformations in the rat developmental toxicity study and increased resorptions in the rabbit developmental toxicity study, which were observed in the absence of maternal toxicity. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The 10-fold PCPA factor was retained. The fetal malformations induced by carbendazim are well characterized and the uncertainties relating to potential sensitivity of the young were considered to be subsumed by the 10-fold PCPA factor. Thus, the CAF is 1000.

$$\text{ADI}_{(\text{females } 13-49 \text{ years of age})} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{10 \text{ mg/kg bw/day}}{1000} = 0.01 \text{ mg/kg bw/day of carbendazim}$$

3.2.4 Chronic Dietary Exposure and Risk Assessment

The chronic dietary risk was calculated using the average consumption of different foods and drinking water and the average residue values on those foods and in drinking water. The estimated exposure was then compared to the ADI. The ADI is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects. When the estimated exposure is less than the ADI, the chronic dietary risk is shown to be acceptable.

The chronic assessment was conducted by using the average residue values from CFIA and PDP food monitoring data for thiophanate-methyl and carbendazim.American field trial data were used for soybean, tree nuts, sugarbeets and peanuts, and the CODEX MRL was used for spices. Chronic drinking water EECs for residues of thiophanate-methyl and carbendazim were obtained from water modelling (see Section 3.3). All other inputs were the same as those used in the acute assessment.

For thiophanate-methyl, the chronic exposure from food and drinking water is less than 1% of the ADI for the general population and all population subgroups. Therefore, chronic dietary risk is shown to be acceptable.

For carbendazim, the chronic dietary exposure from food and drinking water for all subpopulations ranged from 1% to 5% of the ADI, with infants less than one year of age being the most exposed subpopulation. Therefore, chronic dietary risk is shown to be acceptable for carbendazim.

3.2.5 Cancer Assessment

A threshold approach was not supported as there was insufficient mode of action data available for liver tumours. As such, a linear low-dose extrapolation approach for cancer risk assessment was conducted. For thiophante-methyl, a q_1* of 7.96×10^{-3} $(mg/kg\ bw/day)^{-1}$ was derived based on the combined incidence of hepatocellular adenomas and carcinomas in male mice; this estimate is considered protective of the increase in liver tumours in female mice. For carbendazim, a q_1* of 1.09×10^{-3} $(mg/kg\ bw/day)^{-1}$ was derived based on the combined incidence of hepatocellular adenomas and carcinomas in female mice. This estimate is protective of the ovarian tumours noted in a separate 22-month dietary oncogenicity study in mice.

3.2.6 Dietary Cancer Exposure and Risk Assessment

The cancer dietary risk (from food and drinking water) was conducted for the general population by using the same residue values and inputs as described for the chronic assessment in Section 3.2.4. The estimated chronic exposure was then multiplied by the q_1* to determine the lifetime cancer risk. A lifetime cancer risk that is equal to or less than 1×10^{-6} (one-in-a-million) is usually considered acceptable for the general population when exposure occurs through pesticide residues in or on food and drinking water, or to otherwise unintentionally exposed persons.

Based on the linear low-dose extrapolation approach, the lifetime cancer risk estimate for the general population from dietary exposure from food and drinking water is 2×10^{-7} for thiophanate-methyl and 3×10^{-7} for carbendazim. Therefore, cancer risks are shown to be acceptable.

3.3 Exposure from Drinking Water

Residues of thiophanate-methyl and carbendazim in potential drinking water sources were estimated from water modelling.

3.3.1 Concentrations in Drinking Water

Estimated Concentrations in Drinking Water Sources: Level 2 Modelling

EECs of thiophanate-methyl and carbendazim in potential drinking water sources (groundwater and surface water) were generated using computer simulation model Pesticide in Water Calculator (PWC) V1.52 and using regional inputs with respect to application rate, application timing, and geographic scenario. A standard Level 2 turf scenario was used when modelling for surface water, in other words, a small reservoir adjacent to an agricultural field. EECs in groundwater were calculated by selecting the highest EEC from several selected scenarios representing different regions of Canada. The modelling was run for 50 years.

The scenario modelled included 2 applications of 2.1 kg a.i./ha at an interval of 10 days for controlling dollar spot, 1 application of 4.2 kg a.i./ha for controlling brown patch, and 1 application of 12.25 kg a.i./ha for controlling pink snow mould. The daily surface water EECs for thiophanate-methyl and carbendazim (66 µg/L and 58 µg/L, respectively) were used in the acute assessment, and the yearly surface water EECs (0.63 µg/L and 19 µg/L, respectively) were used for the chronic assessment. The overall (average daily concentrations) surface water EECs for thiophanate-methyl and carbendazim (0.17 µg/L and 10 µg/L, respectively) were used in the cancer risk assessment.

3.3.2 Drinking Water Exposure and Risk Assessment

Drinking water exposure estimates were combined with food exposure estimates, with EEC values incorporated directly in the dietary (food and drinking water) assessments. Please refer to Sections 3.2.2, 3.2.4 and 3.2.6 for details and conclusions.

3.4 Occupational and Non-Occupational Exposure and Risk Assessment

The occupational and residential assessments were updated to include new toxicology reference values, current exposure models and input values, the registrant-supported use pattern, and comments received during the previous consultation. Forty-seven comments were received in 2011 from various stakeholders including the registrant, users/growers and user associations, provincial governments, academia and the general public. Most comments were related to specific use restrictions that were proposed in the PRVD2011-07. Many of these restrictions have now been removed or altered as a result of this revised risk assessment.

3.4.1 Toxicology Endpoint Selection for Occupational and Non-Occupational Risk Assessment

3.4.1.1 Non-Cancer Risk Assessment

Occupational and non-occupational (residential) risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

Thiophanate-methyl

To estimate the risk from short-term dermal exposure to thiophanate-methyl, a NOAEL of 100 mg/kg bw/day from a 21-day dermal toxicity study in rabbits was selected. This NOAEL was based on decreased body weight and food consumption at 300 mg/kg bw/day.

To estimate the risk from short-term inhalation and incidental oral exposure to thiophanate-methyl, the NOAEL of 10 mg/kg bw/day based on decreased maternal body weight and food consumption from a rabbit developmental toxicity study was selected. An oral endpoint was selected as a repeat-dose inhalation toxicity study was not available. Since an oral NOAEL is used, an inhalation absorption factor of 100% is assumed for route-to-route extrapolation.

To estimate the risk from intermediate- and long-term dermal and inhalation exposures to thiophanate-methyl, the results from both the one-year oral (capsule) dog toxicity study and a two-year chronic dietary toxicity/oncogenicity study in rats were considered co-critical. The NOAELs established in these studies were similar and both studies revealed critical endpoints of concern. The NOAEL of 8 mg/kg bw/day was established in the one-year oral (capsule) dog toxicity study based on increased thyroid weight, thyroid follicular cell hypertrophy, decreased serum thyroxine, body weight effects and cholesterol changes. In the two-year dietary chronic toxicity/oncogenicity study in rats, a NOAEL of 8.8 mg/kg bw/day was based on decreased bodyweight/bodyweight gain, increased thyroid weight, increased incidence of thyroid follicular cell hyperplasia/hypertrophy in males and females, effects on thyroid hormone (decreased T_4, T_3; increased TSH) in males, increased liver weight, increased incidence of centrilobular hepatocellular hypertrophy, and lipofuscin deposition in males and females. An oral endpoint was selected for dermal and inhalation risk assessment, as the 21-day rabbit dermal toxicity study did not assess the endpoints of concern, namely effects on the thyroid, thyroid hormones, developmental effects, and potential neurotoxicity and a repeat-dose inhalation toxicity study was not available.

For residential scenarios, the target MOE selected for these endpoints is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability, as well as a threefold database uncertainty factor to address residual uncertainties with regard to potential sensitivity of the young. The PCPA factor was reduced to onefold. The selection of these studies and target MOE value are considered to be protective of all adults including the unborn children of exposed women.

For occupational scenarios, the target MOE selected for these endpoints is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. As the worker population could include pregnant women, it is necessary to afford adequate protection of the fetus that may be exposed via its mother. In light of concerns regarding prenatal/early postnatal toxicity, a threefold database uncertainty factor to address residual uncertainties with regards to potential sensitivity of the young was applied to these endpoints to protect the sensitive worker population, namely females 13–49 years of age.

Carbendazim

To estimate the risk from short- to long-term dermal and inhalation exposures for females 13–49 years of age only, the results from both the rat and rabbit developmental toxicity studies were considered co-critical. The NOAELs for these studies were identical and both studies revealed critical endpoints of concern. The NOAEL of 10 mg/kg bw/day was based on an increased incidence of fetal malformations in the rat developmental toxicity study and increased resorptions in the rabbit developmental toxicity study, both in the absence of maternal toxicity. Although a

non-guideline inhalation study and several dermal toxicity studies were available, these studies were not selected for use in the risk assessment since the design of these studies do not allow for the assessment of the relevant endpoints of concern, namely, fetal malformations and resorptions.

To estimate the risk from incidental oral exposure to carbendazim, the NOAEL of 20 mg/kg bw/day based on decreased maternal body weight/body weight gain and food consumption from rat and rabbit developmental toxicity studies was selected.

For most residential scenarios (short-, intermediate- and long-term dermal and inhalation, and aggregate oral, dermal, and inhalation for females 13–49 years of age), the target MOE is 1000. Ten-fold factors were applied for interspecies extrapolation and intraspecies variability. The 10-fold PCPA factor was retained. The selection of this study and target MOE is considered protective of all adults including the unborn children of exposed women. For the incidental oral scenario, the target MOE is 300. Ten-fold factors were applied for interspecies extrapolation and intraspecies variability. The threefold database uncertainty factor was applied for residual uncertainties relating to potential sensitivity of the young with regard to potential thyroid effects in the late gestational and early postnatal period, due to the lack of learning and memory assessment in the carbendazim EOGRTS.

For occupational scenarios, the target MOE is 1000. Ten-fold factors were applied for interspecies extrapolation and intraspecies variability. As the worker population could include pregnant women, it is necessary to afford adequate protection of the fetus that may be exposed via its mother. In light of concerns regarding prenatal toxicity, an additional 10-fold factor was applied to this endpoint to protect the sensitive worker population, namely females 13–49 years of age.

3.4.1.2 Cancer Risk Assessment

Refer to section 3.2.5 for cancer potency estimates for thiophanate-methyl and carbendazim.

The cancer risk is determined by calculating the lifetime average daily dose (LADD) from dermal, inhalation and/or oral exposure. The LADD is multiplied by the q1* to obtain a lifetime cancer risk estimate, which is a measurement of probability. A lifetime cancer risk in the range of 1×10^{-5} in worker populations and in the range of 1×10^{-6} in residential populations is generally acceptable.

3.4.1.3 Dermal Absorption

For thiophanate-methyl, a dermal absorption value was not required for the short-term exposure duration, as the toxicological reference value for the dermal exposure route was derived from a dermal study. For the intermediate- and long-term durations of exposure and for the cancer risk assessments, a dermal absorption value is required, as the toxicological reference values were derived from oral studies. For carbendazim, a dermal absorption value is also required, since the toxicological reference value for the dermal exposure route for females 13–49 years of age was derived from an oral study.

For the current evaluation, dermal absorption data for thiophanate-methyl and carbendazim were requested to determine whether further refinements were possible. For thiophanate-methyl the registrant submitted 2 rat in vivo studies, and 2 human and rat in vitro studies; some of which were only received recently at the PMRA. No studies were submitted for carbendazim; therefore, the PMRA is relying, to the extent possible, upon foreign reviews and published literature. A screening review of the thiophanate-methyl dermal absorption studies and other available information for thiophanate-methyl and carbendazim indicates a dermal absorption value of 25% would not underestimate exposure in the current risk assessment.

3.4.2 Non-Occupational Exposure and Risk Assessment

Non-occupational (residential) risk assessment involves estimating risks to the general population, including youths and children, during or after pesticide application.

3.4.2.1 Residential Applicator Exposure and Risk Assessment

A residential applicator assessment was not required, since no domestic class products containing thiophanate-methyl are registered.

3.4.2.2 Residential Postapplication Exposure and Risk Assessment

Residential postapplication exposure occurs when an individual is exposed through dermal, inhalation, and/or incidental oral (non-dietary ingestion) routes as a result of being in a residential environment that has been previously treated with a pesticide by a commercial applicator. For thiophanate-methyl, this would include treatment of turf, including golf courses, and fruit trees in residential areas.

For postapplication scenarios, exposure to thiophanate-methyl as well as its environmental degradation product, carbendazim, was considered. In addition to being a breakdown product of thiophanate-methyl and other carbamate pesticides, carbendazim is also a registered pesticide with its own toxicological profile. This assessment is restricted to consideration of carbendazim exposure resulting from the use of thiophanate-methyl.

Adults (> 16 years old), youth (11 < 16 years old), and children (6 < 11 years old, and 1 < 2 years old) were chosen as the index life stages to assess, based on behavioural characteristics and the quality of the available data. Children 6 years old to < 11 years old are not assessed separately, for some scenarios, because their exposure is expected to be less than that of children 1 < 2 years old. Children (1 < 2 years) are expected to have a greater exposure because of additional routes of exposure (incidental oral) as well as a greater body surface area (cm^2) to body-weight (kg) ratio.

Postapplication residential exposure to thiophanate-methyl and carbendazim is expected to be intermittent short-term in duration (that is, less than 30 days of continuous exposure). It was assumed that individuals would enter previously treated areas on the same day the pesticide is applied. Adults, youth and children have the potential for postapplication dermal exposure. Children (1 < 2 years old) also have the potential for postapplication incidental oral exposure from hand-to-mouth activities or ingesting treated turf or soil. Postapplication inhalation

exposure while performing activities in previously treated turf and fruit trees is expected to be low for thiophanate-methyl and carbendazim due to the combination of low vapour pressure and the expected dilution in outdoor air.

To estimate postapplication dermal exposure, activity-specific transfer coefficients (TCs) from the United States Environmental Protection Agency (USEPA) 2012 Residential Standard Operating Procedures (SOPs) for activities conducted on residential fruit trees, on residential turf, as well as while golfing were used. A TC is a factor that relates dermal exposure to dislodgeable foliar residues (DFR) or turf transferrable residues (TTR). It is the amount of treated surface that a person contacts while performing activities in a given period (usually expressed in units of cm^2 per hour) and is specific to a particular sub-population. Chemical-specific DFR and TTR studies were available for thiophanate-methyl, which also measured carbendazim residues. Inputs and equations from the USEPA Residential SOPs (2012) were also used to estimate postapplication incidental oral exposure.

For the non-cancer residential postapplication risk assessment, calculated MOEs exceeded the target MOEs for thiophanate-methyl and carbendazim for almost all scenarios and thus, risks were shown to be acceptable, with the exception of dermal exposure following application to residential turf. Similarly, for the cancer postapplication risk assessment, risks were less than 1×10^{-6} for all scenarios and therefore acceptable, except for dermal exposure following application to residential turf. To mitigate risk, label directions are proposed to restrict the application of thiophanate-methyl to golf courses and sod farms only, which had acceptable non-cancer and cancer risks.

The results of the residential postapplication risk assessment are summarized in Appendix VIII.

3.4.3 Occupational Exposure and Risk Assessment

There is potential for exposure to thiophanate-methyl in occupational scenarios from workers handling thiophanate-methyl products during mixing/loading and application activities, from handling treated seeds or potato seed pieces, and from workers entering treated areas. There is also potential for exposure to carbendazim in occupational scenarios from postapplication workers entering treated areas where the applied thiophanate-methyl residues have degraded to carbendazim in the environment.

3.4.3.1 Mixer, Loader and Applicator Exposure and Risk Assessment

For commercial-class products, there are potential exposures for mixers, loaders, and applicators. The following scenarios were assessed:

- Mixing/loading liquids;
- Mixing/loading wettable powders;
- Mixing/loading wettable powders in water soluble packaging;
- Airblast application to apple, pear, apricot, cherry (sweet, sour), nectarine, peach, plum, prune, raspberry, outdoor ornamentals, aspen and poplar;

- Groundboom application to strawberry, raspberry, lowbush blueberry, white beans, sugarbeets, roses, outdoor ornamentals, golf courses and sod farms;
- Aerial application to lowbush blueberry and white beans;
- Mixing, loading and applying by backpack to greenhouse potted ornamentals, greenhouse tobacco seedlings, outdoor ornamentals, strawberry, raspberry, lowbush blueberry, aspen, poplar;
- Mixing, loading and applying by manually-pressurized handwand to greenhouse potted ornamentals, greenhouse tobacco seedlings, outdoor ornamentals, strawberry, raspberry, lowbush blueberry, aspen, poplar;
- Mixing, loading and applying by mechanically-pressurized handgun to strawberry, raspberry, lowbush blueberry, greenhouse potted ornamentals, aspen, poplar, greenhouse tobacco seedlings;
- Mixing, loading and applying by turf gun (handgun lawn sprayer);
- Commercial slurry seed treatment for dry common bean;
- On-farm slurry seed treatment for dry common bean;
- On-farm dry hopper box seed treatment for dry common bean and sweet corn;
- On-farm liquid seed box treatment for sweet corn;
- Treatment of potato seed pieces;
- Planting treated seeds and potato seed pieces;
- Dry powder product application to mushroom spawn with mechanical spreading of treated spawn; and
- Mixing, loading and applying by manually-pressurized handwand to mushroom bed casing layer.

The exposure estimates for mixer/loaders and applicators are based on different levels of personal protective equipment (PPE) and engineering controls:

- Baseline PPE: Long pants, long-sleeved shirt and chemical-resistant gloves (unless specified otherwise).
- Mid-Level PPE: Cotton coveralls over long pants, long-sleeved shirt, and chemical-resistant gloves.
- Maximum PPE: Chemical-resistant coveralls over long pants, long-sleeved shirt, and chemical-resistant gloves.
- Engineering Controls: Represents the use of appropriate engineering controls, such as closed cab tractor or closed mixing/loading systems. Engineering controls are limited for handheld application methods.
- Chemical-Resistant Headgear. Chemical-resistant headgear that covers the neck (for example, Sou'Wester hat, rain hat).
- Respirator: a respirator with NIOSH-approved organic-vapour removing cartridge with a prefilter approved for pesticides.
- NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit tested.

Exposure Data:

No appropriate chemical-specific handler exposure data were available for thiophanate-methyl. Therefore, dermal and inhalation exposure for field and greenhouse applications were estimated using data from the Pesticide Handlers Exposure Database (PHED), the Agricultural Handler Exposure Task Force (AHETF), and the Outdoor Residential Exposure Task Force (ORETF).

The PHED is a compilation of generic mixer/loader applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates based on formulation type, application equipment, mix/load systems and level of PPE. The open cab airblast, open cab groundboom, closed cockpit aerial and open mix/load liquids studies from AHETF and professional turf gun application study from ORETF were also used. While there are limitations in the use of non-chemical specific data, these exposure data represent the most reliable information currently available.

Thiophanate-methyl is registered for seed and potato seed piece treatment. PHED scenarios were not considered to be representative of exposure to workers treating or handling seed or potato seed pieces. Surrogate commercial and on-farm treatment exposure studies, as well as exposure studies for planting treated seeds or potato seed pieces, were used to estimate worker exposure. These are the best data available for the assessment of worker exposure during the treatment and handling of seeds and potato seed pieces.

Thiophanate-methyl is also registered for white button mushroom spawn treatment and casing layer treatment. There were no applicator studies available for these specific scenarios. Therefore, surrogate seed treatment data for workers adding dry product to seed in hopper boxes with open hand mixing was used to assess the mushroom spawn treatment and is not expected to underestimate exposure. The PHED data for mixing, loading and applying with a manually pressurized handwand was used for the casing layer application as this scenario most closely relates to this use based on use pattern information provided.

In most cases, the above studies did not contain appropriate data sets to estimate exposure to workers wearing coveralls (cotton or chemical-resistant), or respirators. Where possible, this was estimated by incorporating a 75% clothing protection factor for coveralls, a 90% protection factor for chemical-resistant coveralls, an 80% protection factor for N95 filtering facepiece respirators (dust masks), and a 90% protection factor for a respirator (such as full and half-face air purifying and supplied air) into the unit exposure data.

Exposure Durations:

Based on the number of applications and timing of application, workers applying thiophanate-methyl would generally have a short-term (<30 days) duration of exposure, except for turf, greenhouse ornamental crops and mushroom houses, where there is potential for intermediate to long-term (up to several months) duration of exposure. For the cancer assessment, agriculture workers were assumed to have a working career of 40 years over a 78-year lifetime. Applicators and workers in commercial seed or potato seed piece treatment facilities were assumed to be exposed for up to a total of 30 days per year, with 10 days per year for on-farm seed and potato

piece seed treatment. Applicators in mushroom houses were assumed to be exposed for up to 50 days per year. Other agricultural applicators may be exposed from 2 to 30 days, depending on whether they are farmers treating their own crops or custom applicators.

Risk Assessment Outcomes:

For agricultural and turf uses, calculated MOEs exceeded target MOEs for most mixing, loading, and application scenarios and therefore, risks were shown to be acceptable, provided engineering controls, personal protective equipment, and limitations on amount handled per day were used. Similarly, cancer risks were below the threshold of 1×10^{-5} when the same mitigation measures as those used for the non-cancer risk assessment were considered, and were therefore acceptable. However, calculated MOEs of wettable powder products by aerial application on blueberry and white bean, and groundboom application on turf, white bean, sugarbeet, aspen and poplar (by custom applicators) were below the target MOE, and therefore, risks were not shown to be acceptable, even when additional mitigation measures were considered. Cancer risks were not shown to be acceptable for these use scenarios. To mitigate risks, it is proposed that these uses are removed from the wettable powder product labels. The results of the risk assessment are summarized in Appendix V, Tables 1–6.

For use on mushroom house spawn and casing treatments, risks were shown to be acceptable. Calculated MOEs exceeded the target MOEs and cancer risks were less than 1×10^{-5} (Appendix V, Tables 7 and 8), provided the current label restrictions are followed and additional PPE are added to the labels (Appendix XI).

For on-farm and commercial seed treatment, as well as for workers planting treated seeds, calculated MOEs exceeded target MOEs and risks were, therefore, shown to be acceptable for most uses, provided engineering controls and PPE are used. Cancer risks were below the threshold of 1×10^{-5}, and therefore, shown to be acceptable when the same mitigation measures as those applied to the non-cancer risk assessment were considered.

Target MOEs were not met and therefore, risks were not shown to be acceptable for potato seed piece treatment for all formulations. Similarly, MOEs were not met for wettable powder products used on dry common beans as a commercial slurry treatment or as an on-farm dry application. To mitigate this risk, cancellation of these uses is proposed. The results of the risk assessment are summarized in Appendix VII.

3.4.3.2 Postapplication Worker Exposure and Risk Assessment

The postapplication occupational risk assessment considered exposures to workers entering treated sites to conduct agronomic activities involving contact with treated material (for example foliage, soil). For outdoor agricultural crops, there is potential for short-term (<30 days) postapplication exposure for workers based on the following considerations: the number of applications is limited to 2 per season; dislodgeable foliar residue studies showed relatively quick dissipation in the field after 2 applications; the timing of application in relation to potential postapplication worker activities; and the number of days of worker activities. For golf courses and sod farms, there is potential for intermediate-term (up to several months) postapplication

exposure for workers, as four applications are supported by the registrant. For greenhouse ornamental uses, there is potential for long-term (>6 months) postapplication exposure, as there is potential for treatment of many different types of ornamentals and multiple crop cycles per year. For greenhouse tobacco seedlings, postapplication exposure is considered short-term, as seedlings are grown in the spring for transplant to the field for the summer. For mushroom houses, exposure would be long-term.

Exposure would be predominantly dermal for workers performing postapplication activities in crops treated with a foliar spray. Based on the vapour pressure of thiophanate-methyl and carbendazim, inhalation exposure is not likely to be of concern provided that the minimum 12-hour restricted-entry interval is followed.

For all scenarios except mushrooms, potential dermal exposure to postapplication workers was estimated using updated activity-specific TCs and dislodgeable foliar residue (DFR) or turf transferable residue (TTR) data. The DFR and TTR refer to the amount of residue that can be dislodged or transferred from a surface, such as leaves of a plant or turf. The TC is a measure of the relationship between exposure and DFRs/TTRs for individuals engaged in a specific activity and is calculated from data generated in field exposure studies. The TCs are specific to a given crop and activity combination (for example, hand harvesting apples, scouting late season corn) and reflect standard agricultural work clothing worn by adult workers. Activity-specific TCs from the Agricultural Re-Entry Task Force (ARTF) were used. For more information about estimating worker postapplication exposure refer to the PMRA's Regulatory Proposal PRO2014-02 (*Updated Agricultural Transfer Coefficients for Assessing Occupational Exposure to Pesticides*).

For workers entering a treated site, REIs are calculated to determine the minimum length of time required before people can safely enter after application. An REI is the duration of time that must elapse in order for residues to decline to a level where risks are shown to be acceptable (that is, performance of a specific activity that results in exposures of both thiophanate-methyl and carbendazim that are above the target MOE, as well as below the acceptable cancer risk threshold of 1×10^{-5}).

The PMRA considered reviews from other regulatory authorities of four chemical-specific DFR and TTR studies in which residues of both thiophanate-methyl and carbendazim were measured following two applications of thiophanate-methyl to apples, strawberries, turf, and greenhouse chrysanthemums and roses. These studies were used in PRVD2011-07 but were re-assessed for the current assessment to address dissipation issues. To ensure that the proposed REIs address potential postapplication risks to both carbendazim and thiophanate-methyl, actual carbendazim residue values from the studies, rather than a percentage of thiophanate-methyl residues, were used in the current risk assessment. Residue values were adjusted proportionally for Canadian application rates. The studies and values used to estimate dislodgeable foliar and turf transferable residues on registered Canadian crops are summarized in Appendix VI, Table 1.

The longest REIs determined from the non-cancer and cancer risk assessments for each crop and activity combination are listed in Appendix VI, Table 2. Postapplication cancer and non-cancer exposure and risk assessments for thiophanate-methyl and carbendazim are summarized in Appendix VI, Tables 3 to 5.

For agricultural scenarios, REIs range from 12 hours to 63 days. For most uses, cancer and non-cancer risks are shown to be acceptable provided that the 12-hour REI is followed or that the REI is increased up to 2 days for some activities. However, the REIs are not considered to be agronomically feasible for the uses listed below. Therefore, these uses are proposed for cancellation.

- Greenhouse tobacco seedlings (foliar spray and foliar drench): 6 day REI
- Greenhouse cut flowers (foliar application): 25 day REI
- Outdoor cut flowers: 2 day REI
- Apples, pears in British Columbia (BC) (due to high application rate): 25–63 day REIs (use in Eastern Canada is not proposed for cancellation as the application rate is lower)
- Peaches, nectarines, plums, prunes, cherries: 21 day REI

The PMRA is aware that changes to the apple orchard architecture may potentially result in lower exposures. Additional worker exposure data, and use pattern information, such as the timing of thiophanate-methyl applications in relation to postapplication activities (including those in different orchard architectures) may help to refine the risk assessment.

For drench application to tobacco seedlings, postapplication exposure was considered to be similar to foliar application. Drench application, at the time this use was registered, was described as overhead application to foliage. As the calculated REI for foliar application (6 days) is not considered to be agronomically feasible, this use is proposed for cancellation.

For soil drench application to greenhouse cut flowers, postapplication exposure was considered to be minimal, as long as the pesticide solution is directed to the soil and does not contact plant foliage, and a 12-hour REI is followed. For greenhouse non-cut flower ornamentals, risks are acceptable for foliar spray, foliar drench and soil drench application with a 12-hour REI.

For outdoor non-cut flower ornamentals, risks are acceptable with a 12-hour REI.

For mushroom cultivation in general, harvesting is the postapplication activity that results in the most contact with the growth media or the mushrooms. However, the registered use of thiophanate-methyl involves application as either a spawn treatment or a casing drench application. It is not directly applied to mushrooms. Therefore, worker contact with the mushroom bedding and compost is expected to be limited.

In terms of harvesting, based on the timing and nature of application, as well as information from food residue field trial data in mushrooms, residues of thiophanate-methyl and carbendazim would be low, and the amount of residue on the surface of the mushroom that is transferable to workers at harvest is expected to be minimal for both application methods. A 12-hour REI is proposed for application in mushroom houses.

3.5 Aggregate Exposure and Risk Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation).

3.5.1 Toxicology Reference Values for Aggregate Risk Assessment

Aggregate exposure to thiophanate-methyl may be comprised of food, drinking water and residential exposure, specifically from residential trees and golf courses. Reduction in body weight and food consumption was observed in short-term repeated dose studies via both the oral and dermal routes of exposure. No repeat-dose inhalation study was available; however, it was assumed that these effects would also be relevant to this route of exposure. For the oral and inhalation routes of exposure, the NOAEL of 10 mg/kg bw/day based on decreased body weight in maternal animals in the rabbit developmental toxicity study was selected. A NOAEL of 100 mg/kg bw/day based on bodyweight effects observed in the 21-day rabbit dermal toxicity study was selected for the dermal route of exposure. The target MOE for this scenario is 300. This includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as a threefold database uncertainty factor to address residual uncertainties with regard to potential sensitivity of the young. The PCPA factor was reduced to onefold. The selection of these studies and MOE is considered to be protective of all populations, including nursing infants and the unborn children.

Carbendazim is the primary metabolite of thiophanate-methyl. Therefore, the aggregate risk assessment would also consider carbendazim exposure from food or drinking water and residential exposure from residential trees and golf courses resulting from thiophanate-methyl use. No systemic toxicity was observed in short-term dermal toxicity studies with carbendazim. In oral toxicity studies, decreased bodyweight and/or body-weight gain were consistent endpoints of concern. Despite the absence of a guideline repeat-dose inhalation study, it was assumed that body weight effects would also be a critical endpoint by this route of exposure. Thus, to assess short-term aggregate exposure via the oral and inhalation route for the general population excluding females 13 to 49 years of age, the developmental toxicity studies in rats and rabbits were considered co-critical. In both studies, a NOAEL of 20 mg/kg bw/day was established based on decreased body weight and body weight gain in parental animals. For the general population excluding females 13 to 49 years of age, the target MOE is 300. This includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as a threefold database uncertainty factor to address residual uncertainties with regard to potential sensitivity in the young. The PCPA factor was reduced to onefold.

For females of childbearing age, an additional endpoint of concern for short-term aggregate exposure to carbendazim was the increased incidence of fetal malformations noted in developmental toxicity studies. The results from the rat and rabbit developmental toxicity studies were considered co-critical. The NOAEL of 10 mg/kg bw/day was based on an increased incidence of fetal malformations in the rat developmental toxicity study and increased resorptions in the rabbit developmental toxicity study, which were observed in the absence of maternal toxicity. These effects were considered relevant to all routes of exposure, as the available dermal

and inhalation toxicity studies did not assess the relevant endpoint of concerns, namely fetal malformations and resorption. The target MOE is 1000. This includes the standard uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability as well as a PCPA factor of 10-fold. The threefold database uncertainty factor identified for concerns regarding potential sensitivity of the young is subsumed by the 10-fold PCPA factor.

For the thiophanate-methyl aggregate cancer risk assessment, the q_1* of 7.96×10^{-3} (mg/kg bw/day)$^{-1}$ was based on the combined incidence of hepatocellular adenomas and carcinoma in orally treated male mice, and was considered relevant for all routes of exposure.

For the carbendazim aggregate cancer risk assessment, the q_1* of 1.09×10^{-3} (mg/kg bw/day)$^{-1}$ was based on increased hepatocellular tumours in orally treated female mice, and was considered relevant for all routes of exposure.

3.5.2 Aggregate Exposure and Risk Assessment

In an aggregate risk assessment, the combined potential risk associated with food, drinking water and various residential (non-occupational) exposure pathways is assessed. A major consideration is the likelihood of co-occurrence of exposures and durations of exposures. Additionally, only exposures from routes that share common toxicological effects are aggregated.

Only the individual use scenarios that were shown to have acceptable risks were aggregated. This included the dietary risks, as well as postapplication risks following application to golf courses and residential fruit trees. Since the residential turf use, except for golf courses, was not shown to have acceptable risk and is proposed for cancellation, an aggregate assessment was not conducted for that use.

The following activities have the potential for co-occurrence:

Golf courses:

- Thiophanate-methyl – Adults and youth (6 to <11 years): residential postapplication dermal + chronic dietary
- Carbendazim – Adults (females 13 to 49 years) and youth (6 to <11 years): residential postapplication dermal + chronic dietary

Residential fruit trees:

- Thiophanate-methyl – Adults and youth (6 to <11 years): residential postapplication dermal + chronic dietary
- Carbendazim – Adults (females 13–49 years) and youth (6 to <11 years): residential postapplication dermal + chronic dietary

The results of the aggregate assessment are presented in Appendix IX, Tables 1–3.

The calculated aggregate MOEs exceeded the target MOE for all age groups, and cancer risks were less than 1×10^{-6}. Therefore, aggregate risks for thiophanate-methyl and carbendazim were shown to be acceptable when the proposed mitigation measures for thiophanate-methyl are considered.

3.6 Cumulative Risk Assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Thiophanate-methyl is a carbamate fungicide. Carbendazim, a metabolite and environmental degradant of thiophanate-methyl, is also a carbamate fungicide and registered pesticide in Canada for non-food uses. This assessment considers the potential cumulative risk of thiophanate-methyl and carbendazim from use of thiophanate-methyl only.

A cumulative assessment for the pesticidal uses of thiophanate-methyl and carbendazim will be considered upon completion of the thiophanate-methyl assessment. Furthermore, both thiophanate-methyl and carbendazim belong to a class of fungicides called benzimidazole fungicides, which also includes other fungicides such as benomyl, thiabendazole and fuberidazole. The need for a cumulative assessment for this class of fungicides will also be assessed upon completion of the thiophanate-methyl assessment.

3.6.1 Toxicology Reference Values for Cumulative Risk Assessment

A review of the available toxicity information did not reveal any common mechanism of toxicity for non-cancer effects of thiophanate-methyl and carbendazim. However, thiophanate-methyl and its metabolite carbendazim both produce liver tumours in mice. Therefore, a cumulative cancer risk assessment was conducted for these two compounds resulting from thiophanate-methyl use. The cancer potency factor for thiophanate-methyl (7.96×10^{-3} (mg/kg bw/day)$^{-1}$) and carbendazim (1.09×10^{-3} (mg/kg bw/day)$^{-1}$) were considered relevant for all routes of exposure.

3.6.2 Cumulative Exposure and Risk Assessment

Cumulative assessments were conducted for scenarios that were shown to have acceptable risks for the individual chemicals. Cumulative cancer risks were determined for each scenario by adding the cancer risks from thiophanate-methyl plus the cancer risk from carbendazim (see Appendix IX, Table 3).

- The cumulative cancer risk ranged from 6×10^{-7} to 9×10^{-7} for exposure to thiophanate-methyl and carbendazim from food, drinking water and residential postapplication exposure following application of thiophanate-methyl to residential fruit trees.
- The cumulative cancer risk was 1×10^{-6} for exposure to thiophanate-methyl and carbendazim from food, drinking water and residential postapplication exposure following application of thiophanate-methyl to golf courses.

Therefore, the cumulative cancer risk was shown to be acceptable for thiophanate-methyl and carbendazim resulting from application of thiophanate-methyl, when the proposed mitigation measures for thiophanate-methyl are considered.

3.7 Human and Animal Incident Reports

As of 10 October 2018, no human or domestic animal incident reports involving thiophanate-methyl or carbendazim have been submitted to Health Canada.

4.0 Environmental Assessment

The following revisions to the environmental risk assessment have been made to PRVD2011-07:

- Revised maximum cumulative application rate for turf;
- New endpoints for terrestrial plants;
- Updated risk assessment for earthworms;
- New Tier 1 acute and higher tiered endpoints in the risk assessment for pollinators and beneficial arthropods;
- Revised bird and mammal risk assessment based on current methods;
- Revised aquatic risk assessment using more sensitive endpoints; and
- Recalculation of buffer zones for aquatic habitats.

4.1 Fate and Behaviour in the Environment

The fate and behaviour of thiophanate-methyl and its major transformation product, carbendazim, were described previously in REV2007-12. Available environmental fate data were also summarised in PRVD2011-07 (Appendix X, Tables 1 to 4).

The data used to evaluate aerobic soil biotransformation for the current assessment are the same as that used in PRVD2011-07; however, data that were relied upon to characterize aerobic soil biotransformation of carbendazim were not detailed in PRVD2011-07. Therefore, the aerobic soil data for thiophanate-methyl and carbendazim are further characterized below.

Aerobic biotransformation is the most important route of transformation of thiophanate-methyl in soil. Thiophanate-methyl transforms rapidly in the soil environment and was reported to have degraded in less than one day (half-life and DT_{90} <1 day) to the major transformation product, carbendazim. Carbendazim was detected up to a maximum of 83% of applied thiophanate-methyl within three weeks of application to soil. In studies with thiophanate-methyl; carbendazim was found after 12 months at 22 to 36% of applied thiophanate-methyl in two soils tested, and at only 1% in a third soil. Aerobic soil biotransformation half-lives for carbendazim ranged from 20 to 272 days in 8 soils tested. Therefore, in aerobic soil, thiophanate-methyl is considered non-persistent while carbendazim is slightly persistent to persistent. Other minor transformation products identified in aerobic soil include FH-432 and DX-105 (at <10% of applied thiophanate-methyl).The aerobic soil half-lives used to estimate the environmental concentrations for the assessment reported in PRVD2011-07 and for this assessment are summarized in Appendix X, Table 1.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level). Summaries of toxicity data for both terrestrial and aquatic non-target organisms to thiophanate-methyl and carbendazim are presented in Appendix X, Tables 2 and 3.

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the RQ is then compared to the level of concern (LOC). If the screening level RQ is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level RQ is equal to or greater than the LOC, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

4.2.1.1 Earthworms

The risk assessment has been revised with the following changes: increased maximum cumulative rate for turf, a lower half-life for carbendazim in soil and a lower percentage of spray drift expected from the field sprayer in the refined assessment. The results from the risk assessment are presented in Appendix X, Tables 4 and 5.

The RQs for earthworms resulting from acute exposure to thiophanate-methyl do not exceed the LOC at the screening level (RQs $\leq$ 0.1).

The RQs for earthworms resulting from chronic exposure to thiophanate-methyl do not exceed the LOC at the screening level (on-field) for sugarbeets but do exceed the LOC for raspberries/strawberries and turf. The assessment was refined to account for spray drift to off-field habitats. EECs for off-field habitats due to spray drift were calculated using the maximum drift deposition (percent of application rate) at one metre downwind from the point of application. The maximum percent drift deposition will vary depending on the droplet size and type of application equipment that is used. The American Society of Agricultural Engineers (ASAE) classification of 'fine' droplet size was used for early season and late season airblast application and estimates deposition of 74% and 59% of the application rate, respectively, at one metre. The maximum percent drift deposition for an ASAE 'medium' droplet size is 6% of the application rate for field sprayer application. These refinements resulted in RQs for raspberries/strawberries that did not exceed the LOC but the RQ for turf still exceeded the level of concern (turf RQ = 1.2).

The RQs for earthworms resulting from chronic exposure to carbendazim exceed the LOC at the screening level (on-field) for all crop rates tested. Refining the risk to account for spray drift to off-field habitats resulted in RQs for sugarbeets that did not exceed the LOC but RQs for raspberries/strawberries (airblast uses only) and turf still exceeded the level of concern (RQs ranged from 2.7 to 3.6 for both crops).

Therefore, the use of thiophanate-methyl is not expected to pose an acute risk to earthworms, but may pose a chronic risk to earthworms for some uses. A label statement is required to inform users of the potential risks to earthworms.

4.2.1.2 Bees

A risk assessment for bees was conducted according to the Guidance for Assessing Risks to Bees (2014). At the Tier I screening level, risk to adult bees was below the LOC for all labelled soil and seed treatment applications of thiophanate-methyl based on acute and chronic exposures (Appendix X, Tables 6–12). Risk to adult bees was below the LOC for all labelled foliar applications of thiophanate-methyl based on acute and chronic exposures, with the exception of foliar applications on certain turf grass sites. For turf sites containing bee-attractive flowering plants (for example, clover, dandelion), there is a potential risk of concern to adult bee pollinators from both acute and chronic dietary exposures to residues in pollen and nectar. Turf sites containing grass species only (in other words, sod farms and golf courses) are expected to receive routine maintenance (mowing, chemical control) to remove flowering plants and, therefore, negligible risk to bees is expected in these sites. Risk to adult bees from spray drift following foliar spray applications of thiophanate-methyl was below the LOC based on acute and chronic exposures.

A Tier I screening level risk assessment was not conducted for bee larvae as a suitable endpoint was not available for this life stage. A potential risk to bee brood (in other words, colony strength development) was identified at applications above 750 g/ha of thiophanate-methyl in a higher tier field study conducted under semi-field tunnel conditions. Therefore, for relevant labelled uses of thiophanate-methyl above 750 g a.i./ha, a potential risk to bees cannot be ruled out for foliar uses on high exposure crops (apple, pear, cherry, peach, nectarine, plum, prune and turf grass sites

containing bee-attractive flowering plants) and for foliar uses on low/moderate exposure crops (including white bean). For foliar uses on aspen, poplar, lowbush blueberry, raspberry and strawberry, a low risk to bees is expected as the labelled application rate for these crops is only slightly above the 750 g a.i./ha. For seed treatments, minimal risk to bees is expected considering residues in pollen and nectar from seed treatments are expected to be lower than for foliar and soil applications. Similarly, residues in pollen and nectar from soil applications at plant are expected to be lower than directly sprayed flowers. Therefore, the risk to bees from soil drench applications on potted greenhouse ornamentals is expected to be low.

Based on the risk assessment for thiophanate-methyl and considering the pollinator exposure potential in each crop, the following risk characterizations are made for each registered use.

Foliar Applications:

- For the following crops negligible risk to bees is expected as bee-attractive flowers are either not present or are routinely removed:
  - Turf (sod farms and golf courses)
  - Tobacco
  - White button mushroom

- For the following crops, minimal potential for risk to bees is indicated based on Tier I screening assessments and Tier II semi-field tunnel data:
  - Aspen, Poplar
  - Apple, Pear (Eastern Canada Rate)
  - Lowbush blueberry
  - Raspberry
  - Strawberry
  - Outdoor ornamentals, Roses

- For the following crop, a potential for risk to bees is indicated based on Tier II semi-field tunnel data and considering potential for low/moderate pollinator exposure:
  - White beans: The label currently does not restrict application timing. Applications are recommended when conditions of disease are favourable, which is usually during the early stages of bloom.

- For the following crops, a potential for risk to bees is indicated based on Tier I screening assessments and/or Tier II semi-field tunnel data and considering potential for high pollinator exposure:
  - Apple and Pear (British Columbia Rate): The label currently does not restrict application timing. Preventative applications are recommended according to temperature/disease forecasting models in spring.
  - Cherry, Peach, Nectarine, Plum and Prune: Applications are timed to the very early stages of blossoming and at full bloom to ensure adequate protection. In British Columbia, apply at pink and full bloom stage.

- Turf grass sites where clover or other flowering bee-attractive plants are present. The label currently does not restrict application timing.

Seed Treatment Applications:

- For the following crops, minimal potential for risk to bees is indicated based on Tier I screening assessments and Tier II semi-field tunnel data:
  - Sweet Corn
  - Dry Common Bean
  - Potato

Soil Applications:

- For the following crop, minimal potential for risk to bees is indicated based Tier I screening assessments and Tier II semi-field tunnel data:
  - Potted greenhouse ornamentals

Where a potential for risk is identified, additional risk management is proposed for protection of pollinators. Mitigation may include changes to the application timing to reduce bee exposure to the pesticide. With this mitigation in place, risk to pollinators is considered acceptable. Risk mitigation for each use is presented in Appendix X, Table 13 based on the overall pollinator exposure potential (negligible, low-moderate, high) and the application method to the crop (foliar, soil, seed treatment).

4.2.1.3 Beneficial Arthropods (Predators and Parasitoids)

At the screening level, risk to beneficial non-target arthropods including predators and parasitoids was assessed using the maximum cumulative in-field and off-field EECs on plant surfaces, calculated from a direct spray on a field compared to the most sensitive toxicity endpoints (LR_{50}) based on acute exposure on glass plates for representative beneficial arthropods *Aphidius rhopalosiphi* (aphid parasitoid) and *Typhlodromus pyri* (predatory mite). The endpoints considered in the risk assessment for thiophanate-methyl are presented in Appendix X, Table 2. The risk to beneficial arthropods was below the LOC of 2 at the tier I screening level for all representative uses of thiophanate-methyl (RQ ≤ 1.7) except for the use on turf.

For turf, the calculated RQ values resulting from exposure to thiophanate-methyl on glass plates exceeded the LOC of 2 for *A. rhopalosiphi* and *T. pyri* for on-field exposure only (RQs ranged from 4.3–8.2). The off-field RQ values for turf did not exceed the LOC for *A. rhopalosiphi* and *T. pyri* (RQ ≤ 0.50).

The risk to beneficial arthropods was refined for on-field exposure on turf to reflect more realistic exposure by considering foliar interception. The screening level exposure estimates assume deposition to a 2-dimensional structure. Therefore, the values can be corrected to take into account the 3-dimensional structure of a crop canopy, where a certain fraction is intercepted by the crop plants (for in-field exposure) or the off-field vegetation (for off-field exposure). For the in-field EEC, crop-specific foliar interception factors (F_{int}) proposed by Linders *et al.* (2000)

are applied to the application rate. The in-field EECs for turf were refined by applying a foliar deposition factor of 0.4, based on the deposition fraction relevant for grasses. The refined in-field RQs for turf exceeded the LOC of 1 for *A. rhopalosiphi* and *T. pyri* (RQ ≤ 3.3).

The risk to beneficial arthropods in turf was further characterized using acute toxicity (mortality) and sub-lethal (reproduction) endpoints derived from an extended laboratory test based on exposure of *A. rhopalosiphi* female wasps to residues on barley plants. In this toxicity study, mortality did not exceed 5% and the parasitization rate was reduced by 44.9% after 48 hours of exposure to residues compared to the control at doses up to 1500 g a.i./ha, therefore the endpoint from this study is LR_{50}/ER_{50} >1500 g a.i./ha. The endpoint is based on a more realistic exposure scenario and was therefore selected for the risk assessment instead of the more conservative reproduction endpoint based on exposure of *A. rhopalosiphi* female wasps to thiophanate-methyl residues on glass plates. The in-field EEC for turf was further refined by applying a foliar deposition factor of 0.4 as described above. The refined in-field RQ values for turf exceeded the LOC of 1 (RQ ≤ 3.2).

A field study in apple orchards in Germany testing a suspension concentrate (SC) formulation of thiophanate-methyl was presented in the EFSA 2018 review. No adverse effects on populations of *T. pyri* were reported after three applications at 525 g a.i./ha. Assuming a 7 day application interval and 10 day foliar half-life, this represents a maximum cumulative application rate of 1047.2 g a.i./ha which is lower than the maximum cumulative rate for turf. Therefore the results from the study are not considered relevant for informing the risk assessment for turf but are considered relevant for other uses with comparable application rates.

Based on the results of the risk assessment considering tier I data and higher tier information, no risk to beneficial arthropods is expected for all uses of thiophanate-methyl with the exception of the use on turf. For turf a slight potential risk to beneficial arthropods is indicated when thiophanate-methyl is applied on turf at very high rates (2 × 4200 g a.i./ha with a 7 day application interval and 1 × 12 250 g a.i./ha application in the fall). It is noted that the endpoints used in the beneficial arthropod risk assessment were based on greater than values indicating that effects on survival and reproduction did not exceed 50% after exposure to thiophanate-methyl. For beneficial arthropods, a 50% effect is considered to be acceptable since between-season recovery is usually not impeded at this effect level (Candolfi et al., 2000). Therefore, while there were no studies testing rates relevant for the risk assessment for turf, the LOC is not actually expected to be exceeded considering there were no biologically relevant adverse effects at the highest effect endpoints used in the risk assessment and the LOC was only slightly exceeded for turf. In addition, any potential adverse effects are expected to be temporary based on rapid dissipation of this active (DT_{50} = 1 day for soil dissipation) and the potential for recolonization from off-field sites within one season. Considering the LOC was only slightly exceeded for the turf use using greater than endpoint values combined with the potential for rapid dissipation of this active and recolonization in the same season, the use of thiophanate-methyl is expected to pose a low risk to beneficial arthropods.

Risk quotients for screening and refined assessments are shown in Appendix X, Tables 14 and 15.

4.2.1.4 Birds and Mammals

Foliar Applications:

To assess the risk to birds and mammals, the concentration of thiophanate-methyl on various food items (on a dry-weight basis) is used to determine the amount of pesticide in the diet, or estimated daily exposure (EDE). Because exposure is dependent on the body weight of the organism and the amount and type of food consumed, a set of generic body weights is used to represent a range of bird species (20, 100, 1000 g) and mammals (15, 35 and 1000 g), and specialized feeding guilds are considered for each category of animal weights (herbivore, frugivore, insectivore, granivore). Also, as animals may consume large quantities of a given food if they encounter an abundant and/or desirable food source, it is assumed that the diet is comprised entirely (100%) of a particular dietary item.

A screening level assessment is initially carried out to identify uses that do not pose a risk to non-target organisms, groups of organisms that are not expected to be at risk, and areas where there may be a potential for concern and for which further characterization of the risk is required. The screening level risk assessment is based on simple methods, conservative exposure scenarios, and sensitive toxicity endpoints. For this assessment, EDEs are based on EECs that were calculated with maximum residue concentrations from the nomogram. At the screening level, only one feeding guild for each category of bird and mammal weights is selected. The selected feeding guilds are relevant to each specific size of bird or mammal and based on the most conservative residue values (maximum residues determined in the nomogram of Hoerger and Kenaga, 1972 and Kenaga, 1973). A diet consisting of 100% plant material is not considered realistic for small and medium sized birds (20 and 100 g) and small mammals (15 g) and, therefore, was not included in the determination of EDE. The most conservative exposure estimate for these categories of bird and mammal weights is associated with a diet comprised of 100% small insects.

For the birds and mammals screening level assessment, the most sensitive endpoints from acute and reproductive/developmental toxicity studies were chosen for the risk assessment. The endpoints selected for use in the risk assessment are presented in Appendix X, Table 16. A screening level acute risk assessment for birds was done for carbendazim as the endpoint is potentially more sensitive than the endpoint for thiophanate-methyl. The reproductive endpoint for birds for carbendazim indicates it is less toxic than the parent and therefore the risk assessment for thiophanate-methyl captures potential reproductive risks for carbendazim. Screening level EDEs based on the highest single foliar application rate for turf use and RQ calculations for the active ingredient thiophanate-methyl for birds and mammals are presented in Appendix X, Table 17. The only relevant food item considered for the applications to golf course fairways and sod is short grass and insects since these applications would not result in appreciable exposure to grains and seeds, or fruit. The LOC is exceeded for birds and mammals for reproductive endpoints. Screening level EDEs based on the highest single foliar application rate for turf use and acute RQ calculations for the transformation product carbendazim for birds are presented in Appendix X, Table 18. The LOC is not exceeded for carbendazim for birds for acute endpoints.

Given the conservative assumption made at the screening level, the risk to birds and mammals from thiophanate-methyl was further characterized by using the mean residue values for calculating EECs and EDEs instead of the upper bound residue values used in the screening risk assessment. The EDEs were calculated for each bird and mammal size and feeding preference item at the lowest cumulative airblast application rate for apples/pears (437.5 g a.i./ha × 2 at 7-d interval – 706.8 g a.i./ha; Eastern Canada rate), the highest cumulative airblast application rate for apples/pears (1575 g a.i./ha × 2 at 7-d interval; British Columbia rate) and the highest single foliar application rate for turf use (4200 g a.i./ha). The risk associated with the consumption of food items contaminated from spray drift off the treated field was assessed taking into consideration the projected spray drift deposition of spray quality of ASAE medium for ground application to turf (6%) and ASAE fine for airblast application to apples (74%) at 1 m downwind from the site of application.

For mammals, a no observed effect level (NOEL) of 16 mg a.i./kg/day, based on reduced body weight in rat offspring in a two-generation reproductive toxicity study, was used for the screening level assessment. This study showed that effects at the next two dose levels were minimal:

1) A reduction in pup weight of 11 and 13% was observed relative to the control at the 54 and 172 mg a.i./kg bw/day dose levels, respectively;
2) The reduction in pup weight was observed in only one of two litters produced from the F1 generation (F2b); no effects were observed in the F2a litter or the F1generation;
3) The reduction in F2b pup weight was observed only on lactation day 21.

Based on this evidence, it is unlikely that the observed effect reported for F2b pups would result in risks to small mammals in the environment. The NOEL value used in the screening level assessment, therefore, is considered to be highly conservative. The reproductive risk to mammals was further characterized by determining risk quotients based on the next highest dose level, 54 mg a.i./kg bw/day.

The risk to feeding birds and mammals based on maximum and mean residue values on terrestrial food sources is characterized in Appendix X, Tables 19 and 20, respectively. At the lowest cumulative application rate for apples/pears, the LOC for reproductive effects are exceeded for birds feeding on most food items on-field based on maximum and mean residue values (RQ values range from 0.3 to 9.9). For birds feeding adjacent to treated areas, the reproductive LOC is also exceeded for birds feeding on most food items (maximum and mean RQ values range from 0.1 to 7.3). At the highest cumulative application rate for apples/pears, the LOC for reproductive effects are exceeded for birds feeding on all food items on-field and most food items off-field based on maximum and mean residue values (RQ values range from 0.4 to 36). It should be noted that for turf use, insects and short grass are the only relevant food items for birds and mammals feeding on greens and fairways. For the turf use pattern, the LOC for reproductive effects are exceeded for birds feeding on-field (RQ values range from 9 to 59 and 11 to 30 for feeding on insects and short grass, respectively, based on maximum and mean residue values). Although some risk is shown for birds feeding on some food items adjacent to turf treated areas, the risk quotients are relatively low (0.6 to 3.5).

At the lowest cumulative application rate for apples/pears, the LOC for reproductive effects is slightly exceeded for medium sized mammals feeding on short grass and broadleaf vegetation only for the on-field maximum residue values (RQ = 1.2 and 1.1, respectively). At the highest cumulative application rate for apples/pears, the LOC for reproductive effects is exceeded on-field and off-field on several food items based on maximum and mean residue values (RQ values range from 0.1 to 4.3). For the turf use pattern, the reproductive LOC is exceeded for mammals feeding on-field based on maximum and mean residue values; the range of risk quotients are also relatively low (RQ values range from 1.2 to 3.6 and from 1.3 to 7.1 for mammals feeding on insects and short grass, respectively). The LOC for reproductive effects is not exceeded for mammals feeding adjacent to apple orchards or turf treated with thiophanate-methyl.

While potential risks have been identified based on the determination of risk quotients, they are in large part driven by the following assumptions (i) the maximum application rates as well as the maximum number of applications per season will be used, (ii) adverse effects will occur at the exposure concentrations identified by toxicity tests, (iii) dietary items are made up of one type of food, and are all from a pesticide treated area, and (iv) farm activities, including noise, have no repelling effect on birds and mammals, especially during spray treatment. These assumptions are further discussed below.

It should be noted that the bird and mammal risk assessments for orchard use may be overly conservative because, as per standard risk assessment procedures, the determination of thiophanate-methyl residues on food items that birds and mammals eat is based on the shortest interval allowed between applications on the label of the end-use product. In practice, for the purpose of managing diseases' resistance to thiophanate-methyl, all end-use product labels recommend rotating with fungicides having different modes of action. Therefore, under conditions of use, the period between successive applications of thiophanate-methyl may be longer than the 7-day interval used in the risk assessment, allowing more time for dissipation and degradation of the residues from the various sources of food that are eaten by birds and mammals, thereby reducing the actual risk to these organisms. For turf use, the permitted application rate for summer pests ranges from 2100 to 4200 g a.i./ha. Thus, the maximum application rate used in the risk assessment is a conservative assumption as users may use up to 50% less product in the field.

It should also be noted that the assessment for birds was conducted using results reported in the USEPA Re-evaluation Decision for Thiophanate-methyl which only reported No Observed Effect Concentrations (NOECs) which were converted by Health Canada to No Observed Effect Levels (NOELs). Details of the studies were not reported; the Lowest Observed Effect Levels (LOELs) and the type of effects observed in the avian reproductive studies were not available, and therefore the risk could not be further characterized using this information.

Birds may consume a variety of items in their diets from various sources, which may reduce exposure levels. A diet composed only of treated items, and only one type of item may be conservative for assessing the potential for reproductive risk.

The effect of farm activities, including noise, was not considered in the risk assessment for birds and mammals. These factors likely deter birds from nesting in areas with high levels of farming activities, such as apple orchards, and repel birds and mammals during farming operations and spraying activities. These effects would limit the number of birds and mammals that would be exposed to direct spray treatment and may also encourage them to nest and feed off-field.

Overall, the risk assessment shows that foliar applications (apples, turf) of thiophanate-methyl may pose a reproductive risk to birds and mammals. The endpoint used in the mammalian risk assessment was conservative and demonstrated a minimal effect. Using this conservative endpoint, the risk to mammals is low and is mainly from on-field use. The endpoint used for the assessment for birds was based on a NOEL and indicated that insectivores and herbivores were most at risk. It is noted that the highest cumulative airblast application rate for apples/pears (1575 g a.i./ha × 2 at 7-d interval; British Columbia rate) is being proposed for phase-out due to occupational health and safety concerns. With the removal of that rate, off-field risk quotients are all below 8 for the lowest cumulative airblast application rate for apples/pears (437.5 g a.i./ha × 2 at 7-d interval – 706.8 g a.i./ha; Eastern Canada rate) and the highest single foliar application rate for turf use (4200 g a.i./ha).

There are no incident reports showing thiophanate-methyl has been responsible for bird or mammal deaths or poisonings as a result of registered use. Incident reports are typically made when mortalities are observed, and a lack of incident reports is consistent with the lack of acute mortality risk identified for birds and mammals.

A label statement is required to inform the user of the potential hazard to birds and mammals.

Seed Treatments:

When pesticides are used as a seed treatment, the treated seed may be consumed as a food item by both birds and mammals. The risk assessment method for treated seed is similar to that of spray applications, except that the dietary items are treated seeds rather than dietary items sprayed with a pesticide. Thiophanate-methyl is registered as a seed treatment on dry beans, sweet corn and potato pieces. A risk assessment was conducted for birds and mammals to address the consumption of treated seed.

The exposure of birds and mammals to a pesticide through consumption of treated seed is a function of the amount of pesticide on the seed, the body weight and food ingestion rate of the animal, and the number of seeds available for consumption. In the screening level assessment, it is assumed that the diet consists entirely of treated seeds, and all of the treated seed that is planted is available for consumption *ad libitum*, over an extended period of time. Variables of feeding preference, availability of treated seed, or potential avoidance behaviour toward treated seed are not considered at the screening level.

The risk was assessed using generic bird and mammal body weights as described in the preceding section on foliar applications. The toxicity endpoints selected for use in the risk assessment are presented in Table 17. For each size of organism, the estimated daily exposure (EDE) is calculated using the following equation: EDE (mg a.i./kg bw/day) = (FIR/BW) × EEC.

FIR: Food ingestion rate, in g dry weight per day
BW: Body weight of organism, in g
EEC: Concentration of pesticide in diet, in mg a.i./kg dry weight diet

Screening EECs were determined for the highest seed treatment rate for dry beans (729.4 mg a.i./kg seed). Although thiophanate-methyl can be applied at a higher rate for the treatment of potato seed pieces (750 mg a.i./kg seed), birds typically will not consider seed potato as a food, and mammals are not expected to consume high amounts of potato seed pieces as 100% of their diets; therefore, the potential exposure to wild birds and mammals is expected to be minimal. The Food Ingestion Rate (FIR) is based on allometric equations from Nagy (1987). These equations determine the mass of food consumed per day in dry weight, based on the body weight of the organism.

The screening level EDEs and risk quotients for each size class of birds and mammals feeding on treated seed are presented in Appendix X, Table 21 for thiophanate-methyl. The LOC is exceeded for reproductive effects for all bird and mammal size categories for dry bean, with the exception of large mammals. The screening level EDEs and risk quotients for carbendazim for each size class of birds feeding on treated seed are presented in Appendix X, Table 22. The LOC is not exceeded for carbendazim.

The risk values presented in Appendix X, Tables 21 and 22 for the screening level assessments assume that all planted seed is available. The risk assessment of thiophanate-methyl for birds and mammals was expanded taking into consideration that not all seeds planted will be exposed and available to birds or mammals. De Snoo and Luttik (2004)[5] suggest that the percentage of seeds remaining on the soil surface in field headlands is dependent on the seeding method and the time of year in which seeding occurs; the values reported include 0.5% for precision drilling, 3.3% for standard drilling in spring, and 9.2% for standard drilling in autumn.

This information was used along with typical seeding rate ranges for each seed crop (dry beans and sweet corn) to estimate the minimum and maximum area required for a bird and mammal to find enough seeds to reach the toxicity endpoint; this refinement does not change the RQ determined. Dry beans are assumed to be seeded using standard drilling in spring whereas sweet corn is solely seeded using precision drilling (in other words, planter: vacuum or positive pressure).

In Appendix X, Table 23, the number of seeds needed to be consumed per day to reach the toxicity endpoint can be compared to the foraging area required for birds and mammals to reach the toxicity endpoint. The number of seeds to reach the endpoint is expressed as a range based on known seed size range. Similarly, a range is shown for the area required for foraging based on a range of known seeding rates.

[5] de Snoo, G.R., R. Luttik (2004) Availability of pesticide-treated seed on arable fields. Pest Management Science 60:501-506.

For dry beans, the number of treated seeds needing to be consumed to reach the reproductive LOC for birds and mammals is very low in some cases, in other words, less than 1 seed for a small bird, 3 to 6 seeds for small mammals, and only a few seeds for medium sized birds and mammals (2–4 and 8–13 seeds, respectively). The area required to forage for enough seeds to reach the reproductive endpoint is also very small (in other words, 0.4–2.5 m^2 for small birds, 1.8–13 m^2 for medium sized birds, and 4–11 m^2 for small mammals). However, small birds would not be expected to consume dry bean due to the large seed size. As well, birds of all sizes do not find soybean an attractive food source, and dry bean may be similarly unattractive. For larger birds, harmful effects are considered less likely with thiophanate-methyl treated seed because of the relatively large number of seeds needing to be ingested and the large foraging area necessary to acquire enough treated seed to reach the endpoints. The screening level assessment did not exceed the LOC for large mammals.

For sweet corn, the number of treated seed needing to be consumed to reach the reproductive LOC for birds and mammals is also very low, in other words, approximately 1 seed for a small bird, 5–9 seeds for small mammal, and only a few seeds for medium sized birds and mammals (3–6 and 11–21 seeds, respectively). However, small birds would not be expected to consume corn seed due to the large seed size. In addition, the area required to forage for enough seeds to reach the reproductive endpoint is relatively large (in other words, 11–125 m^2 for small birds, 152–434 m^2 for small mammals, and 54–64 and 35–1012 m^2 for medium sized birds and mammals, respectively). For larger birds, harmful effects from thiophanate-methyl treated seed are less likely due to the relatively large number of treated seeds needing to be ingested and the large foraging area necessary to acquire enough treated seed to reach the endpoints.

Based on the results of the risk assessment, risk from treated seed is typically expected to be low; however, dry bean and sweet corn seed treatments could pose a potential reproductive risk to some birds and mammals. To reduce the potential for exposure to birds and small wild mammals associated with feeding on treated seed left on the soil surface a hazard label statement is proposed.

4.2.1.5 Terrestrial Plants

The non-target terrestrial plant seedling emergence toxicity (Tier 1) and vegetative vigour toxicity (Tier 1) studies were conducted on four monocot species and six dicot species. Thiophanate-methyl did not significantly affect seedling emergence or vegetative vigour in plants at rates up to 1680 and 1570 g a.i./ha, respectively. There are currently no incident reports involving thiophanate-methyl or carbendazim and terrestrial plants in Canada or the United States. The use of thiophanate-methyl is expected to pose a negligible risk to terrestrial vascular plants.

4.2.2 Risks to Aquatic Organisms

Based on available data, thiophanate-methyl is slightly toxic to moderately toxic to freshwater and marine organisms on an acute basis. Chronic toxicity to thiophanate-methyl is not expected as it transforms quickly to the major transformation product, carbendazim, in water. Carbendazim, is moderately toxic to very highly toxic to freshwater invertebrates, amphibians

and fish for acute exposures. Based on laboratory studies, carbendazim is more toxic than thiophanate-methyl to *Daphnia magna* and freshwater fish. Aquatic endpoints are summarised in Appendix X, Table 3. Incident reports for thiophanate-methyl and carbendazim related to the aquatic environment are summarized in Section 4.2.3.

A screening level risk assessment was conducted for aquatic organisms based on the highest cumulative application rate for turf uses of thiophanate-methyl. Screening level risk quotients exceeded the LOC for both thiophanate-methyl and carbendazim, including acute and chronic effects for freshwater and marine organisms, with the following exceptions: acute risk of *Daphnia* and aquatic vascular plants in freshwater, and acute risk of fish in marine waters did not exceed the LOC for thiophanate-methyl (Appendix X, Table 24). As a result, the risks were further characterized for spray drift and overland runoff of water into freshwater and marine habitats.

4.2.2.1 Assessment of Potential Risk from Runoff

A risk assessment for runoff to aquatic organisms is conducted using modelled concentrations for acute and chronic exposures. Chronic exposures can be further characterized if adequate water monitoring data is available. As monitoring data typically underestimate peak concentrations in water, only water modelling results are used for an assessment of acute risks due to runoff.

Modelled Concentrations in Runoff Water:

The potential risk to aquatic organisms from runoff of thiophanate-methyl and carbendazim to a modelled body of water directly adjacent to the site of application was determined. Concentrations were predicted using the Pesticide Water Calculator (PWC v1.52) model. The highest modelled EECs for the appropriate time period, crop use site, habitat (80 cm depth of water for fish and aquatic invertebrates; 15 cm depth of water for amphibians) and active ingredient were selected and the revised RQ values were calculated. The results reported in this document are for turf, white bean and orchard uses (apple/pear). It should be noted that, although the labelled application rate for use on apples/pears in British Columbia (B.C.) (1.575 kg a.i./ha ×2, 7-day interval) is higher than the that for Eastern Canada (Ontario and Quebec; 0.4375 kg a.i./ha × 2, 7-day interval), the modelled runoff EECs were higher for Ontario and Quebec scenarios and, therefore, were reported here. Higher model estimates are due to regional differences in model input parameters. As the higher EECs are considered to be more conservative, potential risks from runoff for the higher use rate on apples/pears in B.C. will be accounted for by this assessment.

Thiophanate-methyl

For thiophanate-methyl, based on the available toxicity endpoints and EECs representing the 90th percentile of concentrations for a timeframe reflecting the exposure duration of the toxicity tests, the LOC for freshwater and estuarine/marine organisms (acute or chronic) was not exceeded (Appendix X, Tables 25 and 26).

Carbendazim

For carbendazim and marine habitats, a chronic (life-cycle) exposure of the Mysid shrimp, *Americamysis bahia*, to carbendazim exceeded the LOC for turf and white bean application scenarios (RQs = 1.7 and 1.5, respectively) but not for apples and pears (RQ = 0.2) (Appendix X, Table 27). Risk quotients only marginally exceeded the LOC. Precautionary label statements informing users to avoid runoff to these areas are expected to mitigate risks to marine habitats.

For carbendazim and freshwater habitats, chronic exposures of *Daphnia* and channel catfish to carbendazim exceeded the LOC for turf, white bean, and orchard application scenarios. Acute exposures of freshwater fish and amphibians to carbendazim exceeded the LOC for turf and white bean application scenarios but not for apples and pears. Acute data were not available for aquatic plants; however, carbendazim is not expected to pose unacceptable risk to this group of organisms. The risks are characterized as follows (also see Appendix X, Table 27).

- Acute Exposure, 15 cm (amphibian habitat) and 80 cm of water (other aquatic habitats):

Acute toxicity values were available for representative species of both amphibian habitat and other types of freshwater aquatic habitat. For conducting a risk assessment for amphibians, the most sensitive fish acute (LC_{50}) is used as a surrogate endpoint if actual amphibian data is not available. In this case, acute endpoints for effects of carbendazim on the embryonic and tadpole stages of frog development were available. Using the most sensitive amphibian endpoint, RQs were relatively low and ranged from 0.2 (apples/pear) to 1.7 (turf).

For other types of aquatic habitats (80 cm of water) the median hazardous concentration to 5% of species (HC_5) was calculated from a species sensitivity distribution (SSD) for freshwater fish, which was the most sensitive acute value from all aquatic species. The HC_5 is theoretically protective of 95% of all species at the effect level used in the analysis (LC_{50} in this case). Risk quotients varied from 0.5 (apple/pear) to 3.7 (turf) (Appendix X, Table 27). The RQs were not characterized further for acute exposure.

- Chronic exposure, 15 and 80 cm of water:

Chronic toxicity values were also available for representative species of both amphibian habitat and other types of freshwater aquatic habitat. Risk quotients ranged from 10 (apple/pear) to 63 (turf) for amphibian habitat (using a fish early life-stage NOEC) and from 3.0 (apple/pear) to 28.7 (turf) in other aquatic habitats (using a 21-day NOEC for *Daphnia magna*, Appendix X, Table 27). Chronic risk was characterized further using water monitoring data.

Water monitoring data:

In addition to water modelling, available water monitoring data can be used to further characterize the chronic risk to aquatic habitats. Sufficient water monitoring data for thiophanate-methyl and carbendazim were available for consideration in the environmental risk assessment.

Data from ambient surface water bodies, such as rivers, lakes and reservoirs are considered to be relevant for aquatic risk assessment purposes. It should be noted, however, that monitoring data typically underestimate peak concentrations because sampling programs are not tailored to capture peak concentrations.

For thiophanate-methyl, samples were collected in Ontario and Prince Edward Island (PEI). Grab samples were collected in PEI (n = 141) and thiophanate-methyl was detected in 18% of the samples. The maximum concentration detected was 4 µg/L. In Ontario, data were collected from both grab samples and passive sampling using Polar Organic Chemical Integrative Samplers (POCIS). Thiophanate-methyl was detected in all 21 grab samples collected with a maximum detection of 0.024 µg/L. The POCIS were deployed during two consecutive 14-day periods between May and June 2016 in a total of 18 watersheds in southwestern Ontario. The watersheds were mostly located in areas of intensive agriculture but several of the watersheds were also highly urbanized. The highest calculated average concentration over the 28-day period of POCIS deployment for thiophanate-methyl was 0.021 µg/L. For thiophanate-methyl no surface water samples were available from the United States

For carbendazim, samples were collected in Ontario and the American Carbendazim was detected in all 21 grab samples collected in Ontario with a maximum concentration of 0.513 µg/L. Passive sampling was conducted using POCIS deployed during two consecutive 14-day periods between May and June 2016 in a total of 18 watersheds in southwestern Ontario. The highest calculated average concentration over the 28-day period of POCIS deployment for carbendazim was 0.039 µg/L. There were no surface water monitoring data collected for carbendazim in other areas of Canada but this compound was detected often in the United States (38% detection frequency in 10 149 samples). The maximum concentration of carbendazim detected was 4.87 µg/L from a reclamation canal in an agricultural area in California. A reclamation canal may not be representative of aquatic habitat. The next highest detection was 2.53 µg/L from a sample taken in Minnesota.

Based on an assessment of the available monitoring information, chronic exposure to thiophanate-methyl above the LOC for aquatic organisms is not expected because of its rapid transformation in both soil and water. The most sensitive chronic endpoints in the carbendazim aquatic risk assessment are NOEC values of 1.5 µg/L for aquatic invertebrates and 1.9 µg/L for fish and amphibians. In all of the data available for carbendazim surface water samples, only three values exceed the most sensitive chronic endpoint. These values are: 4.78 µg/L taken from a reclamation canal in an agricultural area in California, 2.53 µg/L from a sample taken in Minnesota, and 1.79 µg/L from a sample taken in Georgia. Based on the available monitoring data, chronic risk to aquatic organisms is not expected as levels of carbendazim are not consistently found at concentrations above 1.5 µg/L.

In conclusion, based on the monitoring data available for this assessment, the chronic risks to aquatic organisms from runoff are expected to be acceptable. Relatively low acute risks due to runoff were identified and, therefore, precautionary label statements informing the user of ways to reduce runoff will be required.

Release of Effluent from Greenhouses and Mushroom Houses:

Thiophanate-methyl is registered for use in greenhouses and mushroom houses. A quantitative assessment of the potential for exposure of aquatic habitats from these use sites is not currently conducted by Health Canada. However, as thiophanate-methyl quickly transforms to carbendazim in soil and water matrices, carbendazim may be present in wash-waters or other effluent from these types of operations. As carbendazim is persistent under certain conditions, and is toxic to aquatic organisms, a label statement will be required to inform users to prevent the release of effluents that may contain carbendazim to the environment.

4.2.2.2 Assessment of Potential Risk from Spray Drift

The potential risks to aquatic organisms from spray drift were also characterized. The assessment highlights the risk quotients determined for field sprayers (turf and white bean), airblast (apple/pear in Eastern Canada) and aerial applications (white bean) for various aquatic organisms, marine and freshwater, including the most sensitive endpoints. Instead of assuming a direct application to a water body, as for the screening level assessment, EECs based on spray drift were calculated using the maximum drift deposition (percent of application rate) at one metre downwind from the point of application. The maximum percent drift deposition will vary depending on the droplet size and type of application equipment that is used. The ASAE classification of 'fine' droplet size was used for early season and late season airblast application and estimates deposition of 74% and 59% of the application rate, respectively, at one metre. The maximum percent drift deposition for an ASAE 'medium' droplet size is 6% and 23% of the application rate for field sprayer and aerial (agricultural) application, respectively. The EECs were calculated for freshwater waterbodies 80-cm (fish and invertebrates) and 15-cm deep (amphibians) by using the maximum cumulative rate and these deposition values to adjust the concentration in water. For estuarine/marine habitats, chronic risk from drift is not expected due to high water renewal rates in tidal/estuarine areas; therefore, only acute endpoints are used in the risk assessment. To assess the potential risk from carbendazim to estuarine/marine organisms, the acute endpoint for mysid shrimp was converted using the molecular weight ratio of 0.558 thiophanate-methyl/carbendazim.

The risk quotients obtained using the EECs for maximum drift at one meter from the point of application are presented in Appendix X, Tables 28 (freshwater) and 29 (marine) for thiophanate-methyl and Table 30 (freshwater and marine) for carbendazim.

Based on the results of this assessment, no risks were identified for exposure of aquatic habitats to thiophanate-methyl from spray drift with the exception of turf field sprayers and amphibian habitats, where the RQ was marginally exceeded (RQ = 1.5). For carbendazim, however, risks to freshwater aquatic systems from spray drift were identified. Thiophanate-methyl is expected to transform rapidly in water to carbendazim, which is considered to be moderately persistent. RQs were calculated for early and late airblast application in orchards, field sprayer for turf and white bean, and aerial application for white bean, and are summarized for carbendazim as follows:

- Freshwater invertebrates, RQs range from 5.6 to 36.3
- Freshwater fish, RQs range from 0.6 to 27.2

- Amphibians (using amphibian data when available and freshwater fish data as a surrogate otherwise), RQs range from 0.4 to 145, and
- Marine invertebrates (using the converted thiophanate-methyl endpoint), RQs range from <0.1 to 0.2.

As a result, spray drift buffer zones will be required to mitigate the risks to the following aquatic habitats: amphibian breeding habitat (15 cm water depth) and freshwater habitats (80 cm water depth). As the RQs for the marine scenario were less than one, a default buffer zone of one metre will be required for marine habitats. At the screening level assessment, if the risk exceeds the level of concern (in other words, RQ ≥1), then a Tier 1 assessment is triggered and a minimum buffer zone of 1 m is required. Note that for marine habitats, buffer zones are determined based on acute endpoints and the maximum single application rate only to reflect the lower potential of chronic exposure due to higher water renewal rates in tidal/estuarine areas. Inputs to the buffer zone models are in Appendix X, Table 31.

4.2.3 Environmental Incident Reports

Eleven environmental incidents have been reported in Canada as of November, 2018 (three incidents involved thiophanate-methyl and 10 involved the transformation product, carbendazim; note that two of the incidents reported both substances).

One environmental incident involved a fire in a pesticide storage warehouse which resulted in dousing water entering a nearby stream and killing fish. Many active ingredients were involved; it was considered unlikely that thiophanate-methyl was responsible for the fish deaths.

The remaining ten Canadian incidents involved adverse effects to honeybees (including abnormal behaviour, reproductive impairment, and death). None of the incident reports involving bees were considered to be related to the application of thiophanate-methyl. More than one active ingredient was reported, often including at least one insecticide.

Five environment incident reports involving thiophanate-methyl and four involving carbendazim were found in the USEPA Ecological Incident Information System, which was last updated on 5 October 2015. In the United States, only two of three incidents that reported bee mortality following application to orchards or agricultural sites were possibly associated with thiophanate-methyl application.

Two fish mortality incidents were the result of runoff; one of these incidents was the same incident that was reported in Canada following a fire at a chemical storage warehouse. In the American Ecological Incident Information System , this Canadian incident was considered to be possibly related, while the other fish kill was considered to be unlikely.

Four incidents were also reported to the USEPA for carbendazim. Three incidents reported bee mortality, but were considered unlikely to be related to the active ingredient. One incident that occurred in Australia involved the discovery of deformed mullet and bass embryos and larvae at a fish hatchery located in close proximity to macadamia nut plantations where pesticides, including carbendazim, were being used. The fish hatchery used water from a nearby river which

may have received drift and runoff containing pesticides used at the macadamia nut plantation, of which one was carbendazim. The USEPA concluded that the malformations were probably associated with carbendazim. The amount of information provided with this report was insufficient to determine if the incident was relevant to Canadian uses of thiophanate-methyl.

5.0 Value Assessment

5.1 Value of Thiophanate-Methyl

Thiophanate-methyl is a systemic broad spectrum fungicide with protective and curative action. This fungicide works by disrupting fungal mitosis, which prevents the growth and development of a fungal pathogen. Thiophanate-methyl is registered for use on: greenhouse ornamentals, greenhouse food crops, terrestrial food crops, outdoor ornamentals, turf, and seed treatment for food crops. It is valuable to several sectors as it is currently the only active ingredient in the FRAC Group 1 mode of action registered for certain agricultural uses and therefore, is important for resistance management in susceptible high-risk pathogens, such as powdery mildew and grey mould. With the exception of mushrooms and seed treatments on dry beans and sweet corn, thiophanate-methyl is the only MOA group 1 registered for all uses (Note that thiophanate-methyl is only available in co-formulation with other fungicides for the seed treatments).

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

In accordance with the PMRA Regulatory Directive DIR99-03,[6] the assessment of thiophanate-methyl against Track 1 criteria of Toxic Substances Management Policy (TSMP) under *Canadian Environmental Protection Act* was conducted. It determined that:

- Thiophanate-methyl does not meet all Track 1 criteria, and is not considered a Track 1 substance (refer to PRVD2011-07 for details of the assessment).
- Thiophanate-methyl does not form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical grade active ingredient and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada*

[6] DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy

Gazette.[7] The list is used as described in the Health Canada Notice of Intent NOI2005-01[8] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[9] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). Health Canada has reached the following conclusions:

- Technical grade thiophanate-methyl and its related end-use products do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

7.0 Conclusion of Science Evaluation

Health

Based on the current use pattern of thiophanate-methyl, human health risks were shown to be acceptable for most uses with proposed risk mitigation measures. For certain other uses, occupational risks were not shown to be acceptable and therefore these uses are proposed for cancellation. These uses are:

- Aerial application using wettable powder products.
- Wettable powder products on all turf uses, white bean, sugarbeet, aspen and poplar.
- All turf uses, except on golf courses and sod farms for the liquid and water-soluble packaging products.
- Greenhouse tobacco seedlings (foliar spray and foliar drench applications).
- Greenhouse cut flowers (foliar application).
- Outdoor cut flowers.
- Apples and pears in British Columbia due to the high application rate (this use in Eastern Canada has acceptable risks due to the lower application rate).
- Peach, nectarine, plum, prune, cherry.
- Commercial seed treatment of bean seeds using wettable powder products.
- On-farm dry application to bean seeds using wettable powder products.
- Potato seed piece treatment for all product formulations.

The PMRA is also proposing to clarify the residue definition of thiophanate-methyl for enforcement purposes. The current residue definition of:

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7 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette,* Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

8 NOI2005-01, List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New *Pest Control Products Act*.

9 DIR2006-02, Formulants Policy and Implementation Guidance Document.

> "Methyl N-1H-benzimidazol-2-ylcarbamate (carbendazim) and dimethyl N,N′-[1,2-phenylenebis(iminocarbonothioyl)]bis[carbamate], expressed as carbendazim"

will be changed to:

> "Dimethyl *N,N*′-[1,2-phenylenebis(iminocarbonothioyl)]bis[carbamate] (thiophanate-methyl), including the metabolite methyl *N*-1*H*-benzimidazol-2-ylcarbamate (carbendazim), expressed as carbendazim equivalents."

Environment

The environmental assessment has determined that thiophanate-methyl poses acceptable risks to the environment when used as a foliar spray and seed treatment according to revised label directions. The revised label directions include updated advisory statements and spray buffer zones which can be found in Appendix XI.

Value

Thiophanate-methyl is a broad spectrum systemic fungicide with protective and curative action. Thiophanate-methyl is of particular value for producers where there are few or no registered alternative products. For some uses, thiophanate-methyl is the only active ingredient in the FRAC Group 1 mode of action, which makes it a valuable tool for use in resistant-prone pathogens.

List of Abbreviations

↑	increased
↓	decreased
µg	microgram(s)
♀	females
♂	males
2AB	2-aminobenzimidazole
5-HBC	5-hydroxy-2-benzimidazole carbamate
a.i.	active ingredient
abs	absolute
AD	administered dose
ADI	acceptable daily intake
AHETF	Agricultural Handlers Exposure Task Force
AHP	contaminant (CAZ genotoxicity summary)
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
AST	aspartate aminotransferase
ATPD	area treated per day
BMDL	benchmark dose (lower confidence limit)
BUN	blood urea nitrogen
bw	body weight
bwg	bodyweight gain
CAF	composite assessment factor
CAZ	carbendazim
CFIA	Canadian Food Inspection Agency
ChE	cholinesterase
cm	centimetre
cm^2	centimetres squared
CR	chemical-resistant
CRC	chemical-resistant coveralls
CYP	cytochrome P
d	day(s)
DA	dermal absorption
DAP	2,3-diaminophenazine
DFR	dislodgeable foliar residue
DIR	Regulatory Directive
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
EC	Eastern Canada
EC_{50}	exposure concentration to 50% of the population

ED_{50}	effective dose 50%
EDE	estimated daily exposure
EEC	estimated environmental concentration
EOGRTS	extended-one generation reproductive toxicity study
ER_{50}	median effect rate/emergence rate
F1	first generation
F2	second generation
fc	food consumption
fe	food efficiency
FIR	Food ingestion rate, in g dry weight per day
FRAC	Fungicide Resistance Action Committee
FSH	follicle stimulating hormone
ft	feet
g	gram
GD	gestation day
GnRH	gonadotropin releasing hormone
ha	hectare
HC	historical control
HCG	human chorionic gonadotropin
Hct	hematocrit
Hgb	hemoglobin
hr(s)	hour(s)
i.p.	intraperitoneal
i.v.	intravenous
kg	kilogram
L	litre(s)
LADD	lifetime average daily dose
LC_{50}	lethal concentration required to kill 50% of the test group
LD_{50}	lethal dose required to kill 50% of the test group
LH	leutinizing hormone
ln	natural logarithms
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOEC	lowest observed effect concentration
LR_{50}	median lethal rate
M	molar
M/L/A	mixer/loader/applicator
m^2	metres squared
MCH	mean cell hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
mg	milligram
MIS	maximum irritation score
MOA	Mode of Action
MOE	margin of exposure
MPHG	mechanically-pressurized handgun

MPHW	manually-pressurized handwand
MRL	maximum residue limit
MTD	maximum tolerated dose
NA	not available
N/A	not applicable
NADH	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NR	not reported
°C	degree(s) Celsius
P	parental generation
PCNA	proliferating cell nuclear antigen
PCPA	*Pest Control Product Act*
PCV	packed cell volume
PDP	Pesticide Data Program (United States data)
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
PND	postnatal day
POCIS	Polar Organic Chemical Integrative Sampler
ppm	parts per million
PRVD	Proposed Re-evaluation Decision
RBC	red blood cell
REI	restricted-entry interval
rel	relative
Resp.	respirator
REV	Re-evaluation Note
RNA	ribonucleic acid
RQ	risk quotient
SFO	single first order
SOP	standard operating procedure
T3	triiodothyronine
T4	thyroxine
TC	transfer co-efficient
TPM	thiophanate-methyl
TSH	thyroid stimulating hormone
TSMP	Toxic Substances Management Policy
TTR	turf transferable residue
TWA	time-weighted average
USEPA	United States Environmental Protection Agency
UDP	uridine diphosphate
WBC	white blood cell
wk(s)	week(s)
wt	weight

Appendix I

Registered Thiophanate-methyl (TPM) Products[10]

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Active Ingredient and Guarantee
12279	Commercial	Nippon Soda Company Ltd.	Senator 70WP 1 Fungicide	Wettable powder	TPM: 70%
14599	Commercial	Nippon Soda Company Ltd.	Senator PSPT 1 Potato Seed Piece Treatment	Dust	TPM: 10%
25343	Commercial	Nippon Soda Company Ltd.	Senator 70WP Fungicide	Wettable powder	TPM: 70%
26236	Commercial	Nippon Soda Company Ltd.	Senator PSPT Potato Seed Piece Treatment	Dust	TPM: 10%
26987	Commercial	Norac Concepts Inc.	Caption CT	Wettable powder	TPM: 14% Captan: 18%
27297	Commercial	Nippon Soda Company Ltd.	Senator 70 WP WSB1 Fungicide	Wettable Powder in Water Soluble Package	TPM: 70%
31761	Commercial	Norac Concepts Inc.	TPM Flowable 25% Undyed Liquid Fungicide Seed Treatment	Solution	TPM: 296.5 g/L
31784	Commercial	Nippon Soda Company Ltd.	Thiophanate-Methyl 500 SC Fungicide	Suspension	TPM: 500 g/L
32093	Commercial	Nippon Soda Company Ltd.	Cercobin Fungicide	Suspension	TPM: 500 g/L
32096	Commercial	Nippon Soda Company Ltd.	Senator 50 SC Fungicide	Suspension	TPM: 500 g/L
32097	Commercial	Nippon Soda Company Ltd.	Renovo Fungicide	Suspension	TPM: 500 g/L
27539	Manufacturing Concentrate	Nippon Soda Company Ltd.	Senator 70WP MUP Systemic Fungicide	Wettable powder	70%
32291	Manufacturing Concentrate	Nippon Soda Company Ltd.	TPM 500 SC MUP	Suspension	TPM: 500 g/L
22710	Technical Grade Active Ingredient	Nippon Soda Company Ltd.	TPM Technical	Wettable powder	TPM: 98.3%

[10] As of 11 January 2019, excluding discontinued products or products with a submission for discontinuation

Appendix II Registered and Registrant Supported Commercial and Restricted Class Uses of Thiophanate-methyl[1,2]

Site	Pest(s)	Formulations	Application Method and Equipment	Maximum Single Application Rate (g a.i./ha)	Maximum Cumulative Application Rate per Year(g a.i./ha)	Maximum Number of Applications per year	Minimum Interval Between Applications (Days)
Use-site Category 5 – Greenhouse Food Crops							
White button mushroom - casing	Trichoderma green mould	Wettable powder Suspension	Ground equipment or mechanical spreading of treated spawn	4270	34 160	1 application/crop cycle made either as a casing or a spawning treatment [8 crop cycles per year]	Not applicable
White button mushroom - spawn		Wettable powder		8750	70 000		
Tobacco seedlings, greenhouse	Rhizoctonia damping-off	Wettable powder Suspension Water soluble bags	Ground application equipment	6300	12 600	2	10
Use-site Category 6 – Greenhouse Non-Food Crops							
Greenhouse potted ornamentals	Botrytis, Leaf spots, Powdery mildew	Wettable powder Suspension Water soluble bags	Foliar	595	1190	[2]	7
Greenhouse potted ornamentals	Stem, crown and root rots caused by *Fusarium* and *Rhizoctonia*	Wettable powder Suspension Water soluble bags	Soil drench: ground hydraulic sprayers	1785	3570	[2]	15
Use-site Category 10 – Seed and Plant Propagation Materials Food and Feed							
Dry common beans	Seed-borne anthracnose	Wettable powder Solution	Commercial seed treatment equipment	61	61	1	Not applicable
Potato Seed Piece	Black leg	Dust Suspension Water soluble bags	seed treatment: (1) spray solution applied with nozzle	1528	1528	1	Not applicable
	Black scurf and stolon canker			672			
	Fusarium rot			1528			

Site	Pest(s)	Formulations	Application Method and Equipment	Maximum Single Application Rate (g a.i./ha)	Maximum Cumulative Application Rate per Year(g a.i./ha)	Maximum Number of Applications per year	Minimum Interval Between Applications (Days)
	Seed piece decay (*Rhizoctonia solani*, Fusarium spp., *Erwinia carotovora*, *Pythium* spp.)		mounted over belt which tumbles the seed pieces or (2) Apply in a convenient container or by dust attachment over belt or (3) Apply using a seed dust metering applicator so that cut seed-pieces are thoroughly covered with the mixture.	1528			
	Silver scurf			1528			
	Verticiliium wilt			1528			
Sweet corn	Seed-borne Penicillium oxalicum and Penicillium spp.	Wettable powder Solution	Seed box treatment	10.8	10.8	1	Not applicable
Use-site Category 14 – Terrestrial Food Crops							
Apple, Pear	Scab (V*enturia* spp.) and Powdery mildew	Wettable powder Suspension Water soluble bag	Foliar - ground hydraulic sprayers	Eastern Canada: 437.5 British Columbia.: 1575	Eastern Canada: 875 British Columbia: 3150	[2]	[7]
Cherry, Peach, Nectarine, Plum, Prune	Brown rot	Wettable powder Suspension Water soluble bag	Foliar - ground hydraulic sprayers	1225	2450	[2]	[7]
Lowbush Blueberry	Blossom and twig blight	Wettable powder Suspension Water soluble bag	Ground and aerial hydraulic sprayers	770	[1540]	[2]	10

Site	Pest(s)	Formulations	Application Method and Equipment	Maximum Single Application Rate (g a.i./ha)	Maximum Cumulative Application Rate per Year(g a.i./ha)	Maximum Number of Applications per year	Minimum Interval Between Applications (Days)
Raspberry	Powdery mildew and Fruit rots	Wettable powder Suspension Water soluble bag	Foliar - ground hydraulic sprayers	770	1540	[2]	7
Strawberry	Fruit rot (*Botrytis*) and Leaf spot	Wettable powder Suspension Water soluble bag	Foliar - ground hydraulic sprayers	770	1540	[2]	[7]
Sugarbeet (grown for export only)	Leaf spot (*Cercospora* sp.)	Wettable powder Suspension Water soluble bag	Foliar - ground hydraulic sprayers	392	784	2	14
White bean	White mould	Wettable powder Suspension Water soluble bag	Ground hydraulic sprayers and aerial (fixed wing or rotary aircraft)	1575	3150	[2]	(7)
Use-site Category 27 - Ornamentals Outdoor							
Roses	Black spot	Wettable powder Suspension Water soluble bag	Foliar - ground hydraulic sprayers	525	1050	[2]	10
Ornamentals	Powdery mildew	Wettable powder Suspension Water soluble bag	Foliar - ground hydraulic sprayers	525	1050	[2]	10
Aspen and Poplar	Marssonina leaf spot and Septoria leaf spot	Wettable powder Suspension Water soluble bag	Foliar - ground hydraulic sprayers	770	1540	(2)	10
Use-site Category 30 - Turf							
Turf [3]	Dollar spot	Wettable powder Suspension Water soluble bag	Foliar - ground hydraulic sprayers	2100	[20 650]	[4]	10
	Brown patch			4200		[2 for dollar spot; 1 at max. rate for brown patch.; 1 for pink snow mould]	[7] A second application for brown patch is only possible is applied at the minimum rate of 2100 g a.i./ha
	Pink snow mould			12 250			Not applicable.

[1] As of 11 January, 2019, excluding discontinued products or products with a submission for discontinuation and uses not supported by the Technical Registrant.

[2] All information is derived from registered product labels, except for mitigation measures supported by the registrants which is indicated by [ ], and data calculated by the PMRA which is indicated by ( ).
[3] The label claim for powdery mildew, and the associated application rate, is no longer supported by the technical registrant and is not included in the use pattern.

Appendix III Toxicology Reference Values

Table 1 Toxicological Reference Values for Thiophanate-Methyl Health Risk Assessment

Exposure Scenario	Study	Point of Departure and Endpoint	CAF [1] or Target MOE
Acute dietary	Acute neurotoxicity study rat	LOAEL = 50 mg/kg bw ↓ landing foot splay	1000
	ARfD = 0.05 mg/kg bw		
Chronic dietary	One-year dietary dog toxicity Two-year rat toxicity/oncogenicity	NOAEL = 8 mg/kg bw/day Thyroid effects, ↓ bw, bwg, cholesterol changes NOAEL = 8.8 mg/kg bw/day Including ↓ bw, bwg, ↑ thyroid wt and incidence of thyroid follicular cell hyperplasia/hypertrophy, effects on thyroid hormone (↓T_4, T_3; ↑TSH), ↑ liver wt, ↑ incidence of centrilobular hepatocellular hypertrophy, ↑ lipofuscin deposition	300
	ADI = 0.027 mg/kg bw/day		
Short-term inhalation and incidental oral[3]	Rabbit developmental toxicity	NOAEL = 10 mg/kg bw/day ↓ bwg and fc	300
Short–term dermal[2]	21-day rabbit dermal toxicity	NOAEL = 100 mg/kg bw/day ↓ bw, bwg and fc	300
Intermediate and Long-term dermal and inhalation[2, 3]	One-year dog Two-year rat toxicity/oncogenicity	NOAEL = 8 mg/kg bw/day Thyroid effects, ↓ bw, bwg, cholesterol changes NOAEL = 8.8 mg/kg bw/day Including ↓ bw, bwg, ↑ thyroid wt and incidence of thyroid follicular cell hyperplasia/hypertrophy, effects on thyroid hormone (↓T_4, T_3; ↑TSH), ↑ liver wt, ↑ incidence of centrilobular hepatocellular hypertrophy, ↑ lipofuscin deposition	300
Aggregate (oral, dermal and inhalation)[3]	Rabbit developmental toxicity 21-day rabbit dermal toxicity	Oral and Inhalation NOAEL = 10 mg/kg bw/day Dermal NOAEL = 100 mg/kg bw/day ↓ bw	300
Cancer	18-month mouse oncogenicity	q_1* = 7.96×10^{-3} $(mg/kg\ bw/day)^{-1}$ based on the combined incidence of hepatocellular adenomas and carcinomas in male mice.	

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments.

[2] Since an oral NOAEL was selected, a dermal absorption factor (25%) was used in a route-to-route extrapolation.

[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 2 Toxicological Reference Values for Carbendazim Health Risk Assessment

Exposure Scenario	Study	Point of Departure and Endpoint	CAF [1] or Target MOE
Acute dietary (Males 13+)	Acute oral rat	LOAEL = 50 mg/kg bw Sperm effects	300
	ARfD = 0.16 mg/kg bw		
Acute dietary (Females 13–49 years of age)	Developmental toxicity in rat and rabbit	NOAEL = 10 mg/kg bw/day Fetal malformation/resorption	1000
	ARfD = 0.01 mg/kg bw		
Chronic dietary (General population, excluding Females 13–49 years of age)	Two-year dog	NOAEL = 9 mg/kg bw/day ↓ bwg and changes in biochemical parameters, testicular effects	300
	ADI = 0.03 mg/kg bw/day		
Chronic dietary (Females 13–49 years of age)	Developmental toxicity in rat and rabbit	NOAEL = 10 mg/kg bw/day Fetal malformation/resorption	1000
	ADI = 0.01 mg/kg bw/day		
Short-, Intermediate- and Long-term dermal and inhalation and aggregate oral, dermal, and inhalation for females 13–49 years of age [2,3]	Developmental toxicity in rat and rabbit	NOAEL = 10 mg/kg bw/day Fetal malformation/resorption	1000
Aggregate (oral, and inhalation)[3]; and Incidental Oral for all populations except females 13–49 years of age	Developmental toxicity in rat and rabbit	Oral and Inhalation NOAEL = 20 mg/kg bw/day ↓ bw and fc	300
Cancer	Two year- oncogenicity - mouse	q_1* = 1.09×10^{-3} $(mg/kg\ bw/day)^{-1}$ based on the combined incidence of hepatocellular adenomas and carcinomas in female mice.	

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments.

[2] Since an oral NOAEL was selected, a dermal absorption factor (25%) was used in a route-to-route extrapolation.

[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 3 Toxicity Profile of Technical Thiophanate-methyl

NOTE: Effects noted below are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Effects on organ weights are known or assumed to reflect changes in absolute weight and relative (to bodyweight) weight unless otherwise noted.

Study Type/ Animal/PMRA#	Study Results
Toxicokinetic Studies	
Metabolism Fischer 344 rat PMRA# 1272595	Vehicle: 1% aqueous carboxymethyl cellulose Dosing: Rats received either a single gavage low dose (14 mg/kg bw), a repeat gavage low dose (14 mg/kg bw/day for 14 days of unlabelled thiophanate-methyl followed by a single gavage dose of 14 mg/kg bw), or a single oral high dose (140 mg/kg bw), of radiolabelled [Phenyl-U-^{14}C]-thiophanate-methyl. **Absorption, distribution and excretion**: Rapidly absorbed. The extent of absorption appears to be dose-dependent, decreasing with increasing dose. Less than 0.5% of administered dose (AD) was retained in the body 96 hrs post-dosing. There was no indication of potential accumulation in tissues. The highest residue levels were detected in the liver, thyroid and kidney. Thiophanate-methyl was rapidly excreted. Within 96 hrs, ≥ 97% of the AD was excreted via the urine or feces. Excretion in expired air was negligible. Following administration of a single low dose, urinary excretion was the predominant route of elimination (69% of AD), while fecal excretion was predominant following administration of a single high dose (61% of AD). Repeated low dose administration resulted in nearly the same fecal and urinary excretion (51% of AD was recovered in urine and 48% of AD in feces). Elimination half-lives were 2.5 to 2.8 hrs, 1.6 to 2.2 hrs and 4.0 to 4.8 hrs for the single low dose, repeated low dose and single high dose, respectively. **Biotransformation:** The dose and sex did not affect the profile of metabolites. Unchanged thiophanate-methyl in feces, accounted for approximately 20–40% of AD after repeated low doses, 1% after a single low dose, and 50% after a single high dose. Carbendazim and its secondary metabolite, 5-hydroxy-1H-benzimidazole-2-yl carbamate (2%); 5-(2-methoxycarbonylamino) benzimidazolyl sulfate (21–42%); and 4-hydroxythiophanate-methyl (2%) were the primary metabolites in urine. 5-hydroxy-1H-benzimidazole-2-yl carbamate (2.5%) and 4-hydroxythiophanate-methyl (6–10%) were the primary metabolites in the feces in addition to unchanged thiophanate-methyl.
Metabolism Fischer 344 rat PMRA# 1272611	**Supplemental: Follow-up metabolism study due to technical difficulties which resulted in lower dosing in animals in the high-dose group.** Vehicle: 1% aqueous carboxymethyl cellulose Dosing: Rats received a single dose (♂: 173 mg/kg bw, ♀ 210 mg/kg bw) of [Phenyl-U-^{14}C]-thiophanate-methyl. Maximum blood concentrations were reached 2 to 4 hrs after dosing. Half-lives were 2–4 hrs in ♂ and 3.1 hrs in ♀.

Study Type/ Animal/PMRA#	Study Results
Acute Toxicity Studies	
Oral Toxicity (gavage) Sprague Dawley rat PMRA# 1085860	**LD_{50} > 5000 mg/kg bw (♂/♀)** No clinical signs **Low Toxicity**
Oral Toxicity (gavage) Wistar rat PMRA# 2976565	**LD_{50} = 7500 mg/kg bw (♂)** **LD_{50} = 6640 mg/kg bw (♀)** Whole body tremors and tonic/clonic convulsions when touched, nose bleeding and lacrimation **Low Toxicity**
Oral Toxicity (gavage) mouse PMRA# 2976565	**LD_{50} = 3514 mg/kg bw (♂)** **LD_{50} = 3400 mg/kg bw (♀)** Tremors within 1–2 hrs after dosing; sensitivity to touch leading to tonic and clonic convulsions **Low Toxicity**
Oral Toxicity rabbit PMRA# 2976565	**LD_{50} = 2270 mg/kg bw (♂)** **LD_{50} = 2500 mg/kg bw (♀)** Increased sensitivity to touch after 3–6 hrs with tremors, and tonic and clonic convulsions **Low toxicity**
Dermal Toxicity mouse PMRA# 2976565	**LD_{50} > 10000 mg/kg bw** **Low toxicity**
Dermal Toxicity Wistar rat PMRA# 2976565	**LD_{50} > 10000 mg/kg bw** **Low toxicity**
Dermal Toxicity rabbit PMRA# 2976565	**LD_{50} > 10000 mg/kg bw** **Low toxicity**
Dermal Toxicity Japanese rabbit PMRA# 1085861	**LD_{50} > 2000 mg/kg bw** Reddening at application site, which resolved within 72 hrs **Low toxicity**
Inhalation Toxicity (Whole-body) Sprague Dawley rat PMRA# 1085863	**LC_{50} = 1.7 mg/L (♂)** **LC_{50} > 1.6 mg/L (♀)** **Clinical signs:** ↓ motor activity, ataxia, ptosis, tremors and urinary incontinence. **Slightly acutely toxic**
Skin Irritation	No reaction was observed at any site

Study Type/ Animal/PMRA#	Study Results
New Zealand rabbit PMRA# 1085865	**Non-irritating**
Eye Irritation New Zealand rabbit PMRA# 1085864	MIS = 2/110 @ 1 hr. Slight conjunctivitis resolved within 48 hrs **Minimally Irritating**
Skin Sensitization Hartley guinea pig PMRA# 2976565	Positive skin sensitization response **Potential skin sensitizer**
Skin Sensitization (Maximization test) Hartley guinea pig PMRA# 1085866	Redness and swelling at application sites up to 72 hrs after challenge (positive skin sensitization response in Maximization test**)** **Potential skin sensitizer**
Skin Sensitization (Buehler test) Hartley guinea pig PMRA# 1085867	**Supplemental-Methodological limitations** Not a skin sensitizer
Short-Term Toxicity Studies	
21-day Dermal Toxicity New Zealand White rabbit PMRA# 1085862	**NOAEL = 300/100 mg/kg bw/day (♂/♀)** **≥ 300 mg/kg bw/day**: ↓ bwg (♂/♀); ↓ bw, ↓ fc (♀) **1000 mg/kg bw/day:** ↓ bw, ↓ fc (♂) Slight dermal erythema was observed at all dose levels
6-month Oral Toxicity (dietary) mouse PMRA# 963010	**NOAEL = 48 mg/kg bw/day** **≥ 240 mg/kg bw/day**: ↓ RBC and hct ,↑ incidence of hepatic-cell irregularity (♂/♀); ↓ bw (♀) **1200 mg/kg bw/day**: ↑ liver wt, ↑ incidence of large swollen hepatocytes with edematous or granular protoplasm (♂/♀); ↓ bw (♂)
90-day Oral Toxicity (dietary) Fischer 344 rat PMRA# 1085868	**NOAEL = 14/16 mg/kg bw/day (♂/♀)** **≥ 14/16 mg/kg bw/day:** ↑ thyroid wt (♀) (not adverse at this dose level) **≥ 155/173 mg/kg bw/day:**↑ thyroid follicular cell hypertrophy and hyperplasia, slight anaemia (↓ hgb, hct, MCV, MCH, MCHC), ↑ hepatocyte swelling and lipofuscin deposit (♂/♀);↑ thyroid wt ,↑ kidney wt, ↑ glomerulonephrosis (♂); ↑ liver wt, ↑ serum cholesterol and albumin in females **≥ 293/323 mg/kg bw/day:** ↑ liver wt, ↑ serum cholesterol and albumin, ↑ serum cholinesterase (♂); ↑ fatty degeneration of adrenal cortex, (♀)

Study Type/ Animal/PMRA#	Study Results
	≥ 427/479 mg/kg bw/day: ↑ urine protein, ↑ fatty degeneration of adrenal cortex (♂); ↓ serum cholinesterase (♀) **565/647 mg/kg bw/day**: ↑ T_3 (♂/♀); ↑ kidney wt, ↑ incidence of glomerulonephrosis (♀)
6-month Oral toxicity (dietary) Sprague Dawley rat PMRA# 963010	**Supplemental: Non-guideline. Methodological limitations: incomplete haematological and clinical chemistry examinations. Test substance analysis not reported and detailed clinical observations and ophthalmoscopic examinations were not made.** **400 mg/kg bw/day:** ↓ bw and bwg, ↓ RBC, hct, ↑ blood cholesterol,↑ thyroid wt, ↑ rel liver wt, ↑ thyroid with small follicles, thickened follicular epithelium and decreased colloidal substance (♂/♀); ↑ thymus wt (♀)
90-day Oral Toxicity (capsule) Beagle dog PMRA# 1085857	**NOAEL = 50 mg/kg bw/day** **≥ 50 mg/kg bw/day:** ↑ thyroid follicular hypertrophy/hyperplasia (dose dependant; not adverse) **≥ 200 mg/kg bw/day:** ↑ dehydration, thinnest and lethargy, ↓ bw, ↓ fc (30–70%), anaemia (↓ hct and hgb),↑ platelets and blood cholesterol,↓ albumin, ↑ thyroid and liver wt, ↑ spleen lymphoid cells depletion, ↓ vesiculation of hepatocellular cytoplasm and atrophy of pancreatic acinar cell (♂/♀); one treatment-related mortality, ↑ prostate atrophy and thymus involution(♂); ↓ serum T_4 and T_3 (♀) **800/400 mg/kg/day:** one treatment-related mortality (♂)
One-year Oral Toxicity (capsule) Beagle dog PMRA# 1085858	**NOAEL = 8 mg/kg bw/day** **≥ 40 mg/kg bw/day**: ↓ bw (6%), ↓ bwg (29%),↑ thyroid wt (♂/♀); ↓ serum T_4; ↑ TSH in one male at 6 and 12 months (♂); ↑ cholesterol, ↓ calcium (♂); thyroid follicular cell hypertrophy in females **200 mg/kg bw/day**: Tremors occurred in all dogs 2–4 hrs post-dosing on one or more occasions during first three weeks but not subsequently, ↓ bw and bwg, ↑ liver and thyroid wt, ↑ thyroid follicular cell hypertrophy /hyperplasia, ↑ ALP (♂/♀); ↓ hgb, hct and RBC (slight) ♂; ↑ cholesterol (♀);
Chronic Toxicity/Oncogenicity Studies	
Two-year Oral Toxicity (capsule) Beagle dog PMRA# 2942431, 963010	**Supplemental- limited investigation** **≥ 50 mg/kg bw/day:** ↑ thyroid wt **250 mg/kg bw/day:** ↓ bw and bwg, ↑ thyroid wt, ↓ thyroid colloidal substance and slightly taller thyroid follicular cells (♂/♀); testicular atrophy (♂)
18-month Oncogenicity (dietary) CD-1 mouse PMRA# 1193199, 1193200	**NOAEL = 24/99 mg/kg bw/day (♂/♀)** **≥ 99/123 mg/kg bw/day:** ↑ incidence of hepatocellular hypertrophy (♂) **≥ 468/558 mg/kg bw/day**: ↓ bw (slight), ↓ bwg, ↓ fc, ↑ incidence of enlarged thyroid glands, ↑ thyroid and liver wts, ↑ incidence of hepatocellular centrilobular hypertrophy (♂/♀); ↑ TSH and ↓ T_4 (♂); ↑ incidence of atrial thrombosis (♀) **1079/1329 mg/kg bw/day:** ↑ unscheduled mortality (incidence: 10/12, 11/13,

Study Type/ Animal/PMRA#	Study Results
	14/15, 16/17, 24/23; ♂/♀ n=60),↑ amyloidosis in unscheduled death, ↓ bw, enlarged thyroid glands (♂/♀); ↓ RBC (slight), ↑ incidence of atrial thrombosis (♂); ↓ T_4 ,↑ heart wt (♀) **Due to the high mortality rate, MTD was exceeded at this dose level.** **Neoplastic lesions**: **Hepatic adenoma:** Overall incidence in ♂ receiving 0, 24, 99, 468, 1079 mg/kg bw/day was: 4/50 (8%), 8/50 (16%), 7/50 (14%), **19/50 (38%)*, 24/50(48%)*** respectively [HC mean (♂) = 8.2%; range = 0–16.3%]. Overall incidence in ♀ receiving 0, 29, 123, 468, 1329 mg/kg bw/day was: 0/50, 0/50, 3/50 (6%), **8/50* (16%), 18/50 (36%)*** respectively [HC mean (♀) = 1.4%; range = 0–2.7%] * statistically significant (by Fisher's Exact Test) $p<0.01$ **Hepatic carcinoma** Singular incidences of hepatic carcinoma were noted in ♂ at 99 and 1079 mg/kg bw/day respectively. The incidence of 2% in each group was within the HC incidence (HC mean =1.4%; range 0–6%) **Hepatic hepatoblastoma** Singular incidence of hepatoblastoma in one 7000 ppm ♂ (HC mean: 0.001%). **Hepatic adenoma/carcinoma/hepatoblastoma combined** Overall combined incidence in ♂ receiving 0, 24, 99, 468, 1079 mg/kg bw/day was: 4/50, 8/50, 8/50, 19/50, 24/50 **Evidence of oncogenicity**
Two-year Chronic Toxicity /Oncogenicity (dietary) Fischer 344 rat PMRA# 1193201, 1193298	**NOAEL = 8.8/10 mg/kg bw/day (♂/♀)** **≥ 54/64 mg/kg bw/day:** ↓ bw and bwg, ↑ cholesterol, ↑ incidence of thyroid follicular cell hyperplasia/hypertrophy, ↑ liver, thyroid and kidney wt, ↑centrilobular hepatocellular hypertrophy and lipofuscin deposition, nephropathy (♂/♀); ↑ urinary protein, ↓ T_4 and T_3, ↑ TSH (♂); ↑ lipidosis of adrenal cortex (♀) **281/335 mg/kg bw/day**: ↑ mortality [22 rats died from nephropathy; 10 died from thyroid follicular cell tumours; 6 died from leukemia and 8 died/killed during wk 11–12 due to fractures of nasal bone by feeder plates],↑ ketone bodies, urinary volume and ↓ urinary pH and specific gravity ,↑ platelets, ↑ incidence focal fatty degeneration in liver, ↑ nephropathy associated with parathyroid hypertrophy/hyperplasia and demineralization of bones, ↑ lipidosis of adrenal cortex (♂); anaemia (↓ RBC, Hb and Hct), ↑ urinary protein, ↑ incidence of brownish-black liver and granular/brownish-black kidneys, enlarged thyroids; ↓ T_4 and T_3, ↑ TSH (♀) **Due to the high mortality rate (only 2 animals survived to scheduled termination), MTD was considered to have been exceeded at this dose level in ♂.** **Neoplastic lesions**: **Thyroid follicular adenoma:**

Study Type/ Animal/PMRA#	Study Results
	Overall incidence in ♂ receiving 0, 3.3, 8.8, 54, 281 mg/kg bw/day was: 0/50, 0/50, 4/50 (8%), 12/55*(22%) respectively [HC mean (♂) = 0.7%; range = 0–5%]. Overall incidence in ♀ receiving 0, 3.8, 10, 64, 335 mg/kg bw/day was: 0/50, 0/49, 0/50, 1/50, 2/50 respectively [HC mean (♀) = 0.6%; range = 0–2%] * statistically significant (by chi-square test) $p<0.01$ **Thyroid follicular adenocarcinoma:** Overall incidence in ♂ receiving 0, 3.3, 8.8, 54, 281 mg/kg bw/day was: 0/50, 0/50, 0/50, 3/55 (5%) respectively [HC mean (♂) = 0.5%; range = 0-2%]. **Evidence of oncogenicity**
Two-year Chronic Toxicity (dietary) Sprague Dawley rat PMRA# 2977622	**Supplemental-Methodological limitations** **30/34 mg/kg bw/day**: ↓ bwg (♂/♀); ↑ incidence of decreased colloidal substance in thyroid and hypertrophy of thyroid follicular cells, ↑ atrophy of testes (♂) **No evidence of oncogenicity**
Developmental/Reproductive Toxicity Studies	
Two-generation Reproductive Toxicity (dietary) Sprague Dawley rat P: Premating for 14 wks and mated for 21 days. (F_1) F_1: Premating for 14 wks and mated for 21 days. (F_{2a}). Due to high pup loss during lactation, F_1 maintained an additional 6 wks and mated with the (F_{2b}) Modified functional observational battery performed in pups: Surface righting, gripping and pupillary reflex, auditory response, open field test PMRA# 1085872, 1085873	**Parental**: **NOAEL = 14 mg/kg bw/day** **≥ 14/16 mg/kg bw/day**: ↑ incidence of hepatocyte hypertrophy, ↑ thyroid follicular cell hypertrophy in P and F_1 (♂); ↑ thyroid wt in F_1 (♀) (non-adverse) **≥ 43/54 mg/kg bw/day:** ↓ bwg in F_1 (slight) (♂); ↑ thyroid wt in F_1 (♀) **139/172 mg/kg bw/day**: ↓ bwg F_1 parents (6–7%); ↑ TSH in P and F_1 at 8 wks; ↓ T_4 in P, ↑ thyroid and liver wt in P and F_1 (♂/♀); ↓ bwg of P (-10%) ↓ number of squares touched in the open field test (days 35–37) in F_1(♂); ↓ fc in F_1, ↑ hepatocyte hypertrophy , ↑ thyroid follicular cell hypertrophy P and F_1, ↑ thyroid hyperplasia P only (♀) **Reproductive :** **NOAEL = 172 mg/kg bw/day** No treatment-related reproductive effects. **Offspring:** **NOAEL = 16 mg/kg bw/day** **≧ 54 mg/kg bw/day:** ↓ bw of F_{2b} pups **172 mg/kg bw/day:** ↓ bw of F_{1a} and F_{2a} pups **No evidence of sensitivity of the young**
Three-generation Reproductive Toxicity (dietary)	**Supplemental-due to missing test material purity** **Parental**: No treatment-related adverse effects observed.

Study Type/ Animal/PMRA#	Study Results
CD rat PMRA# 2952509	**Reproductive:** No treatment-related reproductive effects observed. **Offspring:** **32 mg/kg bw/day**: ↓ litter wt (slight) in both mating for all three generations except F_3 litters.
Developmental Toxicity (gavage) IRC mouse PMRA# 2976565, 963010	**Maternal** **NOAEL ≥ 1000 mg/kg bw/day** No treatment-related adverse effects. **Developmental** **NOAEL = 500 mg/kg bw/day** 1000 mg/kg bw/d: ↓ live fetuses partly due partly to ↑ resorptions **No evidence of malformations.** **Sensitivity of the young.**
Developmental Toxicity (gavage) Sprague- Dawley rat PMRA# 1085875	**Supplemental-Range finding** **Maternal** **≥ 1000 mg/kg bw/day:** ↓ bwg **Developmental** Fetuses were not examined.
Developmental Toxicity (gavage) Sprague Dawley rat PMRA#1193321	**Maternal** **NOAEL = 300 mg/kg bw/day** **1000 mg/kg bw/day:** ↓ bwg (GD 6–9 and GD 9–12 (-17%)) **Developmental** **Developmental NOAEL = 1000 mg/kg bw/day**
Developmental Toxicity (gavage) New Zealand White rabbit PMRA# 1085882	**Supplemental-Range finding** **Maternal** Trial 1: **≥ 150 mg/kg bw/day**: ↑ mortality (0/4, 1/4, 1/4, 2/4 at 0, 150, 300, 600 mg/kg bw/day respectively), ↑ bw loss (>20%), ↑ total litter loss (0/4, 2/4, 0/4, 1/4 at 0, 150, 300, 600 mg/kg bw/day respectively) **≥300 mg/kg bw/day**: ↑ abortion (3/4 at this dose level) Trial 2: **Maternal** **≥ 30 mg/kg bw/day:** ↓ fecal output ,↓ fc, ↓ water intake, bw loss during treatment, ↑ abortion (1/15 and 2/15 at 30 and100 mg/kg bw/day respectively) **Developmental** **≥ 30 mg/kg bw/day:** ↑ abortion (1/15 and 2/15 at 30 and 100 mg/kg bw/day respectively)
Developmental Toxicity (gavage) New Zealand White rabbit PMRA# 1085876	**Supplemental- Methodological limitations and possible infection** **Maternal:** **≥ 6 mg/kg bw/day:** bw loss at GD 6–8 **20 mg/kg bw/day:** ↑ abortions (2 vs. 0 in controls), ↓ mean bw (-8.6% at day 10

Study Type/ Animal/PMRA#	Study Results
	due to wt loss GD 6–12), ↓ fc (GD 6-12), ↓ fecal output **Developmental:** **≥ 6 mg/kg bw/day:** ↑ incidences of 13 pairs of ribs, incomplete or asymmetric ossification of 27 pre-sacral vertebrae, asymmetrical pelvis, and thickened ribs (all slight, generally close to or slightly greater than the upper limit of historical controls)
Developmental Toxicity (gavage) New Zealand White rabbit PMRA# 1272594	**Maternal** **NOAEL = 10 mg/kg bw/day** **≥ 20 mg/kg bw/day:** ↓ bw, ↓bwg, ↓ fc **40 mg/kg bw/day**: ↓ fecal output **Developmental** **NOAEL = 20 mg/kg bw/day** **40 mg/kg bw/day:** ↓ fetal bw, ↑ mean number of ossification sites in thoracic vertebrae and ribs-pairs, ↓ lumbar vertebrae, ↑ supernumerary thoracic ribs **No evidence of malformations or sensitivity of the young**
Genotoxicity Studies	
Bacterial Reverse Mutation assay *Salmonella typhimurium* TA 100, TA 1535, TA98, TA 1537, E. coli WP2 uvrA PMRA# 1085881	**Negative with and without metabolic activation**
Gene Mutation *B. subtilis* H17, M45 PMRA# 2977622	**Negative**
Pre-incubation Mammalian Microsome Gene Mutation assay *S. typhimurium* PMRA# 2952509	**Weakly positive** (equivocal). Twofold increases in revertant colonies of strains TA98 and TA100 at ≥ 3333 µg/plate (precipitating concentration) with metabolic activation and negative results in second assay. Negative without metabolic activation
Forward Mutation assay Chinese Hamster V79 Cells PMRA# 1085878	**Negative with and without metabolic activation**
In vitro Cell Transformation assay BALB/c 3T3 cells PMRA# 2952509	**Positive** (at cytotoxic concentrations). Increase in morphologically transformed foci at 25 µg/mL without activation and ≥ 20 µg/mL with activation. Cytotoxicity observed at ≥ 25 µg/mL without S9 (more pronounced at ≥ 50 µg/mL; only weak cytotoxicity with S9 (more pronounced at 100 to 200 µg/mL).
Chromosome Aberration assay	**Negative with or without metabolic activation**

Study Type/ Animal/PMRA#	Study Results
Chinese Hamster Ovary cells PMRA# 1193328	
In vivo Dominant Lethal and Cytogenetic assay (i.p.) ICR mouse Wistar rat Primary Spermatogonial and Bone Marrow cells PMRA# 963010	**Supplemental due to methodological and reporting limitations** **Dominant lethal assay:** **≥ 400 mg/kg bw:** ↑ mortality (♂) Considerable intergroup variation observed but no indication of treatment-related dominant lethal mutation in males. Pregnancy rate was reduced in all treated groups but there was no evidence of dose-response. **Cytogenetic assay:** No abnormal chromosome configurations reported in bone marrow or spermatogonial cells.
Unscheduled DNA Synthesis Primary rat hepatocytes PMRA# 1085880	**Negative**
In vitro Micronucleus assay Human lymphocyte PMRA# 2942431	**Positive** (non-disjunction detected-aneuploidy).
Micronucleus assay (gavage) B6D2F1 mouse PMRA#, 2952509	A slight but significant increase in micronucleated polychromatic erythrocytes in bone marrow in all treated groups at 24 and 48 hrs. **Weakly aneugenic**
Micronucleus assay (gavage) Swiss Albino mouse PMRA# 2952509	Borderline significant increase in frequency of polyploid and hyperdiploid cells; large micronuclei induced **Weakly aneugenic**
Neurotoxicity Studies	
Acute Oral Neurotoxicity (gavage) Sprague Dawley rat PMRA# 1530425	**LOAEL = 50 mg/kg bw (♂/♀)** **Main study** **≥ 500 mg/kg bw:** bw loss days 1–2, ↓ fc days 1–2, ↓ landing foot splay (♂/♀); ↓ motor activity (main study only, equivocal) (♀) **Extension study:** **≥ 50 mg/kg bw:** ↓ landing foot splay (♂/♀) **Evidence of neurotoxicity**
Subchronic Neurotoxicity (dietary) Sprague Dawley rat PMRA# 1530426	**NOAEL = 30/35 mg/kg bw/day (♂/♀)** **150/166 mg/kg bw/day:** ↑ thyroid wt (♂/♀); ↑ liver weight (♂); ↓ overall bw, bwg and fc (♀)

Study Type/ Animal/PMRA#	Study Results
Special Studies (non-guideline)	
Cholinesterase study (gavage) ♂ Wistar rat PMRA# 2942431, 2976565, 963010	No evidence of anti-cholinesterase activity.
2- and 8-days Mechanistic study - Effects on Liver and Thyroid (dietary) ♂ Fischer 344 rat Rats were treated for 2 or 8 days. Some animals were allowed to recover for 8 days following 8 days of exposure. In a separate set of experiment, rats were treated for 8 days and half the animals received daily injection of L-thyroxine PMRA# 2952509	Thiophanate-methyl: **6000 ppm**: ↑ liver and thyroid wt, ↑ serum cholesterol, ↑ TSH, ↓ serum T_3 and T_4 (slight after 8 days) Recovery for eight days caused a reversal of thyroid enlargement. Supplementation with L-thyroxine also prevented thyroid enlargement and ↑ TSH but not changes in liver wt or serum cholesterol. Phenobarbital: ↑ liver wt, ↑ T_3, T_4, TSH and cholesterol at day 8. Recovery for eight days had no significant effect on thyroid wt Propylthiourea: ↑ serum cholesterol, ↑ TSH, ↓ serum T_3 and T_4 (slight)
8-day Mechanistic study - Effects on Hepatic Microsomal Enzymes and Protein Concentration (dietary) ♂ Fischer 344 rat PMRA# 2952509	Thiophanate-methyl: **6000 ppm**: ↑ CYP-450 and b5, ↑ UDP-glucuronosyltransferase, ↑ microsomal protein Phenobarbital: ↑ CYP-450 and b5, ↑ UDP-glucuronosyltransferase, ↑ microsomal protein, ↑ NADPH-cytochrome c reductase
2- and 8-day Mechanistic study - Effects on Hepatocyte Proliferation (Dietary) ♂ Fischer 344 rat ♂ ICR mouse PMRA# 2952509	Thiophanate-methyl: In mice: ↑ liver wt, ↑ PCNA staining after 2 and 8 days of treatment. In rats: ↑ liver wt, ↑ PCNA staining after 2 but not 8 days of treatment Phenobarbital: In mice: ↑ PCNA staining after 2 and 8 days (but less at day 8). In rats: ↑ liver wt, ↑ PCNA staining after 2 but not 8 days of treatment
In vitro Mechanistic study - Effect on Porcine Microsomal Thyroid Peroxidase Activity PMRA# 2952509	Thiophanate-methyl: $ED_{50} = 6 \times 10^{-4}$ M; no inhibition 8×10^{-5} M Propylthiourea: $ED_{50} = 2 \times 10^{-5}$ M; no inhibition 4×10^{-7} M Thiophanate-methyl was approximately 30-fold less potent at inhibiting thyroid peroxidase activity than propylthiourea, a known anti-thyroid chemical and inhibitor of this enzyme

Table 4 Toxicity Profile of Technical Carbendazim

NOTE: Effects noted below are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Effects on organ weights are known or assumed to reflect changes in absolute weight and relative (to bodyweight) weight unless otherwise noted.

Study Type/ Animal/PMRA#	Study Results
Toxicokinetic Studies	
Metabolism (gavage) Wistar rat PMRA# 2946559, 2946557	**Dosing:** 8 mg/kg ^{14}C-carbendazim for 10 days **Excretion:** Approximately 60% of the AD was excreted in the urine. Approximately 35% of AD was excreted in the feces. **Metabolism:** Three polar metabolites were found in the urine and determined to be conjugates of 2-(methoxy-carbonylamino)-5-hydroxybenzimidazole. Two metabolites were discovered in the feces: 2-(methoxy-carbonylamino)-5-hydroxybenzimidazole, and a conjugated form. The main metabolite 2-(methoxy-carbonyl amino)-5-hydroxybenzimidazole becomes conjugated, at least in part, in the liver and is excreted in urine and feces in the conjugated form (and in the latter partially in the unconjugated form). Two of the same conjugates found in the liver were detected in the urine. **Distribution:** liver residues ≈ 0.7 ppm equivalents of carbendazim
Metabolism (gavage) Wistar rat PMRA# 2946557, 2946558	**Dosing:** 2 mg/kg ^{14}C-carbendazim for 10 days ^{14}C-carbendazim was cleared from the blood rapidly with 59% excreted in the urine and 36% in the feces. Elimination was biphasic with a rapid rate during the first 3 days and slower phase thereafter. In the liver, 0.3% and 0.08% of AD remained 7 or 14 days post-dosing. Levels in blood and other organs (kidney, fat, muscle, and gonads) did not exceed 0.03% after 7 days.
Metabolism (gavage) CD rat PMRA# 2946557	**Supplemental-study performed on a single animal** [2-^{14}C] carbendazim was eliminated mainly through the urine (85% AD). Within 24 hrs, 80% of AD was eliminated. At the end of the 72 hrs collection period: CO_2 < 0.1%; urinary metabolites, 88.0%; feces 11.3%, and volatile radioactivity, 0.3% (highest residue) in the gastrointestinal tract; liver, 0.1%; brain, 0.1%; remaining organs and carcass < 0.1% (blood, fat, heart, kidneys, lungs, muscles, spleen, testes) The main urinary metabolite was methyl-5-hydroxy-2-benzimidazole carbamate (5-HBC). Excreted radioactivity is largely accounted for by glucuronide or sulfate conjugates of methyl 5-hydroxy-2-benzimidazolecarbamate
Metabolism (gavage and i.p.) rat PMRA# 2946559	**Dosing:** 20 mg/kg bw ^{14}C-carbendazim by gavage and i.p. injection **Excretion:** Radioactivity was eliminated through the urine (oral - 48%; i.p. - 44%) and feces (oral - 28%; i.p. - 16%) mainly during first 24 hrs. **Metabolism:** The main product of metabolism was 5-HBC, which was eliminated as a conjugate of sulfuric acid.
Metabolism (gavage) Wistar rat and NMRI mouse	**Dosing: 3 or 300** mg/kg bw/day ^{14}C-carbendazim **Absorption:** Rat: C_{max} = 1.03 mg/mL in blood within 15-40 min at 3 mg/kg bw; C_{max} = 16 mg/mL in blood within 0.4–4 h at 300 mg/kg bw. Mouse: similar C_{max} as rat at 3 mg/kg bw, but at 300 mg/kg bw C_{max} was higher (36-53 mg/mL).

Study Type/ Animal/PMRA#	Study Results
PMRA# 2946558	**Excretion:** In rats excretion occurred almost exclusively in urine, irrespective of sex and dose; only about 1% in the feces. Fecal excretion was higher in mice representing 10–27%. Pre-treatment with unlabeled carbendazim had no effect on excretory patterns. The radioactivity was almost completely excreted within 24 hrs after treatment; excretion was faster in rat than mouse where higher concentration in the liver was observed. **Distribution:** Following administration of 3 mg/kg bw [^{14}C]-carbendazim intravenously (i.v.) or by gavage, the excretory organs (liver, kidney) contained the highest tissue concentrations. Concentrations in the gonads were near or below the blood concentrations.
Metabolism (gavage or i.v.) Albino rat PMRA# 2946557, 2946558, 2946559	**Dosing:** Single dose of 12 mg/kg bw ^{14}C-carbendazim administered by gavage or i.v. **Absorption:** Urinary excretion of ^{14}C-carbendazim and two of its metabolites indicated 85% of AD had been absorbed following oral administration **Metabolism:** In urine, 12 hrs after treatment, 94% of AD was as 5-HBC, 3% as 2-aminobenzimidazole (2AB), and 3% as carbendazim. **Distribution:** Highest tissue concentrations of radiolabel were found in kidneys and lowest in blood. **Excretion:** After i.v. administration, elimination followed the kinetics of a 2-compartment model. By 12 hrs, only small quantities of radiolabel were present in blood, liver and kidney.
Metabolism (gavage) C57BL6 and NMRI mouse PMRA# 2946559	Dosing: Single oral doses of carbendazim. Animals sacrificed 10 minutes post-dosing After 10 minutes most of the radiolabel was found in the liver with relatively high amounts also seen in the kidneys. In C57BL, only, accumulation in the retina was seen. Exceedingly low accumulation in testes confined to interstitial spaces.
Metabolism (gavage) Sprague Dawley rat PMRA# 1530450, 2946558, 2946557	**Dosing:** Rats received either a single gavage low dose (50 mg/kg bw), a repeat gavage low dose (50 mg/kg bw/day for 14 days of unlabelled carbendazim followed by a single labelled gavage dose of 50 mg/kg bw), or a single gavage high dose (1000 mg/kg bw) of [phenyl (U)-^{14}C] – carbendazim Carbendazim rapidly absorbed and extensively metabolized in in all dose groups. Radioactivity was excreted primarily via urine for low dose groups (54 to 66% of AD) but following high dose administration, only 41% was excreted in urine. Less than 1% of AD was retained in tissues (liver and carcass). Half-life was about 12 hrs, with 98% excreted by 72 hrs post-dosing. **Metabolism:** The primary metabolic reactions involved oxidation and conjugation at the phenyl ring to yield sulphate and glucuronide conjugates of 5-hydroxy- and 5,6-dihydroxy-carbendazim. Subsequent phenyl-ring oxidation and N-oxidation also occurred, especially in ♀ rats. The main metabolite was 5-HBC-S (21–43%, except in F at the high dose or receiving pre-treatment 5.5–10%); in all groups of F, 5,6-HOBC-N-oxide was the predominant metabolite (10–19%). 5,6-DHBC-S and 5,6-DHBC-G were identified as minor metabolites

Study Type/ Animal/PMRA#	Study Results
Metabolism (gavage) Wistar rat and NMRI mouse PMRA# 2946557, 2946558, 2946559	**Dosing:** Animals received either a single gavage low dose (3 mg/kg bw), a repeat gavage dose of unlabelled carbendazim (3 or 300 mg/kg bw) for 28 days followed by a single labelled gavage dose of 3 or 300 mg/kg bw), or a single gavage high dose (300 mg/kg bw) of radiolabelled–carbendazim **Metabolism:** Urine was collected during first 6 hr. Almost all the metabolites were in the form of glucuronide and sulphate conjugates. TLC after cleavage of these conjugates by β-glucuronidase-arylsulfatase tentatively identified the major compound 5-HBC (39–90%), carbendazim (2–6%), 2AB (<2–4%), hydroxylated-2-amino-benzimidazole (0-5%). Mouse urine contained more compounds that remained polar after enzyme treatment than the urine of rats. **Distribution:** The residual content in the liver was generally lower in rats (12–18%, single dose; 2–4% repeated dose) than mice (26–29%, single dose, <2–28% repeated dose); thus indicating that the detoxification capacity of mouse liver was saturated at a higher dose. There were no sex differences.
Metabolism Percutaneous Absorption rat PMRA# 2946558	Percutaneous absorption of carbendazim is negligible: at 0.6 mg only about 0.2% of AD was excreted in urine and feces within 24 hrs. At 60 mg, only 0.03% of AD was excreted.
Liver Enzyme Induction Albino mouse Sprague Dawley rat PMRA# 2946557, 2946558	**≥ 300 ppm:** ↑ abs liver wt (♀). **≥ 1000 ppm:** ↑ abs liver wt (♂), epoxide hydrolase induced **3000 ppm:** glutathione-S-transferase induced (level of induction slightly greater in ♀; no difference between rats and mice).
Liver Enzyme Induction (gavage) CD1 mouse PMRA# 2946558	↑ styrene-7,8-hydrolase and glutathione-S-transferase activity, ↓ 7-ethoxycoumarin-deethylase activity, total microsomal CYP450 level did not increase. Carbendazim did not cause overall microsomal induction; however, some hepatic microsomal enzymes are induced
Liver Enzyme Induction (dietary) Albino mouse Sprague Dawley rat PMRA# 2946557, 2946558, 2946559	**(1) Mice:** **Dosing:** 0–5000 ppm for 29, 43, or 60 days **≥ 1000 ppm:** ↑ rel liver wt; moderate to marked ↑ in the activities of the phase-I drug metabolizing enzymes including CYP-450 and aminopyrine-*N*-demethylase; ↓ cytochome-c-reductase activity, ↑ glucuronyl transferase and glutathione-S-transferase activity (slight), ↑ glutathione content (slight) **5000 ppm:** ↑ protein concentration in total homogenates and post-mitochondrial fraction of liver. **(2) Rats:** **Dosing:** 0–10 000 ppm for 29, 43, or 60 days **≥ 2000 ppm:** ↑ rel liver wt, slight to moderate ↑ in several phase-I drug metabolizing enzymes (7-ethoxycoumarin-O-deethylase, biphenyl-4-hydroxylase, aniline hydroxylase, 4-methoxybiphenol-N-demethylase, cytochrome-c-reductase), moderate to marked ↑ of phase-II drug metabolizing enzymes glucuronyl transferase I and II, ↑ glutathione content

Study Type/ Animal/PMRA#	Study Results
	10 000 ppm: ↓ growth and fc No measurable difference between rats and mice with regard to the metabolism of carbendazim, although exhaustion of the detoxification mechanism was more evident in mice at high doses. Detoxification and elimination of carbendazim and its metabolites proceeded more rapidly in rats than in mice, as reflected by increased glutathione content of rat liver and increased phase-II enzyme activity.
Effect on Respiratory Chain Enzymes rat PMRA# 2946557	No effect of carbendazim or 5-HBC on mitochondria respiratory function; 2AB inhibited the mitochondrial respiratory chain more strongly in the region of NADH-flavoprotein than in the region of cytochrome b; at high conc. 2AB also exerted a dissociating effect on the oxidising phosphorylation of rat liver mitochondria. The action of carbendazim and its metabolites on the mitochondria respiratory chain does not play a major part in the toxic action of this compound.
Acute Toxicity Studies	
Acute Oral Toxicity mouse PMRA# 2946557, 2946558	LD_{50} > 10 000–15 000 mg/kg bw **Low Toxicity**
Acute Oral Toxicity rat PMRA# 2946557, 2946558, 2946559	LD_{50} > 6400–15 000 mg/kg bw **Low Toxicity**
Acute Oral Toxicity guinea pig PMRA# 2946557, 2946558, 2946559	LD_{50} > 5000 mg/kg bw **Low Toxicity**
Acute Oral Toxicity rabbit PMRA# 2946557, 2946558, 2946559	LD_{50} > 8000 mg/kg bw **Low Toxicity**
Acute Oral Toxicity dog PMRA# 2946557, 2946558, 2946559	LD_{50} > 5000 - 8000 mg/kg bw **Low Toxicity**
Acute Dermal Toxicity rat PMRA# 2946557, 2946558, 2946559	LD_{50} > 2000–20,000 mg/kg bw **Low Toxicity**

Study Type/ Animal/PMRA#	Study Results
Acute Dermal Toxicity rabbit PMRA# 2946557, 2946558, 2946559	LD_{50} > 10,000 mg/kg bw **Low Toxicity**
Acute Inhalation Toxicity rat PMRA# 2946557, 2946558, 2946559, 2952523	LC_{50} > 5–5.8 mg/L **Low Toxicity**
Primary Eye Irritation rabbit PMRA# 2946557, 2946559	**Non- to Mildly Irritating to the eye**
Primary Dermal Irritation guinea pig PMRA# NA	**Non- to Mildly Irritating to the skin**
Primary Dermal Irritation rabbit PMRA# 2946558, 2946559, 2952523	**Non-irritating to the skin**
Dermal Sensitization guinea pig PMRA# 2946557, 2946558, 2946559, 2952523	**Not a skin sensitizer**
Short-Term Toxicity Studies	
2-week Oral Toxicity (gavage) Sprague Dawley rat PMRA# 2946557, 2946558, 2946559	**Supplemental** **≥ 20 mg/kg bw/day:** ↓ rel testes wt (not dose-related non-adverse) (♂) **40 mg/kg bw/day:** ↑ liver wt (♂)
2-week Oral Toxicity (gavage) Wistar rat PMRA# 2946557	**Supplemental** **5000 mg/kg bw/day:** weakness, hair loss, polyuria, small, soft testes and inhibition of spermatogenesis (with no evidence of recovery 10 days after treatment) (♂)
2-week Oral Toxicity (gavage) Sprague Dawley rat	**Supplemental** **5000 mg/kg bw/day:** effects on spermatogenesis were observed

Study Type/ Animal/PMRA#	Study Results
PMRA# 2946557, 2946558	
2-week Oral Toxicity (gavage) CD rat PMRA# 2946557, 2946558, 2946559	**LOAEL = 200 mg/kg bw/day** **≥ 200 mg/kg bw/day:** testes wt and ratio low in 1/3 rats; testes small, discoloured and soft in 1/3 rats sacrificed immediately post-dosing, testes in 2/3 rats showed degeneration of germinal epithelium (less than 10% of tubules), sperm reduced in 2/3 rats sacrificed immediately post dosing. **3400 mg/kg bw/day:** 2/6 deaths, mild diarrhea, bw loss first week, ↓ bwg second week, small, discoloured and soft testes, degeneration of germinal epithelium (70% of tubules) and absence of sperm from epididymis of all rats (3/3). Other compound-related changes (not assessed at 200 mg/kg bw/day): edema and focal necrosis of the duodenum; reduction of blood-forming elements of the bone marrow; decrease in the large globular-shaped centrilobular vacuoles in the liver.
28-day Oral Toxicity (dietary) Sprague Dawley rat PMRA# 2965082	**Supplemental-Range finding** **≥ 100 mg/kg bw/day:** ↑ liver wt **≥ 200 mg/kg bw/day:** ↓ fc and growth (♂/♀); degeneration of testicular tissue, spermatogenesis (♂); oogenesis affected (♀). **400 mg/kg bw/day:** ↑ Hgb, ↑ RBC, ↑ WBC.
30-day Oral Toxicity (dietary) Wistar rat PMRA# 2946557	**Supplemental-Range finding** **≥ 500 mg/kg bw/day:** ↓ bw, ↓ bwg, azoospermia **2500 mg/kg bw/day:** ↑ mortality (16/20 rats), ↓ fc, ↓ leukocytes, ↑ emaciation, ↑ siderosis in liver and kidney
4-Weeks Oral Toxicity (dietary) Wistar rat PMRA# 2946559	**Supplemental-Limited organ histopathology and kidney data** **100 mg/kg bw/day** ↑ liver wt, ↓ spleen wt (♀).
90-day Oral Toxicity (dietary) Sprague Dawley rat PMRA# 2946557, 2946558, 2946559, 2965082	**NOAEL = 106/116 mg/kg bw/day (♂/♀)** **35/39 mg/kg bw/day:** ↑ liver wt (slight, non-adverse) (♀). **106/116 mg/kg bw/day:** ↑ kidney wt (♂); ↑ spleen and thyroid wt, ↓ fc during recovery phase, ↓ total serum proteins (♀). No treatment-related differences in liver wt after a 6 wk recovery period.
93-day Oral Toxicity (Dietary) Wistar Rat PMRA# 2946557, 2965082	**NOAEL = 163/174 mg/kg bw/day (♂/♀)** **≥ 6.5/6.9 mg/kg bw/day:** ↑ liver wt (non-adverse) (♀) **≥ 163/174 mg/kg bw/day:** ↑ liver wt (non-adverse) (♂) **780/847 mg/kg bw/day:** ↑ mortality, slight ↓ growth, slight ↑ uric acid in blood**(♂/♀); ** no effects noted in the histopathological examination of the testes (♂)

Study Type/ Animal/PMRA#	Study Results
90-day Oral Toxicity (gavage) Wistar rat PMRA# 2946557, 2946558, 2946559	**≥ 16 mg/kg bw/day:** kidney effects (tubular dilation and hydropic degeneration), ↓ bw, ↑ ALT (♂). **≥ 32 mg/kg bw/day:** ↓ erythrocyte counts (♂) (trend; not dose-dependent), ↓ BUN (♂), ↑ serum bilirubin, ↑ ALT, kidneys (fibrosis and congestion). **64 mg/kg bw/day:** ↑ ALP (♂), kidney effects (hyalinisation and extensive vascular congestion). Dose-related changes in the liver ranged from sparse infiltration by inflammatory cells to inflammatory and degenerative changes.
28-day Oral Toxicity (dietary) Beagle dog PMRA# 2946557, 2946559	**Supplemental-Range finding** **≥ 19 mg/kg bw/day:** ↑ liver wt, ↑ slightly swollen hepatocytes (♀) **96/99 mg/kg bw/day:** ↑ ALT, ↑ ALP, ↑ disseminated focal lesions in the liver (♂) ↑ greatly enlarged hepatocytes (♀) Testes were not weighed.
90-day Oral Toxicity (dietary) Beagle dog PMRA# 2946557, 2946558	**NOAEL = 9.7/10 mg/kg bw/day** **≥ 9.7/10 mg/kg bw/da**y: ↓ albumin (slight, non-adverse (♂) **49/53 mg/kg bw/da**y: ↓ blood clotting time (slight), ↑ relative liver and thyroid wt, ↓ relative heart wt
90-day Oral Toxicity (dietary) Beagle dog PMRA# 2965082	**NOAEL = 45 mg/kg bw/day** **≥ 45 mg/kg bw/day:** ↑ rel adrenal wt (♂); ↑ liver wt (♀) **135 mg/kg bw/day:** ↓ bw, ↓ heart wt (♀).
90-day Oral Toxicity (dietary) Beagle dog PMRA# 2946557, 2946558, 2946559	**NOAEL = 50/56mg/kg bw/day** **16 mg/kg bw/day:** ↓ testicular wt (non-adverse at this dose level) **50/56 mg/kg bw/day:** ↑ rel adrenal wt, ↑ seminiferous tubule degeneration (in 1/3 dogs; not seen at next dose) (♂); ↑ rel liver wt (♀) (all findings non-adverse at this dose level) **154/177 mg/kg bw/day:** ↓ bwg, ↑ rel liver wt (♂); perivenous infiltrates, unorganised zones of proliferation, local hepatocyte regeneration and local hyperemia noted in 1/3 dogs (♀)
90-day Oral Toxicity (gavage) Mongrel dog PMRA# 2946557	**LOAEL = 80 mg/kg bw/day** **≥ 80 mg/kg bw/day:** ↓ RBC, ↑ incidence of microscopic lesions including mucosal erosion in the stomach, focal degeneration, sinusoidal dilatation and congestion in the liver, patchy congestion in the spleen, degeneration of glomeruli and tubuli in the kidney, degeneration with fibrosis in testes and ovaries. **800 mg/kg bw/day:** ↓ bw

Study Type/ Animal/PMRA#	Study Results
One-year Oral Toxicity (dietary) Beagle dog PMRA# 2946557, 2946558, 2946559, 1530454	**NOAEL = 6.4/7.2 mg/kg bw/day (♂/♀)** **17 mg/kg bw/day:** ↑ serum cholesterol, ↑ platelet counts, ↑ liver wt (♂/♀); ↓ serum calcium (♂), ↑ serum globulin (♀),
10-day Dermal Toxicity New Zealand White rabbit PMRA# 2946557, 2946558, 2946559	**NOAEL(systemic) = 2000 mg/kg bw/day** **2000 mg/kg bw/day:** No systemic toxicity; no treatment-related clinical chemistry or pathological findings. Skin irritation (focal epidermal and sub-epidermal necrosis with polymorphonuclear cell infiltrations) was observed in 5/6 rabbits
21-day Dermal Toxicity New Zealand White rabbit PMRA# 2946557, 2946559	**NOAEL(systemic) = 250 mg/kg bw/day** **250 mg/kg bw/day:** No evidence of systemic toxicity. Dermal effects included erythema, dryness of skin at scarified sites and skin thickening; slight effects on the skin were observed at the lowest dose.
28-day Dermal Toxicity Sprague Dawley rat PMRA# 1783049, 1783063	**NOAEL = 20/120 mg/kg bw/day (♂/♀)** **$BMDL_{10}$ (seminiferous tubule degeneration) = 68 mg/kg bw/day** **≥ 120 mg/kg bw/day:** mild to severe seminiferous tubule degeneration, mild to severe hypospermia in the lumen of epididymal tubules(♂); ↑ liver wt (♀), **≥ 480 mg/kg bw/day:** sperm granulomas, ↓ epididymal sperm concentration, ↑ abnormal sperm, ↓ motile sperm, ↓ % progressively motile sperm (♂); slight ↓ RBC, Hgb, Hct, ↑ forelimb and hindlimb grip strength (♀). **720 mg/kg bw/day:** ↑ rel liver wt, ↓ homogenization-resistant spermatid head concentration, ↓ daily sperm production/testis, ↓ efficiency of daily sperm production, ↑ forelimb grip strength (♂). **10-week recovery group:** **720 mg/kg bw/day:** Seminiferous tubule degeneration, hypospermia in the lumen of epididymal tubules, ↑ abnormal sperm
5-day Inhalation Toxicity (nose-only) Sprague Dawley rat PMRA# 1407065	**Supplemental-Non-guideline** **0.178 mg/L:** ↑ glucose, ↓ kidney wt (♀) (all findings non-adverse)
Chronic Toxicity/Oncogenicity Studies	
80-week Oral Carcinogenicity (dietary) Swiss Random mouse PMRA# 2946557, 2946558, 2946559, 1530454	**Acceptable, non-guideline; methodological limitations** **NOAEL = 23 mg/kg bw/day (♂/♀)** **≥ 23 mg/kg bw/day:** ↑ incidences of foci and nodular hyperplasia. **714 mg/kg bw/day:** ↑ rel liver wt, ↑ incidence of clear cell foci, mixed cell foci and hepatoblastoma in liver (♂); ↑ incidence of clear cell foci and neoplastic nodules in liver (♀).

Study Type/ Animal/PMRA#	Study Results
	A basophilic tumour (hepatoblastoma) was a unique finding and metastasized to the lungs in 2 mice. **Liver tumours (♂/♀ n=100)** mg/kg Adenoma Carcinoma 0 9/1 1/1 22.5 5/1 3/0 43 13/3 4/0 714 14/8 9/0 **Evidence of carcinogenicity**
Two-year Oral Oncogenicity Toxicity (dietary) CD-1 mouse PMRA# 1157209	**NOAEL = 81/125 mg/kg bw/day (♂/♀)** **≥ 81/125 mg/kg bw/day:** centrilobular hepatocellular hypertrophy, ↓ abs thymus and kidney wt, slight ↓ bw (♂); bile duct hyperplasia (♀) (effects considered minimal and non-adverse). **≥ 257/380 mg/kg bw/day:** sperm stasis in testes, thymic lymphoid depletion, ↑ liver wt, single cell hepatocellular necrosis, centrilobular hepatocellular swelling (♂); centrilobular hepatocellular necrosis (♀) **1560/1886 mg/kg bw/day:** ↓ survival (♂); centrilobular hepatocellular hypertrophy, eosinophilic foci of cellular alterations, macrophages containing yellow-brown pigment (♀). **Neoplastic findings** **Animals with hepatocellular neoplasm:** 0 500 1500 7500 ppm ♂ 11/80 13/80 19/80 3/80 ♀ 1/80 8*/79 21*/79 17*/78 ***Statistically significant by Fisher Test (p<0.05)** **Evidence of carcinogenicity**
22-month Oral Oncogenicity study (dietary) HOE:NMRKf (SPF 71) mouse PMRA# 2946557, 2946558, 2946559, 1530454	**Unacceptable guideline study: incomplete examination of most recommended tissues. Additionally blood and urine were not collected for analysis** **NOAEL = 34/42 mg/kg bw/day (♂/♀)** **≥ 34/42 mg/kg bw/day:** non-statistical ↑ granulosa cell tumours and luteomas in the ovaries. **522/648 mg/kg bw/day:** ↑ relative liver wt, marked liver cell hypertrophy in the centrilobular and intermediate areas, other liver effects (necrosis, mitotic cells, pigmented Kupffer cells, clear cell foci). **Evidence of carcinogenicity**
Two-year Chronic Toxicity /Carcinogenicity (dietary) Wistar rat PMRA# 2946557, 2946558,	**NOAEL = 18/19 mg/kg bw/day** **600/640 mg/kg bw/da**y: ↑ liver wt (♂/♀);↑ Hgb and PCV, ↑ BUN, ↓ AST (♂); ↓ bw and bwg, ↓ Hgb (F), ↓ Hct, ↓ PCV, ↑ ALP, ↑ ALT, ↓ total serum protein (♀) **No evidence of carcinogenicity**

Study Type/ Animal/PMRA#	Study Results
2946559	
Two-year Chronic Toxicity (dietary) Beagle dog PMRA# 2946557, 2946558, 2946559, 1530454	**Supplemental - Study conducted with wettable powder formulation 72.2% or 53%, concentrations adjusted for active ingredient** **≥ 12.5 mg/kg bw/day:** ↑ mortality, ↓ bw, anorexia, , ↑ cholesterol, ↑ BUN, ↑ ALT, ↑ total protein, ↑ ALP, ↑ albumin and albumin/globulin ratio, hepatitis, liver cirrhosis. **No evidence of carcinogenicity**
Two-year Chronic Toxicity (dietary) Beagle dog PMRA# 2946557, 2946558, 2946559	**NOAEL = 9.3/8.9 mg/kg bw/day (♂/♀)** **80.8/84.2 → 150.4/135.8 mg/kg bw/day:** ↓ bw and bwg, ↓ clotting time, ↑ ALP (34–62%), ↑ liver wt, ↑ rel. pituitary, ↑ thyroid wt (♂/♀); 1/4 male showed a few atrophic tubules and interstitial mononuclear inflammatory cell infiltrates of the testes (♂); one animal sacrificed in moribund state after wk 36, ↑ incidence of dull dry coat, ↓ fc (slight) (♀) **No evidence of carcinogenicity**
Developmental/Reproductive Toxicity Studies	
Two-generation Reproductive Toxicity Wistar rat PMRA# 2946557	**Parental, offspring and reproductive NOAEL = 27 mg/kg bw/day (♂/♀)** No signs of toxicity in parents and offspring and no reproductive effects noted.
Three-generation Reproductive Toxicity Wistar rat PMRA# 2946557, 2946558, 2946559	**Parental, offspring and reproductive NOAEL = 100 mg/kg bw/day (♂/♀)** No signs of toxicity in parents and offspring and no reproductive effects noted.
Extended One Generation Reproductive Toxicity (dietary) Wistar rat PMRA# 2490664	**Parental Toxicity – P Generation** **NOAEL (♂) = 107 mg/kg bw/day** **NOAEL (♀) = 16 mg/kg bw/day** **≥ 53/68 mg/kg bw/day:** ↑ thyroid hypertrophy (2/29, 3/23 at 67.6 and 136.8 mg/kg bw/day respectively) ↑ TSH and T_4, ↑ thyroid follicular cell height, ↓ colloid area (♀). **107/137 mg/kg bw/day:** ↓ monocytes (♂) **F1/F2 Generation – Post-Weaning** **NOAEL (♂) = 16.2 mg/kg bw/day** **NOAEL (♀) = 67.6 mg/kg bw/day** **≥ 53/68 mg/kg bw/day:** ↑ TSH and T_4, ↑ thyroid follicular cell height, ↓colloid area (F1 ♂ at PND 23). **107/137 mg/kg bw/day:** ↓ bw, ↓ fe in F1 (♂); ↑ TSH, ↑ thyroid follicular cell height, ↓ colloid area (F1 ♀ at PND 23 and F2 at PND 45); ↓ brain wt (♀). **Offspring Toxicity – F_1/F_2 Generation** **NOAEL (♂/♀) = 16 mg/kg bw/day**

Study Type/ Animal/PMRA#	Study Results
	≥ 68 mg/kg bw/day: ↓ T_4 (F1 PND 4), ↑ liver wt (♂/♀); ↓ bw, ↓ overall bwg (F1 ♂) **137 mg/kg bw/day:** delay in vaginal patency in F1 and F2 (♀) **Reproductive Toxicity** **NOAEL (♂/♀) = 53/137 mg/kg bw/day** **≥ 53/68 mg/kg bw/day:** ↓ testosterone (slight, P1 only), ↑ testicular sperm count (all findings not adverse) (♂) **107/137 mg/kg bw/day:** ↓ testes wt, ↑ testicular atrophy (P1 only), ↓ testosterone (slight non-adverse, P1 only), ↑ progressive sperm motility (♂)
Developmental Toxicity (dietary) Sprague Dawley rat PMRA# 2946557, 2946559	**Supplemental-Non-guideline, fetal effects only assessed at the highest dose level.** **Maternal** No maternal toxicity observed. **Developmental** **100 mg/kg bw/day:** ↑ incidence of thoracic vertebral bodies being reduced in number, ↑ incidence of absent ossification in cervical vertebral bodies, ↑ incidence of incomplete ossification of skull bones **Increased sensitivity of the young**
Developmental Toxicity (dietary) Wistar rat PMRA# 2946557, 2946558, 2946559	**Maternal:** **NOAEL = 141 mg/kg bw/day** **371 mg/kg bw/day:** ↓ bw, ↓ fc **Developmental:** **LOAEL = 45 mg/kg bw/day** **45 mg/kg bw/day:** ossification significantly delayed or absent in cervical vertebral bodies. **371 mg/kg bw/day:** ossification significantly delayed or absent, in forelimbs, hindlimbs, sternebrae, and skull bones, ↑ supernumerary ribs. **Increased sensitivity of the young**
Developmental Toxicity (gavage) Sprague Dawley rat PMRA# 2946557, 2946558, 2946559, 1530454	**Maternal:** **NOAEL = 20 mg/kg bw/day** **90 mg/kg bw/day:** ↓ bwg, ↑ liver wt, ↓ live fetuses /litter, ↑resorption **Developmental:** **NOAEL = 10 mg/kg bw/day** **≥ 20 mg/kg bw/day:** ↓ fetal wt, ↑ skeletal variations. **90 mg/kg bw/day:** ↓ live fetuses /litter, ↑resorption, ↑ fetal malformations (hydrocephaly, microphthalmia, anophthalmia, malformed scapulae, and axial malformations). **Increased sensitivity of the young** **Evidence of fetal malformations**

Study Type/ Animal/PMRA#	Study Results
Developmental Toxicity (gavage) Sprague Dawley rat PMRA# 2946557, 2946558, 2946559	**Maternal:** **NOAEL = 30 mg/kg bw/day** **60 mg/kg bw/day:** ↓ bw, 2/23 animals aborted, ↑ (51%) resorptions. **Developmental:** **NOAEL = 10 mg/kg bw/day** **30 mg/kg bw/day:** ↑ malformations affecting the head, spine, ribs and sternum (42% of the fetuses in 19/21 litters at this dose level) **60 mg/kg bw/day:** ↑ resorptions, ↑malformations (90% of fetuses, and all litters were affected) **100 mg/kg bw/day:** only 4 live fetuses in 3 litters, all of which were malformed. **≥ 300 mg/kg bw/day:** 100% early resorptions, no live fetuses. **Increased sensitivity of the young** **Evidence of fetal malformations**
Developmental Toxicity (gavage) Sprague Dawley rat PMRA# 2946557, 2946559	**Maternal:** **NOAEL = 30 mg/kg bw/day** **30 mg/kg bw/day:** No effect on maternal animals observed **Developmental:** **NOAEL = 10 mg/kg bw/day** **30 mg/kg bw/day:** ↓ placenta wt, ↓ fetal wt, ↑ malformations, variations and retardations (hydrocephalus in 17/358 fetuses; malformations of the head, spine and ribs in 81/358 fetuses from 22 litters). **Increased sensitivity of the young** **Evidence of fetal malformations**
Developmental Toxicity (gavage) Wistar rat PMRA# 2946557	**Maternal:** **NOAEL = 30 mg/kg bw/day** **60 mg/kg bw/day:** ↓ maternal bw **Developmental:** **NOAEL = 10 mg/kg bw/day** **≥ 30 mg/kg bw/day:** ↑ resorption, ↓ fetal bw **Increased fetal sensitivity**
Developmental Toxicity (gavage, single dose) Albino rat PMRA# 2946557	**Supplemental** **Developmental** Doses of 250–5000 mg/kg bw on GD 11 produced no live fetuses in any of the dose groups. Doses of 250 –5000 mg/kg bw on GD 13 produced live fetuses but all had anomalies esp. encephalon and limbs. Doses of 15.6–125 mg/kg bw on GD 13 produced higher rate of stillbirth; meningocele and an increased postnatal period were also observed.

Study Type/ Animal/PMRA#	Study Results
	Evidence of malformation
Developmental Toxicity (gavage, single dose) rat PMRA# 2946557, 2946559	**Supplemental** **Developmental** **≥ 31.2 mg/kg bw:** ↓ number of live-born/litter, ↓ offspring viability. **62.5 mg/kg bw:** hydrocephalus (20% - 3/14). Possible behavioural teratogenic effects observed at 31.2 and 62.5 mg/kg bw, but could not be conclusively established. **Evidence of fetal malformation**
Developmental Toxicity (gavage) rat PMRA# 2946557	**Supplemental** **Developmental** **≥ 19 mg/kg bw/day:** ↑ embryolethality, ↑ external anomalies, in particular exencephalia, ↓ fetal wt **Evidence of fetal malformations**
Developmental Toxicity (gavage, single dose GD 10) Wistar rat PMRA# 2946557, 2946559	**Supplemental** **Developmental** **≥ 30 mg/kg bw:** ↓ number of live fetuses due to deaths and resorptions, ↑ runts. No significant or dose -related increase in the incidence of malformations, but at 30 mg/kg bw one fetus had exencephaly, and one had hydrocephalus; two fetuses at 60 mg/kg bw had hydrocephaly. **Evidence of fetal malformations**
Developmental Toxicity (gavage, single dose GD 8) Golden hamster PMRA# 2946557, 2946558, 2946559	**Supplemental** **Maternal:** **≥ 75 mg/kg bw:** ↓ bwg **Developmental:** **≥ 30 mg/kg bw:** slight ↑ resorptions/dead fetuses. **≥ 75 mg/kg bw:** ↓ fetal wt, ↑ malformations including exencephaly, ↑ fused ribs (10/57, 14/52 at 75, 150 mg/kg bw/ day respectively) **150 mg/kg bw**: ↓ fetuses/litter **Increased sensitivity of the young** **Evidence of fetal malformations**
Developmental Toxicity (gavage, single dose) New Zealand White rabbit PMRA# 2946557, 2946559	**Supplemental** **Developmental** **10 mg/kg bw/day (dosing GD 10, 13, and 18):** ↑ runts (22%) **10 mg/kg bw/day (dosing GD 8, 10, and 12):** slight ↑ dead /resorbed fetuses. **60 mg/kg bw/day (dosing GD 8, 10 and 12):** ↓ fetuses/litter (31 live fetuses from 40 implantations), ↑ runts (26%), ↑ incidence of fused ribs

Study Type/ Animal/PMRA#	Study Results
	150 mg/kg bw (dosing GD 9): ↓ in fetuses/litter (28 live fetuses from 54 implantations) ↑ runts (30%), ↑ incidence of fused ribs(57%) **150 mg/kg bw/day (dosing GD 8, 10 and 12):** no live fetuses. **300 mg/kg bw (dosing GD 9):** no live fetuses. **Evidence of fetal malformation**
Developmental Toxicity (gavage) New Zealand White rabbit PMRA# 2946557, 2946558, 1530454	**Maternal** **NOAEL = 20 mg/kg bw/day** **125 mg/kg bw/day:** ↓ bw **Developmental** **NOAEL = 10 mg/kg bw/day** **≥ 20 mg/kg bw/day:** ↑ resorptions , ↓ live litter size **125 mg/kg bw/day:** ↑malformed fetuses/litter (malformed cervical vertebrae and interrelated malformation of the ribs and proximate thoracic vertebrae).
Special Studies: Female fertility/Oocyte maturation	
Effect on Uterine Decidual Cell Response During Pseudo-Pregnancy rat PMRA# 2946557, 2946558, 2946559	**Supplemental** **400 mg/kg bw/day:** partial inhibition of decidual growth Only treatment related effect observed in pseudopregnant animals was reduced uterine wt which is a measure of uterine decidual growth during pseudopregnancy. No changes in ovarian wt, number of corpora lutea, bw gain or serum progesterone and estradiol levels
Acute Effect On Microtubule-Dependent Meiotic Events hamster PMRA# 2946558	**Supplemental** **During meiosis I:** **≥ 250 mg/kg bw:** ↓ average number live pups. **≥ 750 mg/kg bw:** ↓% pregnant animals. **During meiosis II:** **1000 mg/kg bw:** ↓ average number live pups (no change in % pregnant animals). Administration of carbendazim at the time of microtubule-dependent meiotic events can result in early pregnancy loss in hamsters.
Special Studies: Male Fertility/Hormonal Effects and Spermatogenesis	
Acute Oral Toxicity Effects on Spermatogonia (gavage) rat PMRA# 2946559	**Supplemental** No chromosome aberrations in spermatogonia. ↑ mitotic index and induced development of c-mitosis in dividing cells (reaction was more intense with carbendazim than colchicine). Carbendazim-induced inhibition of cell division (increased mitotic index) and accumulation of c-metaphases was reversible.
Acute Oral Toxicity Effects on fertility (gavage) Wistar rat	**Supplemental** **≥ 1000 mg/kg bw:** pathological changes in testes (soft). **≥ 1500 mg/kg bw:** pathological changes in testes (soft, small, occasionally dark), interference with spermatogenesis. **≥ 5000 mg/kg bw:** initial wt loss, diarrhea.

Study Type/ Animal/PMRA#	Study Results
PMRA# 2946558	**11 000 mg/kg bw:** cellular degeneration (testes).
Acute Oral Toxicity Effects on fertility (gavage) CD rat PMRA# 2946558	**Supplemental** **≥ 1000 mg/kg bw:** ↓ sperm in epididymis; germinal epithelium degeneration with multinucleated giant cells. **≥ 2250 mg/kg bw:** testes discoloured, small and soft and sometimes of unequal size (except at 7500 mg/kg bw). **≥ 3400 mg/kg bw:** sperm absent from epididymis. **≥ 11 000 mg/kg bw:** ↓ testis wt. Effects not fully dose-related: fewer tubules affected at 5000 and 7500 mg/kg bw.
10-day Oral Toxicity Effects on reproduction/fertility (gavage) Wistar rat PMRA# 2946559	**Supplemental-Methodological limitations, dosing period not long enough to cover full spermatogenesis period.** **400 mg/kg bw/day**: ↓ testicular wt, ↓cauda and caput epididymal wt, ↓total epidiymal sperm count and vas deferens sperm concentration, ↑ serum FSH levels, bilateral seminiferous tubular atrophy (14/16 ♂ vs. 0/16 ♂ in controls), ↓ male fertility (96% to 60 % by the end of week 1 post-exposure, with maximal depressions occurring 4 weeks post exposure)
Acute Oral Toxicity Effects on fertility (gavage) Wistar rat PMRA# 2946557	**Supplemental** **200 mg/kg bw:** Carbendazim reversibly blocked division of spermatogonia at the metaphase stage without producing chromosome aberrations
Acute Toxicity (i.p.) Effects on fertility Wistar rat PMRA# 2946557	**Supplemental** **Dosing:** 859 µmol/kg via i.p. injection or 1.37 µmol injected into testis of benomyl or carbendazim Little testicular damage was caused by injection of benomyl after 1 or 2 hrs; carbendazim elicited severe disruption of the seminiferous epithelium. Results strongly suggest that benomyl metabolite carbendazim, not benomyl, is mediator of benomyl-induced testicular toxicity and inhibitor of testicular microtubule assembly.
Acute Oral Toxicity Effects on testes, efferent ductules, and spermatozoa (gavage) Sprague Dawley rat PMRA# 2946558	**Supplemental** Animals sacrificed on day 2 or 70 post-dosing **On day 2:** **50 mg/kg bw:** missing immature germ cells with round spermatids (stage I and II), elongated spermatids sloughed from stage VII epithelium. **≥ 100 mg/kg bw:** ↑ testicular wt, absence of germ cells, sloughing of spermatids extended to stages XII and XIV, swollen rete testis with sloughed germ cells, ≥50% efferent ductules were occluded. **≥ 200 mg/kg bw:** germ cells missing at most stages. **≥ 400 mg/kg bw:** ↑ mean seminiferous tubular diameter **On day 70:** ↓ testicular wt and seminiferous tubule diameter due to ↑ seminiferous tubular atrophy.

Study Type/ Animal/PMRA#	Study Results
Acute Oral Toxicity Effects on testes, efferent ductules, and spermatozoa (gavage) Sprague Dawley rat PMRA# 2946558	**Supplemental** Animals sacrificed at 2, 4 or 8 hrs or 1, 4, 8, 16, or 32 days post-dosing **400 mg/kg bw:** ↑ testicular wt at 8 hrs (↓ day 16 and 32 in 5/16), ↓ sperm head counts/testis at 8 and 24 hrs and day 8, after which some recovery. ↑ epididymal wt on day 4, but ↓% normal sperm. By day 8 many spermatozoa heads were separated from their flagella and 10% of the heads were misshapen. Numerous sloughed, round germ cells and cytoplasmic debris, were evident. Sperm motility was ↓ on days 8 and 16, control levels on day 32.
5-day Oral Toxicity (gavage) C57BL6*C3H/HeF1 mouse PMRA# 2946558	**Supplemental** Animals sacrificed on days 7, 24 and 39 post-dosing. **≥ 500 mg/kg bw/day:** ↓ % round spermatids (7 and 24 days), ↑ sperm head abnormalities (day 39). **1000 mg/kg bw/day:** ↓ testis wt, ↑ sperm head abnormalities (days 7, 24 and 39), chromatin structure altered (days 7 and 39).
10-day Oral Toxicity Effect on fertility (gavage) Sprague Dawley rat PMRA# 2946559	**Supplemental** ♂ bred once a week for 14 weeks following treatment **400 mg/kg bw/day:** ↓ testis, cauda and caput epididymal wt, ↓ total epididymal sperm count and vas deferens sperm concentration, ↑ serum FSH levels, bilateral seminiferous tubular atrophy, ↓ male fertility
Oral Toxicity Effects on developmental stage (gavage) Long-Evans rat Syrian hamster PMRA# 2946558	**Supplemental** **Rats** ♂/♀ dosed from weaning, through puberty, gestation and lactation; ♂ examined 50 days post-dosing **≥ 50 mg/kg bw/day:** ↓ caudal epididymal sperm count. **≥ 100 mg/kg bw/day:** a few malformed pups. **≥ 200 mg/kg bw/day:** ↓ litter size, ↓ reproductive potential due to effects on sperm production and fetal viability, altered sperm morphology, ↓ testicular and epididymal wt, ↓ sperm number, altered testicular histology, fertility, sperm mobility and hormonal levels in ♂ with very low sperm count. **400 mg/kg bw/day:** ↑ post-implantation loss. **Hamsters:** Dosed from weaning, through puberty, gestation and lactation; (0, 400 mg/kg bw/day) **400 mg/kg bw/day:** ↓ testicular and epididymal sperm counts, ↓ testis and seminal vesicle wt. Overall, carbendazim was less toxic to hamsters than to rats: the only reproductive effect was on sperm measures. In hamsters, fertility as well as fetal and neonatal viability was not altered.
85-day Oral Toxicity Effects on testes and endocrine function (gavage)	**Supplemental** **≥ 200 mg/kg bw/day:** ↓ testes and caput epididymides wt, ↓ seminiferous tubule fluid volume, ↑ androgen binding protein in interstitial and seminiferous

Study Type/ Animal/PMRA#	Study Results
Long Evans rat PMRA# 2946558	tubule fluid, ↑ testosterone in seminiferous tubule fluid. **400 mg/kg bw/day:** ↓ interstitial fluid volume, ↑ testosterone concentration in interstitial fluid, ↑ serum androgen binding protein. HCG stimulation of the decapsulated testes caused ↑ in in vitro testosterone synthesis/release at 200 and 400 mg/kg bw/day after 1, 2 and 3 hrs incubation. Conclusion: Carbendazim directly affects the gonads causing testicular atrophy with secondary hormone changes.
85-day Oral Toxicity Effects on testes and endocrine function (gavage) Long Evans rat PMRA# 2946558	**Supplemental** Each ♂ paired with 1 ♀ for 20 days 64 days after beginning of treatment **50 mg/kg bw/day:** ↑ anterior hypothalamic GnRH (progressive ↓ at higher doses). **≥ 100 mg/kg bw/day:** ↑ anterior pituitary LH, slight ↓ medio-basal hypothalamic GnRH. **≥ 200 mg/kg bw/day:** ↑ serum FSH (particularly in fertile rats), ↑ serum LH (not at 400 mg/kg bw/day). Carbendazim-induced testicular damage is accompanied by compensatory changes in hypothalmic and pituitary regulation of the testis.
Short-term Oral Toxicity (dietary) Wistar rat PMRA# 2946558	**Supplemental** Fertility parameters, testicular wt, seminiferous tubules, interstitial tissue, epididymal structures and enzyme activities were not affected by treatment. **≥ 0.5 mg/kg bw/day:** ↑ preleptonene spermatocyte nuclear area. **≥ 3.5 mg/kg bw/day:** ↑ incidence of 'degenerating' germ cells undergoing meiosis and spermatogenesis. **25 mg/kg bw/day**: effects indicate that carbendazim affects the physiological 'germinal elimination process'. No biologically significant effects on spermatogenesis.
Neurotoxicity	
Acute Delayed Neurotoxicity (Gavage) Leghorn chicken PMRA# 2946558	**NOAEL = 2500 mg/kg bw** **5000 mg/kg bw:** systemic toxicity, transient/reversible neurotoxic signs (slight leg weakness, ataxia) (♀)
21-day Neurotoxicity Leghorn chicken PMRA# 2946557	**400 mg/kg bw/day:** ↑ serum ChE (33.5%), slight ataxia for approximately 2 days (1/3 ♀ only) (♀)

Study Type/ Animal/PMRA#	Study Results	
Summary - Genotoxicity Studies		
Study (# of studies)	**Purity or Dose (mg/kg bw)**	**Results/Effects**
Bacterial reverse mutation - *S. typhimurium* (36); *S. cervisiae* (1) PMRA# 2946557, 2946558, 2946559	various	Negative in 14 studies ±S9. Weakly positive to positive +S9, or at very high concentrations in one or more strains in 15 studies (in some cases, the purity was unknown). Positive in 8 studies using test material with DAP and AHP contaminant.
Carbendazim with differing amounts of DAP and AHP seemed to be the reason for positive Ames tests. Also, 2-amino-benzimidazole (a minor metabolite in the rat) was positive in both forward and reverse mutation tests. Highly purified carbendazim and its main metabolite in mammals, 5-OH carbendazim, were not mutagenic.		
Fungi/plant cytogenetics (2) PMRA# 2946559	unknown	Chromosome aberrations and mitotic non-disjunction observed.
Mammalian Cells in vitro - Mouse lymphoma, Chinese hamster ovary cells (5) PMRA# 2946557, 2946558, 2946559	unknown or 100%	Negative in 3 studies (100% purity in 2/3 studies). Positive (unknown purity) in 2 studies (1 at highly toxic concentrations).
Chromosomal Effects (10) PMRA# 2946557, 2946558, 2946559, 2976563	unknown	Positive for aneuploidy in 9 studies (threshold response).
In vivo genotoxicity (15) PMRA# 2946557, 2946558, 2946559	97–99% or unspecified	Negative for clastogenicity in 8 studies. Positive for micronucleus formation in 7 studies: aneugenic rather than clastogenic.
Tubulin/mitotic effects/DNA synthesis in vitro/in vivo (9) PMRA# 2946557, 2946559	unknown	Inhibits tubulin polymerization and therefore mitosis; ↓ DNA, RNA and protein synthesis - a reflection of mitotic arrest.
Dominant Lethal (4) PMRA# 2946557, 2946558, 2946559	94%	Negative in all 4 studies.
DNA damage and repair (7) PMRA# 2946557, 2946558, 2946559	99% or not specified	Negative; but the minor rat metabolite 2-amino-benzimidazole induced DNA damage in *E. coli* strains WP_2 uvrA and CM 611.
In vivo Germ Cell Tests		
DNA binding - rat liver DNA synthesis inhibition - rat gonads PMRA# 2946557, 2946559	2, 20, 200	Negative for DNA binding. The compound reached the gonads and inhibited DNA and protein synthesis at ≥ 2 mg/kg bw. The affinity of the agent for hepatic proteins, penetration into gonads, and inhibition of DNA and protein synthesis at high doses suggest an epigenetic mechanism of action on reproductive cells.
Mouse sperm FISH assay - Aneugenic effects on male germ cells (gavage) PMRA# 2976563	20, 50, 150, 500	No aneugenic effect up to the highest dose of 500 mg/kg bw.

Study Type/ Animal/PMRA#	Study Results	
Aneuploidy frequency in unfertilized ocytes/preimplantation embryonic development - hamster PMRA# 2976563	1000	↑ aneuploidy frequency in unfertilized oocytes. In animals allowed to mate, the fertilization rate was not impaired; however, there was a significant ↑ in proportion of pre-implantation embryos that failed to reach expected stage of development (8-cell, morula, blastocyte stage) and ↓ number of implantation sites.
Chromosome aberrations in sperm and micronuclei in peripheral RBC – rat (single oral dose) PMRA# 2976563	2.5, 800	↑ in diploid epididymal sperm sampled after 31 days; induction of aneuploid sperm was not observed; no evidence of micronucleus induction in the erythrocytes.
Induction of micronulei in round (immature) spermatids – rat (single gavage dose) PMRA# 2976563	50, 100, 400	**100 mg/kg bw:** ↑ micronucleus incidence at 24 hrs; ↑ micronuclei with kinetochores, suggesting that the micronuclei in treated rat-spermatids are due to aneuploidy rather than to clastogenic activity.

Appendix IV Dietary Exposure and Risk Estimates

Table 1 Dietary Risk Assessment for Thiophanate-methyl (TPM)

Population	Food				Food + Drinking Water			
	Acute Exposure	% ARfD [1]	Chronic Exposure	% ADI [2]	Acute Exposure	% ARfD [1]	Chronic Exposure	% ADI [2]
General population	0.0026	5	0.000027	< 1	0.0054	11	0.000040	< 1
All infants (<1 year old)	0.0083	17	0.000060	< 1	0.016	31	0.00011	< 1
Children 1–2 years old	0.0096	19	0.000096	< 1	0.012	24	0.00011	< 1
Children 3–5 years old	0.0076	15	0.000073	< 1	0.0095	19	0.000087	< 1
Children 6–12 years old	0.0038	8	0.000042	< 1	0.0060	12	0.000053	< 1
Youth 13–19 years old	0.0019	4	0.000021	< 1	0.0040	8	0.000030	< 1
Adults 20–49 years old	0.0018	4	0.000020	< 1	0.0045	9	0.000032	< 1
Adults 50+ years old	0.0021	4	0.000021	< 1	0.0043	9	0.000034	< 1
Females13–49 years old	0.0019	4	0.000020	< 1	0.0046	9	0.000032	< 1

[1] TPM ARfD = 0.05 mg/kg body weight. Acute dietary risk estimates are based on the 95th percentile of exposure.

[2] ADI = 0.027 mg/kg body weight/day

Table 2 Acute Dietary Exposure and Risk Estimates for Carbendazim + 2AB

Acute Dietary [1] (95th Percentile)				
Population Subgroup	Food Only		Food + Drinking Water	
	Exposure (mg/kg bw)	% ARfD	Exposure (mg/kg bw)	% ARfD
Males 13–19 years old	0.0070	4	0.0082	5
Males 20–49 years old	0.0059	4	0.0078	5
Male Adults 50+ years old	0.0060	4	0.0074	5
Females 13–49 years old	0.0065	65	0.0084	84

[1] Acute Reference Dose (ARfD) of 0.16 mg/kg body weight applies to males aged 13 years and older. ARfD of 0.01 mg/kg body weight applies to females 13–49 years of age. An acute risk assessment was not required for other population groups. Acute dietary risk estimates are based on the 95th percentile of exposure.

Table 3 Chronic Dietary Exposure and Risk Estimates for Carbendazim + 2AB

Chronic Dietary [1]				
Population Subgroup	Food		Food + Drinking Water	
	Exposure (mg/kg bw/day)	% ADI	Exposure (mg/kg bw/day)	% ADI
General population	-	-	-	-
All Infants (<1 year old)	0.00020	< 1	0.0016	5
Children 1–2 years old	0.00027	< 1	0.00043	3
Children 3–5 years old	0.00020	< 1	0.00080	2
Children 6–12 yrs old	0.00011	< 1	0.00043	1
Males 13–19 yrs old	0.000061	< 1	0.00031	1
Males 20–49 yrs old	0.00059	< 1	0.00043	1
Adults 50+ years old	0.000059	< 1	0.00043	1
Females 13–49 years old	0.000057	< 1	0.00043	4

[1] Acceptable Daily Intake (ADI) of 0.01 mg/kg bw/day applies to females 13–49 years old. ADI of 0.03 mg/kg

bw/day applies to all other population subgroups.

Table 4 Individual and Cumulative Dietary Cancer Risk for Thiophanate-Methyl (TPM) and Carbendazim

Population Subgroup	Risk from Exposure to TPM [1]		Risk from Exposure to Carbendazim + 2AB [2]		Cumulative Risk from Exposure to TPM and Carbendazim + 2AB [3]
	Food + Drinking Water		Food + Drinking Water		Food + Water
	Exposure (mg/kg bw/day)	Cancer Risk (mg/kg bw/day)$^{-1}$	Exposure (mg/kg bw/day)	Cancer Risk (mg/kg bw/day)$^{-1}$	Cancer Risk (mg/kg bw/day)$^{-1}$
General population	0.000031	2E-07	0.00030	3E-07	6E-07

1 TPM $q_1^* = 7.96 \times 10^{-3}$ (mg/kg bw/day)$^{-1}$

2 Carbendazim $q_1^* = 1.09 \times 10^{-3}$ (mg/kg bw/day)$^{-1}$

3 Cumulative cancer risk from dietary exposure was calculated by adding the cancer risk for TPM with the cancer risk for and carbendazim.

Appendix V Occupational Handler Exposure and Risk Estimates for All Uses except Seed Treatment

Table 1 Mixer, Loader, Applicator Agricultural Non-Cancer Risk Assessment for Wettable Powder Formulation

Crop	Application Equipment [a]	Appl. Rate [b] (kg a.i./ha)	ATPD (ha) [c]	Exposure (mg kg bw/day)		MOE		
				Dermal [d]	Inhalation [e]	Dermal [f]	Inhalation [g]	Combined [h]
Label PPE: Not specified. Assessed at single layer and gloves unless otherwise specified.								
Apple and pear (EC)	Airblast	0.4375	20	4.70E-01	7.14E-03	213	1400	185
	Airblast (CR hat)			1.04E-01	7.14E-03	966	1400	572
Apple and pear (BC)	Airblast	1.575	20	1.69	2.57E-02	59	389	51
	Airblast (CR hat, CRC, Resp for M/L/A)			1.76E-01	2.57E-03	570	3890	497
Stone fruit	Airblast	1.225	20	1.32	2.00E-02	59	389	51
	Airblast (CR hat, CRC, Resp for M/L)			2.31E-01	4.50E-03	570	3890	497
Lowbush blueberry	Groundboom	0.77	26	1.39E-01	1.45E-02	718	690	352
	Aerial M/L (CRC + Resp)		200	6.53E-01	1.08E-02	153	924	131 [i]
	Aerial A		200	5.14E-03	1.87E-05	19500	536000	18800
	Backpack		0.15	8.63E-03	1.71E-04	11600	58600	9670
	MPHW			2.85E-02	2.05E-03	3510	4870	2040
	MPHG		3.8	2.24E-01	7.58E-03	447	1320	334
Strawberry and Raspberry	Groundboom	0.77	26	1.39E-01	1.45E-02	718	690	352
	Airblast		20	8.28E-01	1.26E-02	121	796	105
	Airblast (CR hat)		20	1.82E-01	1.26E-02	549	796	325
	Backpack		0.068	3.91E-03	7.74E-05	25600	129000	21300
	MPHW			1.29E-02	9.31E-04	7740	10700	4500
	MPHG		1.73	1.02E-01	3.45E-03	982	2900	733
White beans	Groundboom (f) (CRC + Resp for M/L/A)	1.575	107	7.39E-01	1.22E-02	135	820	116
	Groundboom (c) (CRC + Resp for M/L/A)		360	2.49	4.10E-02	40	244	35
	Aerial M/L (CRC + Resp)		400	2.67	4.43E-02	37	226	32 [i]
	Aerial A		400	2.10E-02	7.63E-05	4760	131000	4590
Sugarbeets	Groundboom (f)	0.392	107	2.92E-01	3.03E-02	343	330	168
	Groundboom (c) (CRC + Resp for M/L/A)		360	6.19E-01	1.02E-02	162	979	139

Crop	Application Equipment [a]	Appl. Rate [b] (kg a.i./ha)	ATPD (ha) [c]	Exposure (mg kg bw/day)		MOE		
				Dermal [d]	Inhalation [e]	Dermal [f]	Inhalation [g]	Combined [h]
Label PPE: Not specified. Assessed at single layer and gloves unless otherwise specified.								
Outdoor Roses and Ornamentals	Backpack	0.525	0.15	5.88E-03	1.16E-04	16700	85900	14200
	MPHW			1.94E-02	1.40E-03	5150	7140	2990
	MPHG		3.8	1.53E-01	5.17E-03	656	1940	490
	Groundboom		26	9.50E-02	9.88E-03	1050	1010	516
	Airblast		20	5.64E-01	8.57E-03	177	1170	154
	Airblast (CR hat)		20	1.24E-01	8.57E-03	805	1170	476
Aspen and Poplar	Backpack	0.77	0.15	8.63E-03	1.71E-04	11600	58600	9670
	MPHW			2.85E-02	2.05E-03	3510	4870	2040
	MPHG		3.8	2.24E-01	7.58E-03	447	1320	334
	Groundboom (f) (CRC + Resp for M/L/A)		107	3.61E-01	5.96E-03	277	1680	238
	Groundboom (c) (CRC + Resp for M/L/A)		360	1.22	2.01E-02	82	499	71
	Airblast		20	8.28E-01	1.26E-02	121	796	105
	Airblast (CR hat)		20	1.82E-01	1.26E-02	549	796	325
Greenhouse tobacco seedlings	Backpack	6.3	0.0608	2.86E-02	5.66E-04	3490	17700	2920
	MPHW			9.45E-02	6.81E-03	1060	1470	615
	MPHG			2.93E-02	9.92E-04	3410	10100	2550
Turf [j]	Groundboom golf course (CRC + Resp for M/L)	2.1	16	3.83E-02	3.07E-03	209	2610	194 [i]
	Groundboom sod farm (CRC + Resp for M/L)	2.1	30	7.18E-02	5.75E-03	111	1392	103 [i]
	Handgun lawn sprayer (coveralls for M/L)	4.2	1	9.41E-03	2.74E-02	850	292	217 [i]
		2.1		9.41E-03	2.74E-02	1700	584	435
Greenhouse ornamentals	Backpack	0.595	0.15	1.67E-03	1.32E-04	4800	60600	4450
	MPHW			5.51E-03	1.59E-03	1450	5040	1130
	MPHG		3.8	4.32E-02	5.86E-03	185	1370	163
	MPHG (coveralls for M/L/A)			2.00E-02	5.86E-03	401	1370	310

Shaded text indicates MOEs that are less than the target.

a. M/L = Mixer/Loader; A = Applicator; Groundboom (c) = custom groundboom application; Groundboom (f) = farmer groundboom application; MPHW = manually-pressurized handwand; MPHG = mechanically-pressurized handgun; CR = chemical-resistant; CRC = chemical-resistant coveralls; Resp = respirator.

b. Maximum listed label rate in kilograms of active ingredient per hectare (kg a.i./ha). Handheld equipment application rates were calculated from the dilution rate on the label and the default amounts handled per day (L).

c. Based on default assumptions except for aerial application for lowbush blueberry which was based on use pattern information provided by the registrant. Handheld equipment areas treated were calculated from default amounts handled per day (L) and the dilution rate on the label.

d. Where dermal exposure µg/kg bw/day = unit exposure × area treated × application rate × dermal absorption / 80 kg bw. Dermal absorption of TPM = 25%.
e. Where inhalation exposure µg/kg bw/day = unit exposure × area treated × application rate / 80 kg bw.
f. Based on the short-term NOAEL of 100 mg/kg bw/day from a dermal rabbit toxicity study, target MOE of 300. Turf and greenhouse ornamentals based on intermediate- to long-term NOAEL of 8 mg/kg bw/day from an oral one-year dog study, target MOE of 300.
g. Based on the short-term oral NOAEL of 10 mg/kg bw/day, target MOE of 300. Turf and greenhouse ornamentals based on intermediate- to long-term NOAEL of 8 mg/kg bw/day from an oral one-year dog study, target MOE of 300.
h. Combined MOE = 1 / (1 / dermal MOE + 1 / inhalation MOE).
i. Use does not reach the target MOE (risk is not acceptable) and no further mitigation is possible.
j. Turf rates range from 2.1 to 12.25 kg a.i./ha depending on the disease being treated. The low rate is shown as MOEs were less than the target even at this lowest rate (except handheld equipment).

Table 2 Mixer, Loader, Applicator Agricultural Non-Cancer Risk Assessment for Wettable Powder Formulation in Water Soluble Packaging

Crop	Application Equipment[a]	Appl. Rate[b] (kg a.i./ha)	ATPD (ha)[c]	Exposure (mg kg bw/day)		MOE		
				Dermal[d]	Inhalation[e]	Dermal[f]	Inhalation[g]	Combined[h]
Label PPE: Coveralls over single layer plus gloves for M/L/A								
Apple and pear (EC)	Airblast	0.4375	20	3.73E-01	1.01E-03	268	9870	261
	Airblast (CR hat)			1.81E-02	1.01E-03	5511	9870	3540
Apple and pear (BC)	Airblast	1.575	20	1.34	3.65E-03	75	2740	73
	Airblast (CR hat)			6.53E-02	3.65E-03	1530	2740	982
Stone fruit	Airblast	1.225	20	1.04	2.84E-03	96	3530	93
	Airblast (CR hat)			5.08E-02	2.84E-03	1970	3530	1260
Lowbush blueberry	Groundboom	0.77	26	5.53E-03	4.65E-04	18100	21500	9820
	Aerial M/L		200	1.52E-02	3.47E-04	6560	28900	5340
	Aerial A		200	5.14E-03	1.87E-05	19500	536100	18800
	Backpack		0.15	3.76E-03	8.99E-05	26600	111000	214500
	MPHW			1.07E-03	6.55E-05	93200	153000	57900
	MPHG		3.8	9.00E-02	5.53E-03	1110	1810	688
Strawberry and Raspberry	Groundboom	0.77	26	5.53E-03	4.65E-04	18100	21500	9820
	Airblast		20	6.56E-01	1.78E-03	152	5610	148
	Airblast (CR hat)		20	3.19E-02	1.78E-03	3130	5610	2010
	Backpack		0.068	1.70E-03	4.08E-05	58700	245000	47300
	MPHW			4.86E-04	2.97E-05	206000	337000	12800
	MPHG		1.73	4.10E-02	2.52E-03	2440	3970	1510
White beans	Groundboom (f)	1.575	107	4.66E-02	3.92E-03	2150	2550	1170
	Groundboom (c)		360	1.57E-01	1.32E-02	638	759	347
	Aerial M/L		400	6.24E-02	1.42E-03	1600	7060	1310

Crop	Application Equipment[a]	Appl. Rate[b] (kg a.i./ha)	ATPD (ha)[c]	Exposure (mg kg bw/day)		MOE		
				Dermal[d]	Inhalation[e]	Dermal[f]	Inhalation[g]	Combined[h]
Label PPE: Coveralls over single layer plus gloves for M/L/A								
	Aerial A		400	2.10E-02	7.63E-05	4760	131000	4590
Sugarbeets	Groundboom (f)	0.392	107	1.16E-02	9.75E-04	8630	10250	4690
	Groundboom (c)		360	3.90E-02	3.28E-03	2560	3050	1390
Outdoor Roses and Ornamentals	Backpack	0.525	0.15	2.56E-03	6.13E-05	39000	163000	31500
	MPHW			7.32E-04	4.47E-05	138000	224000	84900
	MPHG		3.8	6.14E-02	3.77E-03	1630	2650	1010
	Groundboom		26	3.77E-03	3.17E-04	26500	31500	14400
	Airblast		20	4.47E-01	1.22E-03	224	8230	218
	Airblast (CR hat)		20	2.18E-02	1.22E-03	4590	8230	2950
Aspen and Poplar	Backpack	0.77	0.15	3.76E-03	8.99E-05	26600	111000	21500
	MPHW			1.07E-03	6.55E-05	93200	153000	57900
	MPHG		3.8	9.00E-02	5.53E-03	1110	1810	688
	Groundboom (f)		107	2.28E-02	1.92E-03	4390	5220	2390
	Groundboom (c)		360	7.66E-02	6.44E-03	1305	1552	709
	Airblast		20	6.56E-01	1.78E-03	152	5610	148
	Airblast (CR hat)		20	3.19E-02	1.78E-03	3130	5610	2010
Greenhouse tobacco seedlings	Backpack	6.3	0.0608	1.25E-02	2.98E-04	8020	33600	6470
	MPHW			3.56E-03	2.17E-04	28100	46000	17400
	MPHG			1.18E-02	7.24E-04	8490	13800	5260
Turf [i]	Groundboom golf course	12.25	16	1.35E-02	4.56E-03	591	1760	442
	Groundboom sod farm	12.25	30	2.54E-02	8.54E-03	315	936	236
	Groundboom sod farm (closed cab)			1.42E-02	1.10E-03	565	7260	524
	Handgun lawn sprayer	12.25	1	2.26E-02	6.69E-03	354	1200	273
Greenhouse ornamentals	Backpack	0.595	0.15	7.27E-04	6.95E-05	11011	115139	10100
	MPHW			2.07E-04	5.06E-05	38600	158000	31000
	MPHG		3.8	1.74E-02	4.27E-03	460	1870	369

Shaded text indicates MOEs that are less than the target.

a. M/L = Mixer/Loader; A = Applicator; Groundboom (c) = custom groundboom application; Groundboom (f) = farmer groundboom application; MPHW = manually-pressurized handwand; MPHG = mechanically-pressurized handgun; CR = chemical-resistant; CRC = chemical-resistant coveralls; Resp = respirator.

b. Maximum listed label rate in kilograms of active ingredient per hectare (kg a.i./ha). Handheld equipment application rates were calculated from the dilution rate on the label and the default amounts handled per day (L).

c. Based on default assumptions except for aerial application for lowbush blueberry which was based on use pattern information provided by the registrant. Handheld equipment areas treated were calculated from default amounts handled per day (L) and the dilution rate on the label.
d. Where dermal exposure µg/kg bw/day = unit exposure × area treated × application rate × dermal absorption / 80 kg bw. Dermal absorption of TPM = 25%.
e. Where inhalation exposure µg/kg bw/day = unit exposure × area treated × application rate / 80 kg bw.
f. Based on the short-term NOAEL of 100 mg/kg bw/day from a dermal rabbit toxicity study, target MOE of 300. Turf and greenhouse ornamentals based on intermediate- to long-term NOAEL of 8 mg/kg bw/day from an oral one-year dog study, target MOE of 300.
g. Based on the short-term oral NOAEL of 10 mg/kg bw/day, target MOE of 300. Turf and greenhouse ornamentals based on intermediate- to long-term NOAEL of 8 mg/kg bw/day from an oral one-year dog study, target MOE of 300.
h. Combined MOE = 1 / (1 / dermal MOE + 1 / inhalation MOE).
i. Turf rates range from 2.1 to 12.25 kg a.i./ha depending on the disease being treated. The high rate is shown as MOEs were above the target at the highest rate with mitigation.

Table 3 Mixer, Loader, Applicator Agricultural Non-Cancer Risk Assessment for Liquid Formulation

Crop	Application Equipment[a]	Appl. Rate[b] (kg a.i./ha)	ATPD (ha)[c]	Exposure (mg kg bw/day)		MOE		
				Dermal[d]	Inhalation[e]	Dermal[f]	Inhalation[g]	Combined[h]
Label PPE: Coveralls over single layer plus gloves for M/L/A								
Apple and pear (EC)	Airblast	0.4375	20	3.75E-01	1.06E-03	267	9420	259
	Airblast (CR hat)			2.07E-02	1.06E-03	4830	9420	3190
Apple and pear (BC)	Airblast	1.575	20	1.35	3.82E-03	74	2620	72
	Airblast (CR hat)			7.45E-02	3.82E-03	1340	2620	887
Stone fruit	Airblast	1.225	20	1.05	2.97E-03	95	3360	93
	Airblast (CR hat)			5.80E-02	2.97E-03	1730	3360	1140
Lowbush blueberry	Groundboom	0.77	26	1.14E-02	5.78E-04	8780	17300	5820
	Aerial M/L		200	6.03E-02	1.21E-03	1660	8250	1380
	Aerial A		200	5.14E-03	1.87E-05	1500	536000	18800
	Backpack		0.15	3.75E-03	8.97E-05	26700	112000	21500
	MPHW			1.06E-03	6.53E-05	94200	153000	58300
	MPHG		3.8	8.97E-02	5.52E-03	1110	1810	690
Strawberry andand Raspberry	Groundboom	0.77	26	1.14E-02	5.78E-04	8780	17300	5820
	Airblast		20	6.60E-01	1.87E-03	151	5350	147
	Airblast (CR hat)		20	3.64E-02	1.87E-03	2740	5350	1810
	Backpack		0.068	1.67E-03	3.99E-05	59900	250000	48300
	MPHW			4.73E-04	2.91E-05	211000	344000	131000
	MPHG		1.73	4.10E-02	2.52E-03	2440	3970	1510
White beans	Groundboom (f)	1.575	107	9.59E-02	4.87E-03	1040	2060	692
	Groundboom (c)		360	3.23E-01	1.64E-02	310	611	206
	Groundboom (c) (CRC +			2.64E-01	1.64E-03	379	6110	356

Crop	Application Equipment[a]	Appl. Rate[b] (kg a.i./ha)	ATPD (ha)[c]	Exposure (mg kg bw/day)		MOE		
				Dermal[d]	Inhalation[e]	Dermal[f]	Inhalation[g]	Combined[h]
	Resp for M/L/A)							
	Groundboom (c) (closed M/L)			1.69E-01	1.27E-02	593	788	338
	Aerial M/L		400	2.47E-01	4.96E-03	405	2020	338
	Aerial A		400	2.10E-02	7.63E-05	4760	131000	4590
Sugarbeets	Groundboom (f)	0.392	107	2.39E-02	1.21E-03	4190	8260	2780
	Groundboom (c)		360	8.03E-02	4.07E-03	1250	2450	826
Outdoor Roses and Ornamentals	Backpack	0.525	0.15	2.56E-03	6.11E-05	39100	164000	31600
	MPHW			7.24E-04	4.45E-05	138000	223000	85600
	MPHG		3.8	6.12E-02	3.77E-03	1630	2660	1010
	Groundboom		26	7.77E-03	3.94E-04	12900	25400	8540
	Airblast		20	4.50E-01	1.27E-03	222	7850	216
	Airblast (CR hat)		20	2.48E-02	1.27E-03	4030	7850	2660
Aspen and Poplar	Backpack	0.77	0.15	3.75E-03	8.97E-05	26700	112000	21500
	MPHW			1.06E-03	6.53E-05	94200	153000	58300
	MPHG		3.8	8.97E-02	5.52E-03	1110	1810	690
	Groundboom (f)		107	4.69E-02	2.38E-03	2130	4200	1420
	Groundboom (c)		360	1.58E-01	8.00E-03	634	1250	421
	Airblast		20	6.60E-01	1.87E-03	151	5350	147
	Airblast (CR hat)		20	3.64E-02	1.87E-03	2740	5350	1810
Greenhouse tobacco seedlings	Backpack	6.3	0.0608	1.24E-02	2.97E-04	8040	33600	6490
	MPHW			3.52E-03	2.16E-04	28400	46200	17600
	MPHG			1.17E-02	7.23E-04	8510	13800	5270
Turf[i]	Groundboom golf course	12.25	16	2.79E-02	5.66E-03	287	1410	239
	Groundboom golf course (CRC + Resp M/L/A)			2.28E-02	5.66E-04	350	14100	342
	Groundboom sod farm	12.25	30	5.23E-02	1.06E-02	153	754	127
	Groundboom sod farm (closed M/L + closed cab)			1.61E-02	7.81E-04	497	10200	474
	Handgun lawn sprayer	12.25	1	2.43E-02	6.58E-04	329	12200	320
Greenhouse ornamentals	Backpack	0.595	0.15	7.24E-04	6.93E-05	11000	115000	10100
	MPHW			2.05E-04	5.04E-05	39000	157000	31300
	MPHG		3.8	1.73E-02	4.27E-03	461	1880	370

Shaded text indicates MOEs that are less than the target.

a. M/L = Mixer/Loader; A = Applicator; Groundboom (c) = custom groundboom application; Groundboom (f) = farmer groundboom application; MPHW = manually-pressurized handwand; MPHG = mechanically-pressurized handgun; CR = chemical-resistant; CRC = chemical-resistant coveralls; Resp = respirator.

b. Maximum listed label rate in kilograms of active ingredient per hectare (kg a.i./ha). Handheld equipment application rates were calculated from the dilution rate on the label and the default amounts handled per day (L).
c. Based on default assumptions except for aerial application for lowbush blueberry which was based on use pattern information provided by the registrant. Handheld equipment areas treated were calculated from default amounts handled per day (L) and the dilution rate on the label.
d. Where dermal exposure µg/kg bw/day = unit exposure × area treated × application rate × dermal absorption / 80 kg bw. Dermal absorption of TPM = 25%.
e. Where inhalation exposure µg/kg bw/day = unit exposure × area treated × application rate / 80 kg bw.
f. Based on the short-term NOAEL of 100 mg/kg bw/day from a dermal rabbit toxicity study, target MOE of 300. Turf and greenhouse ornamentals based on intermediate- to long-term NOAEL of 8 mg/kg bw/day from an oral one-year dog study, target MOE of 300.
g. Based on the short-term oral NOAEL of 10 mg/kg bw/day, target MOE of 300. Turf and greenhouse ornamentals based on intermediate- to long-term NOAEL of 8 mg/kg bw/day from an oral one-year dog study, target MOE of 300.
h. Combined MOE = 1 / (1 / dermal MOE + 1 / inhalation MOE).
i. Turf rates range from 2.1 to 12.25 kg a.i./ha depending on the disease being treated. The high rate is shown as MOEs were above the target at the highest rate with mitigation.

Table 4 Mixer, Loader, Applicator Agricultural Cancer Exposure Assessment for Wettable Powder Formulation

Crop	Application Equipment[a]	Appl. Rate[b] (kg a.i./ha)	ATPD (ha)[c]	Exposure (mg kg bw/day)		Cancer		
				Dermal[d]	Inhalation[e]	Exposure (days/yr)	LADD[f]	Cancer[g]
Label PPE: Not specified. Assessed at single layer and gloves unless otherwise specified.								
Apple and pear (EC)	Airblast	0.4375	7	1.65E-01	2.50E-03	4	2.45E-04	2E-06
	Airblast (CR hat)			3.62E-02	2.50E-03	4	6.49E-05	5E-07
Apple and pear (BC)	Airblast	1.575	7	5.93E-01	9.00E-03	4	8.83E-04	7E-06
	Airblast (CR hat)			1.30E-01	9.00E-03	4	2.34E-04	2E-06
Stone fruit	Airblast	1.225	7	4.61E-01	7.00E-03	4	6.87E-04	5E-06
	Airblast (CR hat)			1.01E-01	7.00E-03	4	1.82E-04	1E-06
Lowbush blueberry	Groundboom	0.77	12	6.43E-02	6.69E-03	4	1.28E-04	1E-06
	Aerial M/L (CRC + Resp)		200	6.53E-01	1.08E-02	30	7.33E-03	6E-05 [h]
	Aerial A		200	5.14E-03	1.87E-05	30	5.49E-05	4E-07
	Backpack		0.15	8.63E-03	1.71E-04	4	1.31E-05	1E-07
	MPHW			2.85E-02	2.05E-03	4	5.16E-05	4E-07
	MPHG		3.8	2.24E-01	7.58E-03	4	3.57E-04	3E-06
Strawberry and Raspberry	Groundboom	0.77	12	6.43E-02	6.69E-03	4	1.28E-04	1E-06
	Airblast		7	2.90E-01	4.40E-03	4	4.32E-04	3E-06
	Airblast (CR hat)		7	6.38E-02	4.40E-03	4	1.14E-04	9E-07
	Backpack		0.068	3.91E-03	7.74E-05	4	5.93E-06	5E-08
	MPHW			1.29E-02	9.31E-04	4	2.34E-05	2E-07
	MPHG		1.73	1.02E-01	3.45E-03	4	1.62E-04	1E-06

Crop	Application Equipment[a]	Appl. Rate[b] (kg a.i./ha)	ATPD (ha)[c]	Exposure (mg kg bw/day)		Cancer		
				Dermal[d]	Inhalation[e]	Exposure (days/yr)	LADD[f]	Cancer[g]
Label PPE: Not specified. Assessed at single layer and gloves unless otherwise specified.								
White beans	Groundboom (f)	1.575	60	6.58E-01	6.84E-02	4	1.31E-03	1E-05
	Groundboom (c)		240	2.63	2.73E-01	30	3.92E-02	3E-04
	Aerial M/L (CRC + Resp)		318	2.12	3.52E-02	30	2.39E-02	2E-04 [i]
	Aerial A		318	1.67E-02	6.07E-05	30	1.79E-04	1E-06
Sugarbeets	Groundboom (f)	0.392	60	1.64E-01	1.70E-02	4	3.26E-04	3E-06
	Groundboom (c) (CRC + Resp for M/L)		240	4.29E-01	8.58E-03	30	4.88E-03	4E-05
Outdoor Roses and Ornamentals	Backpack	0.525	0.15	5.88E-03	1.16E-04	30	6.69E-05	5E-07
	MPHW			1.94E-02	1.40E-03	30	2.64E-04	2E-06
	MPHG		3.8	1.53E-01	5.17E-03	30	1.83E-03	1E-05
	Groundboom		12	4.38E-02	4.56E-03	30	6.54E-04	5E-06
	Airblast		7	1.98E-01	3.00E-03	30	2.21E-03	2E-05
	Airblast (CR hat)		7	4.35E-02	3.00E-03	30	5.84E-04	5E-06
Aspen and Poplar	Backpack	0.77	0.15	8.63E-03	1.71E-04	4	1.31E-05	1E-07
	MPHW			2.85E-02	2.05E-03	4	5.16E-05	4E-07
	MPHG		3.8	2.24E-01	7.58E-03	4	3.57E-04	3E-06
	Groundboom (f)		60	3.22E-01	3.34E-02	4	6.40E-04	5E-06
	Groundboom (c)		240	1.29	1.34E-01	30	1.92E-02	2E-04
	Airblast		7	2.90E-01	4.40E-03	4	4.32E-04	3E-06
	Airblast (CR hat)		7	6.38E-02	4.40E-03	4	1.14E-04	9E-07
Greenhouse tobacco seedlings	Backpack	6.3	0.0608	2.86E-02	5.66E-04	4	4.34E-05	3E-07
	MPHW			9.45E-02	6.81E-03	4	1.71E-04	1E-06
	MPHG			2.93E-02	9.92E-04	4	4.67E-05	4E-07
Turf [i]	Groundboom golf course	5.16	16	5.75E-01	5.97E-02	4	1.14E-03	9E-06
	Groundboom sod farm		30	1.08E+00	1.12E-01	4	2.14E-03	2E-05
	Groundboom sod farm (Coveralls + Resp for M/L)		30	7.67E-01	1.41E-02	4	1.16E-03	9E-06
	Handgun lawn sprayer		1	1.65E-01	3.37E-02	4	4.21E-04	3E-06
Greenhouse ornamentals	Backpack	0.595	0.15	6.67E-03	1.32E-04	30	7.58E-05	6E-07
	MPHW			2.20E-02	1.59E-03	30	2.99E-04	2E-06
	MPHG		3.8	1.73E-01	5.86E-03	30	2.07E-03	2E-05
	MPHG (coveralls for			7.98E-02	5.86E-03	30	1.09E-03	9E-06

Crop	Application Equipment[a]	Appl. Rate[b] (kg a.i./ha)	ATPD (ha)[c]	Exposure (mg kg bw/day)		Cancer		
				Dermal[d]	Inhalation[e]	Exposure (days/yr)	LADD[f]	Cancer[g]
Label PPE: Not specified. Assessed at single layer and gloves unless otherwise specified.								
	M/L/A)							

Shaded boxes indicate MOEs that are less than the target.

a. M/L = Mixer/Loader; A = Applicator; Groundboom (c) = custom groundboom application; Groundboom (f) = farmer groundboom application; MPHW = manually-pressurized handwand; MPHG = mechanically-pressurized handgun; CR = chemical-resistant; CRC = chemical-resistant coveralls; Resp = respirator.

b. Maximum listed label rate in kilograms of active ingredient per hectare (kg a.i./ha).

c. Based on default assumptions except for aerial application for lowbush blueberry which was based on use pattern information provided by the registrant. Handheld equipment areas treated were calculated from default amounts handled per day (L) and the dilution rate on the label.

d. Where dermal exposure µg/kg bw/day = unit exposure × area treated × application rate × dermal absorption / 80 kg bw. Dermal absorption of TPM = 25%.

e. Where inhalation exposure µg/kg bw/day = unit exposure × area treated × application rate / 80 kg bw.

f. LADD = lifetime average daily dose = [daily exposure × exposure days per year × working lifetime (40 years)]/[365 days/year × lifetime (78 years)].

g. Cancer risk = LADD × q_1*. Thiophanate-methyl q_1* is $(7.96 \times 10^{-3}$ mg/kg bw/day$)^{-1}$.

h. i Cancer risk is greater than 1×10^{-5} (risk is not acceptable) and no further mitigation is possible.

i. j Turf accepted use pattern is 2 applications for dollar spot (2.1 kg a.i./ha), 1 application for brown patch (4.2 kg a.i./ha) and 1 application for pink snow mould (12.25 kg a.i./ha). The average of the 4 applications was used for the cancer risk assessment.

Table 5 Mixer, Loader, Applicator Agricultural Cancer Exposure Assessment for Wettable Powder formulation in Water Soluble Packaging

Crop	Application Equipment[a]	Appl. Rate[b] (kg a.i./ha)	ATPD (ha)[c]	Exposure (mg kg bw/day)		Cancer		
				Dermal[d]	Inhalation[e]	Exposure (days/yr)	LADD[f]	Cancer[g]
Label PPE: Coveralls over single layer plus gloves for M/L/A								
Apple and pear (EC)	Airblast	0.4375	7	1.30E-01	3.54E-04	4	1.85E-04	1E-06
	Airblast (CR hat)			6.35E-03	3.54E-04	4	1.09E-05	9E-08
Apple and pear (BC)	Airblast	1.575	7	4.70E-01	1.28E-03	4	6.67E-04	5E-06
	Airblast (CR hat)			2.29E-02	1.28E-03	4	3.93E-05	3E-07
Stone fruit	Airblast	1.225	7	3.65E-01	9.93E-04	4	5.19E-04	4E-06
	Airblast (CR hat)			1.78E-02	9.93E-04	4	3.06E-05	2E-07
Lowbush blueberry	Groundboom	0.77	12	2.55E-03	2.15E-04	4	4.80E-06	4E-08
	Aerial M/L		200	2.42E-02	5.51E-04	4	2.79E-04	2E-06
	Aerial A		200	8.17E-03	2.97E-05	4	8.74E-05	7E-07
	Backpack		0.15	3.76E-03	8.99E-05	4	5.79E-06	5E-08
	MPHW			1.07E-03	6.55E-05	4	1.88E-06	1E-08

Crop	Application Equipment[a]	Appl. Rate[b] (kg a.i./ha)	ATPD (ha)[c]	Exposure (mg kg bw/day)		Cancer		
				Dermal[d]	Inhalation[e]	Exposure (days/yr)	LADD[f]	Cancer[g]
Label PPE: Coveralls over single layer plus gloves for M/L/A								
	MPHG		3.8	9.00E-02	5.53E-03	4	1.58E-04	1E-06
Strawberry and Raspberry	Groundboom	0.77	12	2.55E-03	2.15E-04	4	4.80E-06	4E-08
	Airblast		7	2.30E-01	6.24E-04	4	3.26E-04	3E-06
	Airblast (CR hat)		7	1.12E-02	6.24E-04	4	1.92E-05	2E-07
	Backpack		0.068	1.70E-03	4.08E-05	4	2.62E-06	2E-08
	MPHW			4.86E-04	2.97E-05	4	8.50E-07	7E-09
	MPHG		1.73	4.10E-02	2.52E-03	4	7.17E-05	6E-07
White beans	Groundboom (f)	1.575	60	2.61E-02	2.20E-03	4	4.90E-05	4E-07
	Groundboom (c)		240	1.04E-01	8.79E-03	4	1.47E-03	1E-05
	Aerial M/L		318	4.96E-02	1.13E-03	30	5.70E-04	5E-06
	Aerial A		318	1.67E-02	6.07E-05	30	1.79E-04	1E-06
Sugarbeets	Groundboom (f)	0.392	60	6.50E-03	5.47E-04	4	1.22E-05	1E-07
	Groundboom (c)		240	2.60E-02	2.19E-03	30	3.66E-04	3E-06
Outdoor Roses and Ornamentals	Backpack	0.525	0.15	2.56E-03	6.13E-05	30	2.96E-05	2E-07
	MPHW			7.32E-04	4.47E-05	30	9.59E-06	8E-08
	MPHG		3.8	6.14E-02	3.77E-03	30	8.06E-04	6E-06
	Groundboom		12	1.74E-03	1.46E-04	30	2.45E-05	2E-07
	Airblast		7	1.57E-01	4.25E-04	30	1.67E-03	1E-05
	Airblast (CR hat)		7	1.94E-02	4.25E-04	30	2.23E-04	2E-06
Aspen and Poplar	Backpack	0.77	0.15	3.76E-03	8.99E-05	4	5.79E-06	5E-08
	MPHW			1.07E-03	6.55E-05	4	1.88E-06	1E-08
	MPHG		3.8	9.00E-02	5.53E-03	4	1.58E-04	1E-06
	Groundboom (f)		60	1.28E-02	1.07E-03	4	2.40E-05	2E-07
	Groundboom (c)		240	5.11E-02	4.30E-03	30	7.19E-04	6E-06
	Airblast		7	2.30E-01	6.24E-04	4	3.26E-04	3E-06
	Airblast (CR hat)		7	1.12E-02	6.24E-04	4	1.92E-05	2E-07
Greenhouse tobacco seedlings	Backpack	6.3	0.0608	1.25E-02	2.98E-04	4	1.44E-04	1E-06
	MPHW			3.56E-03	2.17E-04	4	4.67E-05	4E-07
	MPHG			1.18E-02	7.24E-04	4	1.55E-04	1E-06
Turf[h]	Groundboom golf course	5.16	16	2.28E-02	1.92E-03	4	4.28E-05	3E-07
	Groundboom sod farm		30	4.28E-02	3.60E-03	4	8.03E-05	6E-07
	Handgun lawn sprayer		1	1.26E-01	2.82E-03	4	1.93E-04	2E-06
Greenhouse ornamentals	Backpack	0.595	0.15	2.91E-03	6.95E-05	30	3.36E-05	3E-07
	MPHW			8.29E-04	5.06E-05	30	1.09E-05	9E-08

Crop	Application Equipment[a]	Appl. Rate[b] (kg a.i./ha)	ATPD (ha)[c]	Exposure (mg kg bw/day)		Cancer		
				Dermal[d]	Inhalation[e]	Exposure (days/yr)	LADD[f]	Cancer[g]
Label PPE: Coveralls over single layer plus gloves for M/L/A								
	MPHG		3.8	6.96E-02	4.27E-03	30	9.13E-04	7E-06

a. M/L = Mixer/Loader; A = Applicator; Groundboom (c) = custom groundboom application; Groundboom (f) = farmer groundboom application; MPHW = manually-pressurized handwand; MPHG = mechanically-pressurized handgun; CR = chemical-resistant; CRC = chemical-resistant coveralls; Resp = respirator.

b. Maximum listed label rate in kilograms of active ingredient per hectare (kg a.i./ha).

c. Based on default assumptions except for aerial application for lowbush blueberry which was based on use pattern information provided by the registrant. Handheld equipment areas treated were calculated from default amounts handled per day (L) and the dilution rate on the label.

d. Where dermal exposure µg/kg bw/day = unit exposure × area treated × application rate × dermal absorption / 80 kg bw. Dermal absorption of TPM = 25%.

e. Where inhalation exposure µg/kg bw/day = unit exposure × area treated × application rate / 80 kg bw.

f. LADD = lifetime average daily dose = [daily exposure × exposure days per year × working lifetime (40 years)]/[365 days/year × lifetime (78 years)].

g. Cancer risk = LADD × q_1*. Thiophanate-methyl q_1* is $(7.96 \times 10^{-3}$ mg/kg bw/day$)^{-1}$.

h. Turf accepted use pattern is 2 applications for dollar spot (2.1 kg a.i./ha), 1 application for brown patch (4.2 kg a.i./ha) and 1 application for pink snow mould (12.25 kg a.i./ha). The average of the 4 applications was used for the cancer risk assessment.

Table 6 Mixer, Loader, Applicator Agricultural Cancer Exposure Assessment for Liquid Formulation

Crop	Application Equipment[a]	Appl. Rate[b] (kg a.i./ha)	ATPD (ha)[c]	Exposure (mg kg bw/day)		Cancer		
				Dermal[d]	Inhalation[e]	Exposure (days/yr)	LADD[f]	Cancer[g]
Label PPE: Coveralls over single layer plus gloves for M/L/A								
Apple and pear (EC)	Airblast	0.4375	7	1.31E-01	3.72E-04	4	1.87E-04	1E-06
	Airblast (CR hat)			7.25E-03	3.72E-04	4	1.23E-05	1E-07
Apple and pear (BC)	Airblast	1.575	7	4.73E-01	1.34E-03	4	6.72E-04	5E-06
	Airblast (CR hat)			2.61E-02	1.34E-03	4	4.42E-05	4E-07
Stone fruit	Airblast	1.225	7	3.68E-01	1.04E-03	4	5.22E-04	4E-06
	Airblast (CR hat)			2.03E-02	1.04E-03	4	3.44E-05	3E-07
Lowbush blueberry	Groundboom	0.77	12	5.26E-03	2.67E-04	4	8.88E-06	7E-08
	Aerial M/L		200	9.59E-02	1.93E-03	4	1.09E-03	9E-06
	Aerial A		200	1.04E-01	1.96E-03	4	1.18E-03	9E-06
	Backpack		0.15	3.75E-03	5.65E-05	4	5.59E-06	4E-08
	MPHW			1.06E-03	6.53E-05	4	1.86E-06	1E-08
	MPHG		3.8	8.97E-02	5.52E-03	4	1.57E-04	1E-06
Strawberry and Raspberry	Groundboom	0.77	12	5.26E-03	2.67E-04	4	8.88E-06	7E-08
	Airblast		7	3.96E-01	1.12E-03	4	5.63E-04	4E-06
	Airblast (CR hat)		7	5.26E-03	2.67E-04	4	8.88E-06	7E-08
	Backpack		0.068	1.70E-03	2.56E-05	4	2.53E-06	2E-08
	MPHW			4.81E-04	2.96E-05	4	8.42E-07	7E-09
	MPHG		1.73	4.09E-02	2.51E-03	4	7.15E-05	6E-07
White beans	Groundboom (f)	1.575	60	5.38E-02	2.73E-03	4	9.09E-05	7E-07
	Groundboom (c)		240	2.15E-01	1.09E-02	4	2.73E-03	2E-05
	Groundboom (c) (closed M/L, closed cab)		240	6.63E-02	8.03E-04	30	7.32E-04	6E-06
	Aerial M/L		318	1.96E-01	3.94E-03	30	2.23E-03	2E-05
	Aerial M/L (closed M/L)		318	6.02E-02	6.89E-04	30	6.63E-04	5E-06
	Aerial A		318	1.67E-02	6.07E-05	30	1.79E-04	1E-06
Sugarbeets	Groundboom (f)	0.392	60	1.34E-02	6.79E-04	4	2.26E-05	2E-07
	Groundboom (c)		240	5.35E-02	2.72E-03	30	6.78E-04	5E-06
Outdoor Roses and Ornamentals	Backpack	0.525	0.15	2.56E-03	3.85E-05	30	2.86E-05	2E-07
	MPHW			7.24E-04	4.45E-05	30	9.50E-06	8E-08

Crop	Application Equipment[a]	Appl. Rate[b] (kg a.i./ha)	ATPD (ha)[c]	Exposure (mg kg bw/day)		Cancer		
				Dermal[d]	Inhalation[e]	Exposure (days/yr)	LADD[f]	Cancer[g]
	MPHG		3.8	6.12E-02	3.77E-03	30	8.03E-04	6E-06
	Groundboom		12	3.58E-03	1.82E-04	30	4.54E-05	4E-07
	Airblast		7	1.58E-01	4.46E-04	30	1.68E-03	1E-05
	Airblast (CR hat)		7	8.70E-03	4.46E-04	30	1.10E-04	9E-07
Aspen and Poplar	Backpack	0.77	0.15	3.75E-03	5.65E-05	4	5.59E-06	4E-08
	MPHW			1.06E-03	6.53E-05	4	1.86E-06	1E-08
	MPHG		3.8	8.97E-02	5.52E-03	4	1.57E-04	1E-06
	Groundboom (f)		60	2.63E-02	1.33E-03	4	4.44E-05	4E-07
	Groundboom (c)		240	1.05E-01	5.34E-03	30	1.78E-04	1E-06
	Airblast		7	2.31E-01	6.54E-04	4	3.28E-04	3E-06
	Airblast (CR hat)		7	1.28E-02	6.54E-04	4	2.16E-05	2E-07
Greenhouse tobacco seedlings	Backpack	6.3	0.0608	1.02E-03	1.54E-05	4	1.52E-06	1E-08
	MPHW			2.89E-04	1.78E-05	4	5.07E-07	4E-09
	MPHG			2.45E-02	1.51E-03	4	4.30E-05	3E-07
Turf[h]	Groundboom golf course	5.16	16	4.70E-02	2.38E-03	4	7.94E-05	6E-07
	Groundboom sod farm		30	8.81E-02	4.47E-03	4	1.49E-04	1E-06
	Handgun lawn sprayer		1	4.10E-02	2.77E-04	4	5.91E-05	5E-07
Greenhouse ornamentals	Backpack	0.595	0.15	2.90E-03	4.36E-05	30	3.24E-05	3E-07
	MPHW			8.20E-04	5.04E-05	30	1.08E-05	9E-08
	MPHG		3.8	6.93E-02	4.27E-03	30	9.11E-04	7E-06

Shaded boxes indicate MOEs that are less than the target.

a. M/L = Mixer/Loader; A = Applicator; Groundboom (c) = custom groundboom application; Groundboom (f) = farmer groundboom application; MPHW = manually-pressurized handwand; MPHG = mechanically-pressurized handgun; CR = chemical-resistant; CRC = chemical-resistant coveralls; Resp = respirator.

b. Maximum listed label rate in kilograms of active ingredient per hectare (kg a.i./ha).

c. Based on default assumptions except for aerial application for lowbush blueberry which was based on use pattern information provided by the registrant. Handheld equipment areas treated were calculated from default amounts handled per day (L) and the dilution rate on the label.

d. Where dermal exposure µg/kg bw/day = unit exposure × area treated × application rate × dermal absorption / 80 kg bw. Dermal absorption of TPM = 25%.

e. Where inhalation exposure µg/kg bw/day = unit exposure × area treated × application rate / 80 kg bw.

f. LADD = lifetime average daily dose = [daily exposure × exposure days per year × working lifetime (40 years)]/[365 days/year × lifetime (78 years)].

g. Cancer risk = LADD × q_1*. Thiophanate-methyl q_1* is $(7.96 \times 10^{-3}$ mg/kg bw/day$)^{-1}$.

h. Turf accepted use pattern is 2 applications for dollar spot (2.1 kg a.i./ha), 1 application for brown patch (4.2 kg a.i./ha) and 1 application for pink snow mould (12.25 kg a.i./ha). The average of the 4 applications was used for the cancer risk assessment.

Table 7 Mixer, Loader, Applicator Non-Cancer and Cancer Risk Assessment for Spawn Treatment of Mushrooms

Crop	Appl. Rate[a]	Spawn Treated per day[b]	Exposure (mg/kg bw/day)		MOE			Cancer	
			Dermal[c]	Inhalation[d]	Dermal[e]	Inhalation[f]	Combined[g]	LADD[h]	Cancer Risk[i]
PPE: Coveralls over single layer plus gloves and respirator for all tasks									
White button mushroom	0.875	600	8.07E-03	3.82E-04	992	20,900	947	5.94E-04	5E-06

Spawn is typically treated in cement mixer type equipment.

a. Maximum listed label rate in grams of active ingredient per kilogram of spawn (g a.i./kg spawn).
b. Spawn amount treated (kg spawn/day)was calculated based on the label directions of a maximum amount of spawn treated to cover 600 m^2 of bedding at 100 kg spawn per 100 m^2 bedding;
c. Where dermal exposure (mg/kg bw/day) = application rate × kg spawn treated per day × 1 kg/1000g × unit exposure (4.92 mg a.i./kg a.i. handled; Klonne, 2005) × dermal absorption / 80 kg bw. Dermal absorption of TPM = 25%.
d. Where inhalation exposure mg/kg bw/day = exposure estimate (0.0582 mg a.i./kg a.i. handled; Klonne, 2005) × kg spawn treated per day × application rate × 1 kg/1000g / 80 kg bw.
e. Based on intermediate-term NOAEL of 8 mg/kg bw/day, target MOE of 300 from the oral one-year dog study.
f. Based on intermediate-term NOAEL of 8 mg/kg bw/day, target MOE of 300 from the oral one-year dog study.
g. Combined MOE = 1 / (1 / dermal MOE + 1 / inhalation MOE).
h. LADD = [Daily exposure × exposure days (50) × working lifetime (40 years)]/[365 days/year × lifetime (78 years)].
i. Cancer risk (mg kg bw/day) = LADD × q_1* (7.96 × 10^{-3} mg/kg bw/day)$^{-1}$.

Table 8 Mixer, Loader, Applicator Non-Cancer and Cancer Risk Assessment for Casing Drench Treatment in Mushroom Houses

Formulation/ Equipment	Appl. Rate (g a.i./100 m^2)[a]	Casing Treated per day[b]	Exposure (mg kg bw/day)		MOE			Cancer	
			Dermal[c]	Inhalation[d]	Dermal[e]	Inhalation[f]	Combined[g]	LADD[h]	Cancer Risk[i]
PPE: Coveralls over single layer plus gloves and respirator for all tasks									
Wettable Powder/MPHW	42.7	500	7.72E-03	3.80E-04	1040	21,100	988	5.69E-04	5E-06
PPE: Coveralls over single layer plus gloves for all tasks									
Liquid/MPHW	42.7	500	4.91E-04	1.21E-04	16 300	66300	13 100	4.29E-05	3E-07

MPHW = manually-pressurized handwand.

a. Maximum listed label rate in grams of active ingredient per one hundred metres squared of casing (g a.i./100 m^2).
b. Casing area treated (m^2/day) was based on the label directions of a maximum area treated of 500 m^2 per day per worker.
c. Where dermal exposure (mg/kg bw/day) = application rate × m^2 of casing treated per day × 1 kg/1000g × unit exposure × dermal absorption / 80 kg bw. Dermal absorption of TPM = 25%.
d. Where inhalation exposure mg/kg bw/day = unit exposure × m^2 of casing treated per day × application rate / 80 kg bw.

e. Based on intermediate-term NOAEL of 8 mg/kg bw/day, target MOE of 300 from the oral one-year dog study.
f. Based on intermediate-term NOAEL of 8 mg/kg bw/day, target MOE of 300 from the oral one-year dog study.
g. Combined MOE = 1 / (1 / dermal MOE + 1 / inhalation MOE).
h. LADD = [Daily exposure × exposure days per year (50) × working lifetime (40 years)]/[365 days/year × lifetime (78 years)].
i. Cancer risk = LADD × q_1* (7.96×10^{-3} mg/kg bw/day)$^{-1}$.

Appendix VI Occupational Postapplication Exposure and Risk Estimates for All Uses except Seed Treatment

Table 1 DFR and TTR Data Applied For Label Uses Except Mushrooms

Surrogate CDN Crops[a]	DFR/TTR Study						
	Crop (Site)	Application Rate	TPM		CAZ		
			Peak DFR/TTR[b] (µg/cm^2)	Ln Linear Equation[c]	Peak DFR/TTR[d]		TWA DFR[e]
					Day	µg/cm^2	µg/cm^2
Fruit trees (apple, pear) in BC	Apple (Washington)	1.18 kg a.i./ha	2.83	y = -0.0252x + 0.9625	14	0.293	0.182
Fruit trees (apple, pear) in Eastern Canada, peach, nectarine, plum, prune, cherry, aspen and poplar	Apple (New York)		2.30	y = -0.1892x + 1.1862	5, 7, 14	0.203	0.165
Outdoor roses and ornamentals, low bush blueberries strawberries, raspberries, sugarbeets, white beans	Strawberry (North Carolina)	0.806 kg a.i./ha	3.04	y = -0.7401x + 1.1645	Peak	0.065	Peak used
Turf (golf courses, other turf including sod farms)	Turf (Georgia)	17.58 kg a.i./ha	Equation used[f]	y = -0.4992x + 0.8071	Peak	0.054	Peak used
Greenhouse ornamentals (cut flowers and non-cut flowers), tobacco seedlings	Greenhouse roses	1.18 kg a.i./ha	3.97	y = -0.0503x +1.3082	21	0.193	0.133

TPM = thiophanate-methyl; CAZ = carbendazim; DFR = dislodgeable foliar residue; TTR = turf transferable residue; TWA = time-weighted average

a. DFR/TTR studies were used for other crops registered for thiophanate-methyl use in Canada. This was based on various parameters including geographic site, meteorology, crop morphology, and foliage type. The DFR/TTR studies were based on two applications, which is reflective of the supported use for most crops, except turf.

b. Peak DFR value from the study. This value was used to calculate postapplication exposure on Day 0 (the day of the final application) for short-term non-cancer risk assessment for non-turf crops. Values have not been adjusted for the Canadian application rates in this table, but were adjusted for Canadian rates when assessing risks and determining REIs.

c. The equation of the line was derived from linear regression of the study data, calculated by plotting the natural logarithms (ln) of DFR versus dissipation time (postapplication interval). The correlation coefficient (r^2) value must be greater than 0.85 for the equation to be used to predict DFR/TTR in risk assessment (all DFR/TTR data used in this assessment had correlation coefficients greater than 0.85). This equation was used to determine DFR/TTR for days after Day 0, which were used for the short-term non-cancer risk assessment, as well as the days used to calculate the time-weighted average (TWA), used in the intermediate/long-term non-cancer risk assessment and cancer risk assessment.

d. The day that the peak DFR/TTR for carbendazim occurred. For the apple and greenhouse studies, the day at which this occurred was reported and included in this table. For the strawberry and turf study, the day at which the peak occurred was not reported, so only ‘peak’ was included in this table. This

value was used to calculate postapplication exposure for the non-cancer risk assessment. Values have not been adjusted for the Canadian application rates in this table, but were adjusted for Canadian rates when assessing risks and determining REIs.

e. Where carbendazim residue data were reported for each monitored day, a time-weighted average value for 30 days after the final application of thiophanate-methyl was calculated for use in the cancer risk assessment. For the strawberry and turf sites, only the peak value was reported, so a time-weighted average could not be calculated and the peak value was conservatively used in the cancer risk assessment.

f. As more than two applications were supported for turf, the ln linear equation was used to model the peak TTR after multiple applications for the short-term exposure durations.

Table 2 Summary of REIs for Thiophanate-methyl (TPM) and Carbendazim (CAZ)

Crop	Activity	TPM[a]		CAZ REI[b]	REI[c]
		REI	Type of Risk Assessment		
Greenhouse Crops					
Greenhouse tobacco seedling (foliar, drench)	All	6 days	All	Risks acceptable on peak residue day	6 days
Greenhouse cut flowers (foliar)	Hand harvesting, disbudding, hand pruning	16 days	ST non-cancer	Risks acceptable on peak residue day	25 days
		25 days	IT/LT non-cancer, cancer		
	All other activities	12 hours	All		12 hours
Greenhouse ornamental non-cut flowers (foliar)	All activities	12 hours	All	Risks acceptable on peak residue day	12 hours
Tree Fruit					
Apple, pear (BC rate)	Hand thinning fruit	44 days	ST non-cancer	>28 days[d]	63 days
		63 days	Cancer		
	Hand harvesting	8 days	ST non-cancer	21 days	25 days
		25 day	Cancer		
	All other activities	12 hours	All	Risks acceptable on peak residue day	12 hours
Apple, pear (Eastern Canada rate)	All activities	12 hours	All	Risks acceptable on peak residue day	12 hours
Stone fruit	Hand thinning fruit	6 days	All	21 days	21 days
	All other activities	12 hours		Risks acceptable on peak residue day	12 hours
Berries and Field Crops					
Strawberry	All activities	12 hours	All	Risks acceptable on peak residue day	12 hours
Raspberry	Hand harvesting, tying/training (full foliage), handline irrigation	1 day	All	Risks acceptable on peak residue day	1 day
	All other activities	12 hours			12 hours
Low bush blueberry	Handline irrigation	1 day	All	Risks acceptable on peak residue day	1 day
	All other activities	12 hours			12 hours

Crop	Activity	TPM[a]		CAZ REI[b]	REI[c]
		REI	Type of Risk Assessment		
White bean	Scouting, handline irrigation	2 days	All	Risks acceptable on peak residue day	2 days
Sugarbeet	All activities	12 hours	All	Risks acceptable on peak residue day	12 hours
Outdoor Ornamentals					
Outdoor roses and ornamentals (cut flower)	Hand harvesting, disbudding, hand pruning	2 days	All	Risks acceptable on peak residue day	2 days
	All other activities	12 hours			12 hours
Outdoor ornamentals (non-cut flowers)	All activities	12 hours	All	Risks acceptable on peak residue day	12 hours
Aspen, poplar	All activities	12 hours	All	Risks acceptable on peak residue day	12 hours
Turf					
Sod farms, golf courses	Transplanting, planting, harvesting	1 day	All	Risks acceptable on peak residue day	1 day
Sod farms	All other activities	12 hours			12 hours
Golf courses					Until sprays have dried[e]

TPM = thiophanate-methyl; REI = restricted-entry interval; CAZ = carbendazim; MOE = margin of exposure; ST = short-term; IT/LT = intermediate/long-term.

a. Day at which risks were shown to be acceptable for TPM for postapplication workers entering treated areas to conduct activities. Where the REI varied between the short-term or intermediate/long-term non-cancer and cancer risk assessments for TPM, these were specified individually. See Table 3 for the non-cancer risk assessments and Table 5 for the cancer risk assessments.

b. Day at which risks were shown to be acceptable for CAZ for postapplication workers entering treated areas to conduct activities. If risks were shown to be acceptable on the day of the peak residue, then the REI was determined based on thiophanate-methyl REI. If the risks were not acceptable on the peak CAZ residue day, then an REI for CAZ was determined. See Table 4 for the non-cancer and cancer risk assessments for carbendazim.

c. Shaded cells indicate where REIs were not considered to be agronomically feasible. The highest agronomically feasible REI of thiophanate-methyl and carbendazim is proposed.

d. Residues could not be determined after this day as this was the last day of monitoring in the study and the dissipation could not be adequately modelled.

e. This REI is more applicable for golf courses where other essential activities in the treated area are required as soon as residues have dried and vapours have dissipated.

Table 3 Non-Cancer Postapplication Exposure and Risk Assessments for TPM

Crop	Rate (kg a.i./ha)	Postapplication Activity	TC (µg/cm^2)	Short-Term			Intermediate/Long-Term		
				Day 0 DFR/TTR[a] (µg/cm^2)	Day 0 MOE[b] (T=300)	REI[c] (day)	TWA DFR/TTR[d] (µg/cm^2)	TWA MOE[e] (T=300)	REI[c] (day)
Greenhouse Crops - 2 applications, 7 days apart - Greenhouse Cut Flower DFR study (Rose site)									
Cut flowers (foliar application)	0.60	Hand harvesting, disbudding, hand pruning	4000	2.02	124	16	0.284	282	25
		All other activities	230		2150	12 hours	0.999	1390	12 hours
Non-cut flowers (foliar application)		All activities							
Tobacco seedlings (foliar spray and foliar drench applications)	6.30	All activities		21.2	205	6	N/A		
Fruit Trees - 2 applications, 7 day interval - Apple DFR study (Washington site)									
Apple, pear	1.58 (BC rate)	Hand Thinning Fruit	3000	3.81	88	44	N/A[f]		
		Hand harvesting	1400		188	8			
		Hand pruning, scouting, training	580		454	12 hours			
		Orchard maintenance, bird control, hand weeding, propping	100		2635				
Fruit Trees - 2 applications, 7 day interval - Apple DFR study (New York site)									
Apple, pear	0.44 (Eastern Canada rate)	Hand Thinning Fruit	3000	0.861	389	12 hours	N/A[f]		
		Hand harvesting	1400		834				
		Hand pruning, scouting, training	580		2010				
		Orchard maintenance, bird control, hand weeding, propping	100		11,700				
Cherry, nectarine, peach, plum, prune	1.23	Hand Thinning Fruit	3000	2.41	139	6	N/A[f]		
		Hand harvesting	1400		298	12 hours			
		Hand pruning, scouting, training	580		713				
		Orchard maintenance, bird control, hand weeding,	100		4170				

Crop	Rate (kg a.i./ha)	Postapplication Activity	TC (µg/cm²)	Short-Term			Intermediate/Long-Term		
				Day 0 DFR/TTR[a] (µg/cm²)	Day 0 MOE[b] (T=300)	REI[c] (day)	TWA DFR/TTR[d] (µg/cm²)	TWA MOE[c] (T=300)	REI[c] (day)
		propping							
Berries and Field Crops - 2 applications, 7 day interval. Strawberry DFR study (North Carolina site)									
Strawberry	0.77	Hand harvesting	1100	2.90	313	12 hours	N/A[f]		
		Transplanting	230		4500				
		Scouting	210		1640				
		Hand weeding, canopy management	70		4920				
Raspberry	0.77	Handline irrigation	1750	2.90	197	1	N/A[f]		
		Hand harvesting, tying/training (full foliage)	1400		246	1			
		Scouting, hand pruning, hand weeding, tying/training (min foliage)	640		538	12 hours			
		Transplanting	230		1500				
Low bush blueberry	0.77	Handline irrigation	1750	2.90	197	1	N/A[f]		
		Hand harvesting, scouting	1100		313	12 hours			
		Transplanting	230		1500				
		Hand weeding	70		4920				
White bean	1.58	Handline irrigation	1750	5.94	96	2	N/A[f]		
		Scouting	1100		153	2			
Sugarbeet	0.39	Hand harvesting	1100	1.48	615	12 hours	N/A[f]		
		Scouting	210		3220				
		Hand weeding, thinning plants	70		9670				
Outdoor Flowers and Ornamentals (except trees) - 2 applications, 7 day interval - Strawberry DFR study (North Carolina site)									
Outdoor roses and ornamentals (cut flower)	0.53	Hand harvesting, disbudding, hand pruning	4000	1.98	126	2	N/A[f]		
		Handline irrigation	1750		289	12 hours			
		All other activities	230		2200				
Outdoor ornamentals (non-cut flowers)	0.53	Handline irrigation	1750	1.98	289	12 hours	N/A[f]		
		All other activities	230		2200				
Outdoor Ornamental Trees - 2 applications, 7 day interval - Apple DFR study (New York site)									
Aspen and Poplar	0.77	Handline irrigation	1750	1.51	379	12 hours	N/A[f]		
		All other activities	230		3890				

Crop	Rate (kg a.i./ha)	Postapplication Activity	TC (µg/cm²)	Short-Term			Intermediate/Long-Term		
				Day 0 DFR/TTR[a] (µg/cm²)	Day 0 MOE[b] (T=300)	REI[c] (day)	TWA DFR/TTR[d] (µg/cm²)	TWA MOE[e] (T=300)	REI[c] (day)
Turf - 4 applications, 7 day interval - Turf TTR study (California site)[g]									
Dollar Spot (2 applications of 2.1 kg a.i./ha), Brown Patch (1 application of 4.2 kg a.i./ha) and Pink Snow Mould (1 application of 12.25 kg a.i./ha)									
Golf course/sod farm	2.1–4.2	Transplanting/planting,[slab harvesting- sod farm only]	6700	0.544 [h]	274	1	0.092 [i]	518	12 hours
		Mowing, watering, [irrigation- sod farm only], [cup changing, irrigation repair, miscellaneous grooming- golf course only]	3500		525	12 hours		991	
	2.1–12.25	Aerating, fertilizing, hand pruning, scouting, mechanical weeding	1000	1.58[h]	634		0.170[i]	1880	

Shaded cells indicate where the MOE is lower than or not within range of the target MOE and risks are not shown to be acceptable.
TPM = thiophanate-methyl; TC = transfer coefficient; DFR = dislodgeable foliar residue; TTR= turf transferrable residue; MOE = margin of exposure; T = target MOE; REI = restricted-entry interval; TWA = time-weighted average; Avg = average; N/A = not applicable

a. DFR/TTR residue on the day of the second application, following two applications, 7 days apart and adjusted for the Canadian application rate.
b. MOE = NOAEL/exposure. Where exposure = DFR/TTR × 8 hours × TC/body weight (80 kg). A NOAEL of 100 mg/kg bw/day from a 21-day rabbit dermal study, with a target MOE of 300 was used.
c. Point in time the calculated MOE exceeds or is within range of the target MOE when both the short-term and intermediate-/long-term assessments were conducted, the longest REI is proposed.
d. Time-weighted average DFR/TTR. For crops where the DFR residues were based on the apple and greenhouse cut flower DFR studies, residues were averaged over 30 days starting at the REI. For crops where the DFR/TTR residues were based on the strawberry and turf DFR studies, residues were averaged up to day 7, as residues were not quantifiable in the study after this date. Residues were adjusted to the Canadian application rate.
e. MOE = NOAEL/exposure. Where exposure = DFR/TTR × 8 hours × dermal absorption (25%) × TC/body weight (80 kg). A NOAEL of 8 mg/kg bw/day from an oral 1-year dog study was used. Target MOE of 300.
f. An intermediate/long-term risk assessment was not required as only 2 applications per year is supported by the registrant. For greenhouse tobacco seedlings, short-term duration was expected as seedlings are transplanted into the field, so are only grown in greenhouses for a short period of time.
g. Four applications of various application rates are supported for turf.
h. For the short-term risk assessment, the peak TTR from all applicable applications, with a 7 day interval was used. As pink snow mould is only applied at the end of the season, it was only expected to co-occur with scouting activities.
i. For the intermediate-term risk assessment, the 0–7 day time-weighted average from the TTR study was adjusted by the average rate across the three or four applications for each activity. Pink snow mould is only applied at the end of the season, so it was only expected to co-occur with scouting activities. The average rate for this activity was determined based on one seasonal application each for pink snow mould and brown patch and two seasonal applications of dollar spot (12.25+4.20+2.10+2.10 kg a.i./ha /4). For all other activities, the average rate was determined excluding the pink snow mould application.

Table 4 TPM Cancer Postapplication Exposure and Risk Assessments

Crop	Rate (kg a.i./ha)	Activity	TC ($\mu g/cm^2$)	TPM				REI[d] (days)
				TWA DFR/ TTR		LADD[b] (µg/kg bw/day)	Cancer risk[c]	
				Days[a]	$\mu g/cm^2$			
Greenhouse Crops- 2 applications, 7 days apart- Greenhouse Cut Flower DFR study (Rose site)								
Cut flowers (foliar application)	0.60	Hand harvesting, disbudding, hand pruning	4000	25–54	0.284	1.20	1×10^{-5}	25
		All other activities	230	0–29	0.999	0.242	2×10^{-6}	12 hrs
Non-cut flowers (foliar application)		All activities						
Tobacco seedlings (foliar spray and foliar drench applications)	6.30	All activities		6–35	7.76	1.88	1×10^{-5}	6
Tree Fruit- 2 applications, 7 day interval- Apple DFR study (Washington site)								
Apple, pear	1.58 (BC rate)	Thinning Fruit	3000	44–73	0.813	2.57	2×10^{-5}	44
				63–92	0.536	1.70	1×10^{-5}	**63**
		Hand harvesting	1400	8–37	1.77	2.61	2×10^{-5}	8
				25–54	1.23	1.82	1×10^{-5}	**25**
		Hand pruning, scouting, training	580	0–29	2.14	1.31	1×10^{-5}	12 hrs
		Orchard maintenance, bird control, hand weeding, propping	100			0.226	2×10^{-6}	
Tree Fruit- 2 applications, 7 day interval- Apple DFR study (New York site)								
Apple, pear	0.44 (Eastern Canada rate)	Thinning Fruit	3000	0–29	0.168	0.532	4×10^{-6}	12 hrs
		Hand harvesting	1400			0.248	2×10^{-6}	
		Hand pruning, scouting, training	580			0.103	8×10^{-7}	
		Orchard maintenance, bird control, hand weeding, propping	100			0.018	1×10^{-7}	
Cherry, nectarine, peach, plum, prune	1.23	Thinning Fruit	3000	6–35	0.212	0.671	5×10^{-6}	6[e]
		Hand harvesting	1400	0–9	0.471	0.695	6×10^{-6}	12 hrs
		Hand pruning, scouting, training	580			0.288	2×10^{-6}	
		Orchard maintenance, bird control, hand weeding, propping	100			0.050	4×10^{-7}	
Berries and Field Crops- 2 applications, 7 day interval. Strawberry DFR study (North Carolina site)								
Strawberry	0.77	Hand harvesting	1100	0–7	0.729	0.845	7×10^{-6}	12 hrs
		Transplanting	230			0.177	1×10^{-6}	
		Scouting	210			0.161	1×10^{-6}	

Crop	Rate (kg a.i./ha)	Activity	TC (µg/cm^2)	TPM				REI[d] (days)
				TWA DFR/ TTR		LADD[b] (µg/kg bw/day)	Cancer risk[c]	
				Days[a]	µg/cm^2			
		Hand weeding, canopy management	70			0.054	4×10^{-7}	
Raspberry	0.77	Handline irrigation	1750	1–7	0.397	0.731	6×10^{-6}	1
		Hand harvesting, tying/training (full foliage)	1400			0.585	5×10^{-6}	
		Scouting, hand pruning, hand weeding, tying/training (min foliage)	640	0–7	0.729	0.492	4×10^{-6}	12 hrs
		Transplanting	230			0.177	1×10^{-6}	
Low bush blueberry	0.77	Handline irrigation	1750	1–7	0.397	0.731	6×10^{-6}	1
		Hand harvesting, scouting	1100	0–7	0.729	0.845	7×10^{-6}	12 hrs
		Transplanting	230			0.177	1×10^{-6}	
		Hand weeding	70			0.054	4×10^{-7}	
White bean	1.58	Handline irrigation	1750	2–7	0.449	0.827	7×10^{-6}	2
		Scouting	1100			0.520	4×10^{-6}	
Sugarbeet	0.39	Hand harvesting	1100	0–7	0.371	0.430	3×10^{-6}	12 hrs
		Scouting	210			0.082	7×10^{-7}	
		Hand weeding, thinning plants	70			0.027	2×10^{-7}	
Flowers and Ornamentals (except trees)- 2 applications, 7 day interval- Strawberry DFR study (North Carolina site)								
Outdoor roses and ornamentals (cut flowers)	0.53	Hand harvesting, disbudding, hand pruning	4000	2–7	0.150	0.630	5×10^{-6}	2
		Handline irrigation	1750	0–7	0.497	0.917	7×10^{-6}	12 hrs
		All other activities	230			0.121	1×10^{-6}	
Outdoor ornamentals (non-cut flowers)	0.53	Handline irrigation	1750	0–7	0.497	0.917	7×10^{-6}	12 hrs
		All other activities	230			0.121	1×10^{-6}	
Ornamental Trees - 2 applications, 7 day interval - Apple DFR study (New York site)								
Aspen and Poplar	0.77	Handline irrigation	1750	0–29	0.452	0.834	7×10^{-6}	12 hrs
		All other activities	230			0.110	9×10^{-7}	
Turf - 4 applications, 7 day interval - Turf TTR study (Georgia site)[f]								
Golf course/sod farm	2.10–4.20	Transplanting/planting,[slab harvesting- sod farm only]	6700	0–7	0.092	0.651	5×10^{-6}	12 hrs
		Mowing, watering, [irrigation- sod farm only], [cup changing, irrigation repair, miscellaneous grooming- golf course only]	3500			0.340	3×10^{-6}	
	2.10–12.25	Aerating, fertilizing, hand	1000	0–7	0.170	0.179	1×10^{-6}	

Crop	Rate (kg a.i./ha)	Activity	TC (µg/cm^2)	TPM				REI[d] (days)
				TWA DFR/ TTR		LADD[b] (µg/kg bw/day)	Cancer risk[c]	
				Days[a]	µg/cm^2			
		pruning, scouting, mechanical weeding						

Shaded cells indicate where the cancer risk is above the threshold of 1×10^{-5} and risks are not shown to be acceptable.
TPM = thiophanate-methyl; TC = transfer coefficient; CAZ = carbendazim; DFR = dislodgeable foliar residue; TTR= turf transferrable residue; REI = restricted-entry interval; TWA = time-weighted average; LADD = Lifetime average daily dose

a. Days after the final application over which the DFR/TTR residues were averaged to calculate the time-weighted average DFR/TTR. For crops where the DFR residues were based on the apple and greenhouse cut flower DFR studies, residues were averaged over 30 days starting at the REI. For crops where the DFR/TTR residues were based on the strawberry and turf DFR studies, residues were averaged up to day 7 starting at the REI, as residues were not quantifiable in the study after this date. Residues were adjusted to the Canadian application rate.
b. LADD = lifetime average daily dose = [TWA DFR/TTR × 8 hours × dermal absorption (25%) × TC × exposure days (30) × working lifetime (40 years)]/[body weight (80 kg) × 365 days/year × lifetime (78 years)].
c. Cancer risk = LADD × q_1*. Thiophanate-methyl q_1* is $(7.96 \times 10^{-3}$ mg/kg bw/day$)^{-1}$.
d. REI is based on the non-cancer risk assessment for TPM (Table 3) and is shown in italics. Where the cancer risk is greater than the threshold of 1×10^{-5} and risks are not shown to be acceptable at this REI, an REI based on the cancer risk assessment was determined. This value is in bold and will be the proposed REI.
e. Although the REI for TPM is 6 days, the proposed REI is 21 days based on CAZ non-cancer risk (see Table 5 of this Appendix)
f. Similarly to the non-cancer intermediate/long-term risk assessment, the four applications of various application rates were supported for turf. The time-weighted average from the TTR study was adjusted by the average rate across the three-four applications for each activity. Pink snow mould is only applied at the end of the season, so it was only expected to co-occur with scouting activities. The average rate for this activity was determined based on one seasonal application each for pink snow mould and brown patch and two seasonal applications of dollar spot ((12.25 + 4.2 + 2.1 + 2.1)/4). For all other activities, the average rate was determined excluding the pink snow mould application.

Table 5 Carbendazim Postapplication Non-Cancer and Cancer Exposure and Risk Assessments

Crop	Rate (kg a.i./ha)	Postapplication Activity	TC (µg/cm^2)	Non-Cancer				Cancer			
				DFR/TTR		MOE[b]	REI[c] (day)	TWA DFR/TTR		LADD[e] (µg/kg bw/day)	Cancer risk[f]
				Day[a]	µg/cm^2			Days[d]	µg/cm^2		
Greenhouse Crops - 2 applications, 7 days apart - Greenhouse Cut Flower DFR study (Rose site)											
Cut flowers (foliar application)	0.60	Hand harvesting, disbudding, hand pruning	4000	21 (peak)	0.098	1020	Use TPM	0–-29	0.068	0.286	3×10^{-7}
		All other activities	230			17 700				0.016	2×10^{-8}
Non-cut flowers (foliar application)		All activities									
Tobacco seedlings (foliar spray and foliar drench	6.30	All activities	230	21 (peak)	1.03	1680		0–29	0.713	0.173	2×10^{-7}

Crop	Rate (kg a.i./ha)	Postapplication Activity	TC (µg/cm^2)	Non-Cancer				Cancer			
				DFR/TTR		MOE[b]	REI[c] (day)	TWA DFR/TTR		LADD[e] (µg/kg bw/day)	Cancer risk[f]
				Day[a]	µg/cm^2			Days[d]	µg/cm^2		
application)											
Tree Fruit - 2 applications, 7 day interval - Apple DFR study (Washington site)											
Apple, pear	1.58 (BC rate)	Hand thinning fruit	3000	14 (peak)	0.393	340	>28[g]	0–29	0.242	0.766	8×10^{-7}
				28	0.210	635					
		Hand harvesting	1400	14 (peak)	0.393	728	21			0.358	4×10^{-7}
				21	0.263	1090					
		Hand pruning, scouting, training	580	14 (peak)	0.393	1760	Use TPM			0.148	2×10^{-7}
		Orchard maintenance, bird control, hand weeding, propping	100	14 (peak)	0.393	10,200				0.026	3×10^{-8}
Tree Fruit - 2 applications, 7 day interval - Apple DFR study (New York site)											
Apple, pear	0.44 (Eastern Canada rate)	Hand thinning fruit	3000	5, 7, 14 (peak)	0.076	1770	Use TPM	0–29	0.061	0.192	2×10^{-7}
		Hand harvesting	1400			3780				0.090	1×10^{-7}
		Hand pruning, scouting, training	580			9130				0.037	4×10^{-8}
		Orchard maintenance, bird control, hand weeding, propping	100			53,000				0.006	7×10^{-9}
Cherry, nectarine, peach, plum, prune	1.23	Thinning Fruit	3000	5, 7, 14 (peak)	0.212	631	21	0–29	0.172	0.538	6×10^{-7}
				21	0.117	1140					
		Hand harvesting	1400	5, 7, 14 (peak)	0.212	1350	Use TPM			0.251	3×10^{-7}
		Hand pruning, scouting, training	580			3260				0.104	1×10^{-7}
		Orchard maintenance, bird control, hand weeding, propping	100			18,900				0.018	2×10^{-8}
Berries and Field Crops - 2 applications, 7 day interval. Strawberry DFR study (North Carolina site)											
Strawberry	0.77	Hand harvesting	1100	Peak	0.062	5860	Use TPM	Peak	0.062	0.072	8×10^{-8}
		Transplanting	230			28,000				0.015	2×10^{-8}
		Scouting	210			30,700				0.014	1×10^{-8}
		Hand weeding, canopy management	70			92,000				0.005	5×10^{-9}
Raspberry	0.77	Handline irrigation	1750	Peak	0.062	3680	Use TPM	Peak	0.062	0.114	1×10^{-7}
		Hand harvesting,	1400			4600				0.092	1×10^{-7}

Crop	Rate (kg a.i./ha)	Postapplication Activity	TC (µg/cm^2)	Non-Cancer				Cancer			
				DFR/TTR		MOE[b]	REI[c] (day)	TWA DFR/TTR		LADD[e] (µg/kg bw/day)	Cancer risk[f]
				Day[a]	µg/cm^2			Days[d]	µg/cm^2		
		tying/training (full foliage)									
		Scouting, hand pruning, hand weeding, tying/training (min foliage)	640			10,100				0.042	5×10^{-8}
		Transplanting	230			28 000				0.015	2×10^{-8}
Low bush blueberry	0.77	Handline irrigation	1750	Peak	0.062	3680	Use TPM	Peak	0.062	0.114	1×10^{-7}
		Hand harvesting, scouting	1100			5860				0.072	8×10^{-8}
		Transplanting	230			28 000				0.015	2×10^{-8}
		Hand weeding	70			92 000				0.005	5×10^{-9}
White bean	1.58	Handline irrigation	1750	Peak	0.127	1800	Use TPM	Peak	0.127	0.234	3×10^{-7}
		Scouting	1100			2860				0.147	2×10^{-7}
Sugarbeet	0.39	Hand harvesting	1100	Peak	0.037	9970	Use TPM	Peak	0.037	0.042	5×10^{-8}
		Scouting	210			52 200				0.008	9×10^{-9}
		Hand weeding, thinning plants	70			157 000				0.003	3×10^{-9}
Flowers and Ornamentals (except trees)- 2 applications, 7 day interval- Strawberry DFR study (North Carolina site)											
Outdoor roses and ornamentals (cut flowers)	0.53	Handline irrigation	1750	Peak	0.042	5400	Use TPM	Peak	0.042	0.078	9×10^{-8}
		Hand harvesting, disbudding, hand pruning	4000			2360				0.178	2×10^{-7}
		All other activities	230			41 000				0.010	1×10^{-8}
Outdoor ornamentals (non-cut flowers)	0.53	Handline irrigation	1750	Peak	0.042	5400	Use TPM	Peak	0.042	0.078	9×10^{-8}
		All other activities	230			41 000				0.010	1×10^{-8}
Ornamental Trees- 2 applications, 7 day interval- Apple DFR study (New York site)											
Aspen and Poplar	0.77	Handline irrigation	1750	5, 7, 14 (peak)	0.133	1720	Use TPM	0-29	0.108	0.200	2×10^{-7}
		All other activities	230			13 100				0.026	3×10^{-8}
Turf- 4 applications, 7 day interval- Turf TTR study (Peak from Georgia site as California site was <LOQ)											
Dollar Spot (2 applications of 2.1 kg a.i./ha), Brown Patch (1 application of 4.2 kg a.i./ha) and Pink Snow Mould (1 application of 12.25 kg a.i./ha)											
Golf course/sod farm	2.1-4.2	Transplanting/planting, [slab harvesting- sod farm only]	6700	Cumulative Peak	0.0258[h]	2310	Use TPM	Avg Season Peak [i]	0.009	0.050	5×10^{-8}
		Mowing, watering, [irrigation - sod farm	3500			4430			0.009	0.032	3×10^{-8}

Crop	Rate (kg a.i./ha)	Postapplication Activity	TC (µg/cm^2)	Non-Cancer				Cancer			
				DFR/TTR		MOE[b]	REI[c] (day)	TWA DFR/TTR		LADD[e] (µg/kg bw/day)	Cancer risk[f]
				Day[a]	µg/cm^2			Days[d]	µg/cm^2		
		only], [cup changing, irrigation repair, miscellaneous grooming-golf course only]									
	2.1-12.25	Aerating, fertilizing, hand pruning, scouting, mechanical weeding	1000		0.0634[h]	6310		Avg Season Peak[i]	0.016	0.017	2×10^{-8}

Shaded cells indicate where the MOE is lower than or not within range of the target MOE and risks are not shown to be acceptable.
CAZ = carbendazim; TC = transfer coefficient; DFR = dislodgeable foliar residue; TTR= turf transferrable residue; MOE = margin of exposure; T = target MOE; REI = restricted-entry interval; TWA = time-weighted average; LADD = lifetime average daily dose; TPM = thiophanate-methyl; Avg = average; LOQ = limit of quantification; GA = Georgia

a. The number of days after the final application that corresponds to the reported DFR/TTR residue. Where indicated, this is the peak value from the study. The day at which the peak occurred was not always reported. Residues were adjusted to the Canadian application rate.
b. MOE = NOAEL/exposure. Where exposure = DFR/TTR × 8 hours × dermal absorption (25%) × TC/body weight (80 kg). A NOAEL of 10 mg/kg bw/day from oral developmental toxicity studies with a target MOE of 1000 were used. This toxicology reference value is applicable for all durations of exposure.
c. Point in time when the MOE exceeds or is within range of the target MOE for CAZ. If the target MOEs is met at the peak DFR/TTR value, then the REI is determined based on the thiophanate-methyl postapplication risk assessment (Table 3 of this Appendix) indicated by 'use TPM'.
d. Days over which the average DFR/TTR was determined following the final application of TPM, for studies where measured values were reported for each monitored day (apple and greenhouse cut flower DFR studies). Where daily values were not reported (strawberry DFR and turf studies), the peak DFR/TTR value from the study was used; this is considered to be a conservative assumption. Residues were adjusted to the Canadian application rate.
e. LADD = [TWA DFR/TTR × 8 hours × dermal absorption (25%) × TC × exposure days (30) × working lifetime (40 years)]/[body weight (80 kg) × 365 days/year × lifetime (78 years)].
f. Cancer risk = LADD × q_1* $(1.09 \times 10^{-3}$ mg/kg bw/day$)^{-1}$.
g. Last day of sampling in DFR study
h. Four applications of various application rates are supported for turf. For the non-cancer risk assessment, the peak carbendazim residue value from the turf study (GA site) was adjusted for the seasonal cumulative application rate of all applicable applications (one brown patch application, two dollar spot applications; the pink snow mould was also included for the scouting activity). It was assumed that there was no dissipation of carbendazim between applications. This is a conservative assumption.
i. The peak residue value from the TTR study (GA site) was adjusted by the average of the seasonal application rates applicable for each activity. Pink snow mould is only applied at the end of the season, so it was only expected to co-occur with scouting activities. The average seasonal rate for this activity was determined based on one seasonal application each of pink snow mould and brown patch and two seasonal applications of dollar spot. For all other activities, the average rate was determined excluding the pink snow mould application. For example- hand harvesting TTR: 0.054 µg/cm^2 × [(two dollar spot applications (2.10 kg a.i./ha) + one brown patch application (4.20 kg a.i./ha)/3]/site application rate (17.6 kg a.i./ha).

Appendix VII Seed Treatment Exposure and Risk Assessment

Table 1 Commercial Seed Treatment Exposure and Non-Cancer and Cancer Risk Assessment for Dry Common Bean

Form	Activity[a]	Application Rate (g a.i./100 kg seed)	Throughput[b] (kg seed/day)	MOE (Target =300)			LADD[f]	Cancer Risk[g]
				Dermal[c]	Inhalation[d]	Combined[e]		
Krolski, 2010 (corn) - Closed mix/load wearing single layer, CR gloves								
Liquid	Treater	72.9	73,000	587	4041	513	0.0019	2×10^{-5h}
	Bagger, sewer, stacker			632	804	354	0.0022	2×10^{-5h}
	Cleaner			864	455	298	0.0022	2×10^{-5h}
WP	Treater	72.8	73,000	191	251	109	0.0072	6×10^{-5}
	Bagger, sewer, stacker			632	805	354	0.0022	2×10^{-7}
	Cleaner			865	456	299	0.0021	2×10^{-5}
Krolski, 2010 (canola)- Closed mix/load wearing coveralls over single layer, CR gloves								
WP	Treater	72.8	73,000	354	263	151	0.00458	4×10^{-5}
	Bagger, sewer, stacker			20 500	10 000	6740	0.00009	7×10^{-7}
	Cleaner			1950	865	600	0.00103	8×10^{-6}

Shaded cells indicate when MOEs are below the target MOE or cancer risk is above 1×10^{-5} and therefore risks are not shown to be acceptable.
Resp = respirator; Form = formulation; CR = chemical-resistant; Single layer = long-sleeved shirt, long pants; MOE = margin of exposure; LADD = lifetime average daily dose

a. Activities are determined by the tasks performed by workers in each exposure study.
b. Throughput is dependent on seed type.
c. Based on a short-term NOAEL of 100 mg/kg bw/day from a 21-day rabbit dermal study and a target MOE of 300. MOE = NOAEL/exposure. Exposure = [{(application rate × kg/1000 g × throughput) OR (application rate) for cleaners} × unit exposure]/80 kg body weight].
d. Based on a short-term NOAEL of 10 mg/kg bw/day from an oral rabbit developmental study and a target MOE of 300. MOE = NOAEL/exposure. See footnote 'c' for exposure equation.
e. Combined MOE = 1/[(1/dermal MOE)+(1/inhalation MOE)].
f. LADD = lifetime average daily dose = [(dermal exposure × 25% dermal absorption + inhalation exposure, as calculated above) × exposure days (30) × working lifetime (40 years)]/[body weight (80 kg) × 365 days/year × lifetime (78 years)].
g. Cancer risk = LADD × q_1*. Thiophanate-methyl q_1* is $(7.96 \times 10^{-3}$ mg/kg bw/day$)^{-1}$
h. Although this cancer risk is greater than 1×10^{-5}, it is considered be acceptable as the throughput is a high-end value and is considered to overestimate what would typically be handled on a yearly basis. In addition, the unit exposures are based on corn, which is considered to be a conservative surrogate for beans, given the differences in dust-off potential.

Table 2 On-Farm Seed Treatment Exposure and Non-cancer and Cancer Risk Assessment for Mixing/Loading and Planting

Crop	Form	Activity[a]	Application Rate (g a.i./kg seed)	Throughput[b] (kg seed/day)	MOE (Target = 300)			LADD[f]	Cancer Risk[g]
					Dermal[c]	Inhalation[d]	Combined[e]		
Dry application/Seed Box Treatment: Klonne, 2005: Open loading, Closed cab planter, single layer, CR gloves									
Sweet corn	WP, liquid[h]	Mix/load, plant	0.70	550	1990	1830	953	0.00025	2×10^{-6}
Dry common bean	WP		0.728	8300	126	117	61	0.0040	3×10^{-5}
Dry application/Seed Box Treatment: Klonne, 2005: Open loading, Closed cab planter, CR coveralls over single layer, CR gloves									
Dry common bean	WP	Mix/load, plant	0.728	8300	348	117	87	0.0022	2×10^{-5}
Liquid slurry application: Krolski, 2006: Open mixing/loading, Closed cab planter, single layer, CR gloves									
Dry common bean	Liquid	Mix/load, plant	0.735	8300	9030	17,200	5930	0.000047	4×10^{-7}
	WP[i]		0.728		1960	2080	1010	0.00025	2×10^{-6}

Shaded cells indicate when MOEs are below the target MOE or cancer risk is above the threshold of 1×10^{-5}, and therefore risks are not shown to be acceptable.
Form = formulation; CR = chemical-resistant; Single layer = long-sleeved shirt, long pants; MOE = margin of exposure; LADD = lifetime average daily dose ; Inhal = inhalation; Resp = respirator;

a. Activities are determined by the tasks performed by workers in each exposure study.
b. Throughput is dependent on seed type, seeding rate and area planted.
c. Based on a short-term dermal NOAEL of 100 mg/kg bw/day from a 21-day rabbit dermal study and a target MOE of 300. MOE = NOAEL/exposure. Exposure = [(application rate × kg/1000 g × throughput) × unit exposure]/80 kg body weight].
d. Based on a short-term NOAEL of 10 mg/kg bw/day from an oral rabbit developmental study and a target MOE of 300. MOE = NOAEL/exposure. See footnote 'c' for exposure equation.
e. Combined MOE = 1/[(1/dermal MOE)+(1/inhalation MOE)].
f. LADD = lifetime average daily dose = [(dermal exposure × 25% dermal absorption + inhalation exposure, as calculated above) × exposure days (10) × working lifetime (40 years)]/[body weight (80 kg) × 365 days/year × lifetime (78 years)].
g. Cancer risk = LADD × q_1*. Thiophanate-methyl q_1* is $(7.96 \times 10^{-3}$ mg/kg bw/day$)^{-1}$
h. The liquid product is also registered for seed box application. No data are available to assess this application method using a liquid. The Klonne (2005) study was used as surrogate and may overestimate exposure.
i. No acceptable on-farm slurry seed treatment exposure studies were conducted with wettable powders or dusts. To estimate exposure, PHED mixer/loader unit exposure values for wettable powders were added to the liquid mixer/loader/planter unit exposure values.

Table 3 Planting Exposure and Non-Cancer and Cancer Risk Assessment for Commercially Treated Seed[a]

Crop	Form	Application Rate (g a.i./kg seed)	Throughput[b] (kg/day)	MOE (Target = 300)			LADD[f]	Cancer Risk[g]
				Dermal[c]	Inhalation[d]	Combined[e]		
Zietz, 2007: Open loading, closed cab planting, single layer, CR gloves								
Dry common bean	WP, liquid	0.729	8300	873	1600	564	0.00049	4×10^{-6}

WP = wettable powder; Form = formulation; CR = chemical-resistant; Single layer = long-sleeved shirt, long pants; MOE = margin of exposure; LADD = lifetime average daily dose

a. Planting on-farm treated seed was addressed in the on-farm exposure studies.

b. Throughputs are dependent on seed type, seeding rate and area planted.

c. Based on a short-term NOAEL of 100 mg/kg bw/day from a 21-day rabbit dermal study and a target MOE of 300. MOE = NOAEL/exposure. Exposure = [(application rate × kg/1000 g × throughput) × unit exposure]/80 kg body weight].

d. Based on a short-term NOAEL of 10 mg/kg bw/day from an oral rabbit developmental study and a target MOE of 300. MOE = NOAEL/exposure. See footnote 'c' for exposure equation.

e. Combined MOE = 1/[(1/dermal MOE)+(1/inhalation MOE)].

f. LADD = lifetime average daily dose = [(dermal exposure × 25% dermal absorption + inhalation exposure, as calculated above) × exposure days (10) × working lifetime (40 years)]/[body weight (80 kg) × 365 days/year × lifetime (78 years)].

g. Cancer risk = LADD × q_1*. Thiophanate-methyl q_1* is $(7.96 \times 10^{-3}$ mg/kg bw/day$)^{-1}$

Table 4 Exposure and Non-Cancer and Cancer Risk Assessment for Potato Seed Pieces

Activity[a]	Form	Application Rate (g a.i./ kg seed)	Throughput[b] (kg/day)	MOE (Target = 300)			LADD[f]	Cancer Risk[g]
				Dermal[c]	Inhalation[d]	Combined[e]		
Mackie, 2006: Open mix/load, wearing single layer, CR gloves								
Treater	Liquid	0.5	90,000 (40,000 for cancer)	611	1550	438	0.00089	7×10^{-6}
Cutter/sorter				NM	988	N/A	0.00019	2×10^{-6}
Treater/sorter/cutter				611	988	377	0.00096	8×10^{-6}
Lange, 2015: Open loading, closed cab planting, wearing single layer, gloves (no specific type)								
Planter driver/loaders	Liquid	0.5	90,000 (40,000 for cancer)	484	959	322	0.00039	3×10^{-6}
Back of planter				62	284	51	0.0058	5×10^{-5}
Lange, 2015: Open loading, closed cab planting, wearing CR coveralls over single layer, gloves (no specific type)								
Back of planter	Liquid	0.5	90,000 (40,000 for cancer)	271	284	139	0.0080	6×10^{-6}
Maasfield, 2001: Open mix/load, closed cab, wearing single layer, CR gloves								
Mix, load, plant	WP	0.5	90,000 (40,000 for cancer)	42	123	32	0.0042	3×10^{-5}

Shaded cells indicate when MOEs are below the target MOE or cancer risk is above 1×10^{-5} and therefore risks are not shown to be acceptable.
Form = formulation; CR = chemical-resistant; Single layer = long-sleeved shirt, long pants; MOE = margin of exposure; LADD = lifetime average daily dose; WP

= wettable powder

a. Activities are determined by the tasks performed by workers in each exposure study.

b. Throughput is dependent on seed type, seeding rate and area planted.

c. Based on a short-term dermal NOAEL of 100 mg/kg bw/day from a 21-day rabbit dermal study and a target MOE of 300. MOE = NOAEL/exposure. Exposure = [(application rate × kg/1000 g × throughput) × unit exposure]/80 kg body weight].

d. Based on a short-term NOAEL of 10 mg/kg bw/day from an oral rabbit developmental study and a target MOE of 300. MOE = NOAEL/exposure. See footnote ‘c’ for exposure equation.

e. Combined MOE = 1/[(1/dermal MOE)+(1/inhalation MOE)].

f. LADD = lifetime average daily dose = [(dermal exposure × 25% dermal absorption + inhalation exposure, as calculated above) × exposure days (30 for commercial treatment, 10 days for on-farm/planting) × working lifetime (40 years)]/[body weight (80 kg) × 365 days/year × lifetime (78 years)].

g. Cancer risk = LADD × q_1*. Thiophanate-methyl q_1* is $(7.96 \times 10^{-3}$ mg/kg bw/day$)^{-1}$

Appendix VIII Residential, Aggregate and Cumulative Exposure and Risk Assessment

Table 1 TPM Residential Postapplication Dermal, Non-Cancer Exposure and Risk Assessment

Scenario	Sub-population	DFR/TTR (µg/cm^2)[a]	TC[b] (cm^2/hr)	Exposure[c] (mg/kg bw/day)	Dermal MOE[d] (Target = 300)
Fruit Trees - 2 apps, 7 days apart					
Apple, pear- BC rate	Adults	3.81	1700	8.10E-02	1240
	Child (6<11 years)		930	5.54E-02	1810
Apple, pear- Eastern Canada rate	Adults	0.861	1700	1.83E-02	5470
	Child (6<11 years)		930	1.25E-02	7990
Stone fruit	Adults	2.41	1700	5.12E-02	1950
	Child (6<11 years)		930	3.50E-02	2860
Turf - 3 applications (2 dollar spot, 1 brown patch)					
Residential Turf	Adults	0.544[e]	180,000	1.84	54
	Child (1<2 years)		49,000	3.63	28
Golfer	Adults		5,300	0.144	690
	Youth (11<16 years)		4,400	0.168	600
	Child (6<11 years)		2,900	0.197	510

Shaded cells indicate where the MOE is less than the target MOE and risks are not shown to be acceptable.

TPM= thiophanate-methyl; DFR = dislodgeable foliar residue; TTR = turf transferrable residue; TC = transfer coefficient; MOE = margin of exposure

a. DFR = dislodgeable foliar residue. TTR = turf transferrable residues. DFR and TTR values are determined on the last day of application and were calculated using chemical-specific data.

b. TC = transfer coefficient. TCs from the USEPA Residential SOP (2012) were used.

c. Exposure = DFR (µg/cm^2) × TC × duration/Body Weight. Durations for fruit trees were 1 hour for adults and 0.5 hour for children. For residential turf and golfers, durations were 1.5 and 4 hours, respectively, for all sub-populations. Body weights were 80, 57, 32, and 11 kg for adults, youth (11<16 years), children (6<11 years), and children (1<2 years), respectively.

d. Short-term NOAEL of 100 mg/kg bw/day from a dermal rabbit study and target MOE of 300.

e. Peak value was based on 2 dollar spot applications, followed by one brown patch application, with a 7-day application interval. Due to the timing of application, exposure is not expected to occur after snow mould application.

Table 2 CAZ Residential Postapplication Dermal, Non-Cancer Exposure and Risk Assessment

Scenario	Sub-population[a]	DFR/TTR (µg/cm^2)[b]	TC[c] (cm^2/hr)	Exposure[d] (mg/kg bw/day)	Dermal MOE[e] (Target = 1000)
Fruit Trees- 2 apps, 7 days apart					
Apple, pear - BC rate	Adults	0.394 (peak - 14 days)	1700	0.0021	4780

Scenario	Sub-population[a]	DFR/TTR (µg/cm^2)[b]	TC[c] (cm^2/hr)	Exposure[d] (mg/kg bw/day)	Dermal MOE[e] (Target = 1000)
Apple, pear - Eastern Canada rate	Adults	0.076 (peak - 5–14 days)	1700	0.0004	24,700
Stone fruit	Adults	0.213 (peak - 5–14 days)	1700	0.0011	8840
Turf- 3 applications (2 dollar spot, 1 brown patch)					
Residential Turf	Adults	0.0258[f]	180 000	0.022	460
Golfer	Adults		5 300	0.0017	5850
	Youth		4 400	0.0020	5020

Shaded cells indicate where the MOE is less than the target MOE and risks are not shown to be acceptable.
CAZ = carbendazim; DFR = dislodgeable foliar residue; TTR = turf transferrable residue; TC = transfer coefficient; MOE = margin of exposure

a. Although there is potential dermal exposure to children less than 13 years of age, there was no relevant dermal endpoint identified for children. In addition, females aged 13-49 years were considered the most sensitive subpopulation. The risk assessment for females 13-49 would address potential risk for all other subpopulations. Exposure estimates were based on adults 16+ and youth 11<16 years and compared to the toxicology reference value for females 13-49 years.

b. DFR = dislodgeable foliar residue. TTR = turf transferrable residues. Peak carbendazim DFR and TTR residues from the determined using chemical-specific studies. These occurred from day 5-14 after the second application. They were adjusted to the Canadian application rates.

c. TC = transfer coefficient. TCs from the USEPA Residential SOP (2012) were used.

d. Exposure = DFR (µg/cm^2) × dermal absorption (25%) × TC × duration/Body Weight. Duration for fruit trees was 1 hour for adults. For residential turf and golfers, durations were 1.5 and 4 hours, respectively, for all sub-populations. Body weights were 80 and 57 kg for adults and youth respectively.

e. NOAEL of 10 mg/kg bw/day from an oral developmental rat and rabbit studies. Target MOE of 1000.

f. Peak value from the turf study was adjusted for the seasonal cumulative application rate (one brown patch application, and two dollar spot applications). It was assumed that there was no dissipation of carbendazim between applications. This is a conservative assumption as the study is based on two applications.

Table 3 TPM Residential Postapplication Incidental Oral, Non-Cancer Exposure and Risk Assessment for Children (1<2 years old)

Scenario		Hand/Object/Soil Residue[a]	Oral Dose[b] (mg/kg bw/day)	Incidental Oral MOE[c] (Target = 300)
Turf- 3 applications (2 dollar spot, 1 brown patch)				
Residential turf	Hand-to-Mouth	0.800 mg/cm^2	0.013	790
	Object-to-Mouth	0.544 mg/cm^2	0.0023	4400
	Soil Ingestion	28.1 µg/g soil	0.00013	78,000

TPM= thiophanate-methyl; MOE = Margin of exposure

a. Hand residue = Based the dermal postapplication exposure without the body weight/(dermal exposure time (hour) × replenishment intervals (intervals/hr)) × fraction of a.i. on hands compared to body (0.06). Object residue = Turf Transferrable Residue (µg/cm^2). Soil residue = Application rate (kg a.i./ha) × ha/10,000 m^2 × fraction available in the top cm of soil (1) × 1 × 10^9 µg/kg × m^2/10 000 cm^2 × soil volume to weight conversion factor (0.67 cm^3/soil).

b. Oral dose for hands and objects = Hand or object residue (mg/cm^2) × [(fraction of hand mouthed/event (0.13) × Surface Area of one hand (150 cm2)- for hands; or surface area of object mouthed (10 cm2/event)- for object] × (Exposure Time (1.5 hr) × Replenishment Intervals (4/hr)) × (1 – (1 – Saliva Extraction Factor (0.48)) Number events per hour (20 for hands, 8.8 for object)/Replenishment Intervals (4/hr))]/ Body Weight (11 kg).

c. Oral dose for soil ingestion = soil residue (mg/cm^2) × soil ingestion rate (50 mg/day) × g/1 × 10^6 µg]/ Body Weight (11 kg).
d. MOE = NOAEL/Exposure, based on an NOAEL of 10 mg/kg bw/day from oral rabbit developmental study, and a target MOE of 300.

Table 4 CAZ Residential Postapplication Incidental Oral Non-Cancer Exposure and Risk Assessment for Children (1<2 years old)

Scenario		Hand/Object/Soil Residue[a]	Oral Dose[b] (mg/kg bw/day)	Incidental Oral MOE[c] (Target = 1000)
Turf- 3 applications (2 dollar spot, 1 brown patch)				
Residential turf	Hand-to-Mouth	0.038 mg/cm^2	0.0006	33,000
	Object-to-Mouth	0.026 mg/cm^2	0.00011	184,000
	Soil Ingestion	28.1 µg/g soil	0.00013	156,000

CAZ = carbendazim; MOE = Margin of exposure
a. Hand residue = Based the dermal post-application exposure without the body weight/(dermal exposure time (hour) × replenishment intervals (intervals/hr)) × fraction of a.i. on hands compared to body (0.06). Object residue = Turf Transferrable Residue (µg/cm^2). Soil residue = Application rate (kg a.i./ha) × ha/10,000 m^2 × fraction available in the top cm of soil (1) × 1 × 10^9 µg/kg × m^2/10,000 cm^2 × soil volume to weight conversion factor (0.67 cm^3/soil).
b. Oral dose for hands and objects = Hand or object residue (mg/cm^2) × [(fraction of hand mouthed/event (0.13) × Surface Area of one hand (150 cm2)- for hands; or surface area of object mouthed (10 cm2/event)- for object] × (Exposure Time (1.5 hr) × Replenishment Intervals (4/hr)) × (1 – (1 – Saliva Extraction Factor (0.48)) Number events per hour (20 for hands, 8.8 for object)/Replenishment Intervals (4/hr))]/ Body Weight (11 kg).
Oral dose for soil ingestion = soil residue (mg/cm2) × soil ingestion rate (50 mg/day) × g/1 × 106 µg]/ Body Weight (11 kg).
c. MOE = NOAEL/Exposure, based on an NOAEL of 20 mg/kg bw/day from oral developmental studies, and a target MOE of 300.

Table 5 TPM Residential Postapplication Dermal Cancer Risk Assessment

Scenario	Lifestage	TWA DFR/TTR[a] (µg/cm^2)	TC[b] (cm^2/hr)	Exposure Days per Year[c]	LADD[d] (µg/kg bw/day)	Dermal Cancer Risk[e]
Fruit Trees- 2 apps, 7 days apart						
Apple, pear - BC rate	Adults	2.15	1700	3	0.0379	3×10^{-7}
	Youth (11<16 years)		1400	3	0.0017	1×10^{-8}
	Child (6<11 years)		930	3	0.0021	2×10^{-8}
Apple, pear - Eastern Canada rate	Adults	0.236	1700	3	0.0042	3×10^{-8}
	Youth (11<16 years)		1400	3	0.00019	2×10^{-9}
	Child (6<11 years)		930	3	0.00023	2×10^{-9}
Stone fruit	Adults	0.660	1700	3	0.012	9×10^{-8}
	Youth (11<16 years)		1400	3	0.00053	4×10^{-9}
	Child (6<11 years)		930	3	0.00063	5×10^{-9}
Turf- 3 applications (2 dollar spot, 1 brown patch)						
Residential Turf	Adults	0.111[f]	180,000	30	6.24	5×10^{-5}

Scenario	Lifestage	TWA DFR/TTR[a] (µg/cm^2)	TC[b] (cm^2/hr)	Exposure Days per Year[c]	LADD[d] (µg/kg bw/day)	Dermal Cancer Risk[e]
	Youth (11<16 years)		148,000	30	0.496	4×10^{-6}
	Child (1<2 years)		49,000	30	0.981	8×10^{-6}
Golfer	Adults		2800	5	0.0432	3×10^{-7}
	Youth (11<16 years)		2300	5	0.00395	3×10^{-8}
	Child (6<11 years)		1500	5	0.00459	3×10^{-8}

Shaded cells indicate where the cancer risk is above the threshold of 1×10^{-6} and risks are not shown to be acceptable.
TPM = thiophanate-methyl; TC = transfer coefficient; DFR = dislodgeable foliar residue; TTR = turf transferrable residue; TWA = time-weighted average; LADD = Lifetime average daily dose

a. Time-weighted average DFR/TTR from chemical-specific studies. Residues were averaged over the 30 days following the last of 2 applications in the study. Residues were adjusted to the Canadian application rate.
b. Transfer coefficient values and daily durations refined to the 50th percentile from the USEPA Residential SOPs (2012a) were used when available.
c. The default of 30 exposure days per year was used for residential turf. The number of days exposed for fruit trees and golfing was used for TPM in the previous assessment (REV2007-14 and/or PRVD2011-07).
d. LADD = lifetime average daily dose = [DFR/TTR × duration (hrs/day) × TC × exposure days × lifestage duration (63 years as an adult, 5 years as a youth, 5 years as a child)]/[body weight × 365 days/year × lifetime (78 years)]. Durations for fruit trees were 0.5 hrs for adults, 0.25 hrs for children 6<11 and youth; residential turf were 1.5 hrs for adults and children 1<2 and 1.3 hrs for youth; and for golfers was 4 hrs for all sub-populations. Body weights are 80, 57, 32, 11 kg for adults, youth, and children (6<11) and children (1<2), respectively.
e. Cancer risk = LADD × q_1*. Thiophanate-methyl q_1* is $(7.96 \times 10^{-3}$ mg/kg bw/day$)^{-1}$.
f. The time-weighted average from the TTR study was adjusted by the average rate across the three seasonal applications of thiophanate-methyl (excluding snow mould). The average rate was determined based on one seasonal application for brown patch and two seasonal applications of dollar spot.

Table 6 CAZ Residential Dermal Postapplication Cancer Risk Assessment

Scenario	Lifestage	TWA DFR/TTR[a] (µg/cm^2)	TC[b] (cm^2/hr)	Exposure Days per Year[c]	LADD[d] (µg/kg bw/day)	Dermal Cancer Risk[e]
Fruit Trees- 2 apps, 7 days apart						
Apple, pear - BC rate	Adults	0.244	1700	3	0.0043	5×10^{-9}
	Youth (11<16 years)		1400	3	0.00020	2×10^{-10}
	Child (6<11 years)		930	3	0.00023	3×10^{-10}
Apple, pear - Eastern Canada rate	Adults	0.0619	1700	3	0.0011	1×10^{-9}
	Youth (11<16 years)		1400	3	0.00005	5×10^{-11}
	Child (6<11 years)		930	3	0.000059	6×10^{-11}
Stone fruit	Adults	0.173	1700	3	0.0031	3×10^{-9}
	Youth (11<16 years)		1400	3	0.00014	2×10^{-10}
	Child (6<11 years)		930	3	0.00017	2×10^{-10}
Turf- 3 applications (2 dollar spot, 1 brown patch)						
Residential Turf	Adults	0.0086[f]	180 000	30	0.48	5×10^{-7}

Scenario	Lifestage	TWA DFR/TTR[a] (µg/cm^2)	TC[b] (cm^2/hr)	Exposure Days per Year[c]	LADD[d] (µg/kg bw/day)	Dermal Cancer Risk[e]
	Youth (11<16 years)		148 000	30	0.038	4×10^{-8}
	Child (1<2 years)		49 000	30	0.076	8×10^{-8}
Golfer	Adults		2800	5	0.0033	4×10^{-9}
	Youth (11<16 years)		2300	5	0.00030	3×10^{-10}
	Child (6<11 years)		1500	5	0.00035	4×10^{-10}

Shaded cells indicate where the cancer risk is above the threshold of 1×10^{-6} and risks are not shown to be acceptable.
TPM = thiophanate-methyl; TC = transfer coefficient; DFR = dislodgeable foliar residue; TTR= turf transferrable residue; TWA = time-weighted average; LADD = Lifetime average daily dose

a. Time-weighted average DFR/TTR from chemical-specific studies. Residues were averaged over the 30 days following the last of 2 applications in the study for tree fruit, as the apple DFR study review reported all monitored values. For turf, the peak residue value from the study was used; this is considered to be a conservative assumption. Residues were adjusted to the Canadian application rate.

b. Transfer coefficient values and daily durations refined to the 50th percentile from the USEPA Residential SOPs (2012a) were used when available.

c. The default of 30 exposure days per year was used for residential turf. The number of days exposed for fruit trees and golfing was used for TPM in the previous assessment (REV2007-14 and/or PRVD2011-07).

d. LADD = lifetime average daily dose = [DFR/TTR × duration (hrs/day) × TC × dermal absorption (25%) × exposure days × lifestage duration (63 years as an adult, 5 years as a youth, 5 years as a child)]/[body weight × 365 days/year × lifetime (78 years)]. Durations for fruit trees were 0.5 hrs for adults, 0.25 hrs for children 6<11 and youth; residential turf were 1.5 hrs for adults and children 1<2 and 1.3 hrs for youth; and for golfers was 4 hrs for all sub-populations. Body weights are 80, 57, 32, 11 kg for adults, youth, and children (6<11) and children (1<2), respectively.

e. Cancer risk = LADD × q_1*. Carbendazim q_1* is $(1.09 \times 10^{-3}$ mg/kg bw/day$)^{-1}$.

f. The peak residue value from the TTR study was adjusted by the average rate across the three seasonal applications of thiophanate-methyl (excluding snow mould). The average rate was determined based on one seasonal application for brown patch and two seasonal applications of dollar spot.

Table 7 TPM and CAZ Combined (Dermal and Oral) Postapplication Cancer Risk Assessment

Scenario	Lifestage[a]	TPM			CAZ		
		Dermal Cancer Risk[b]	Incidental Oral Cancer Risk[c]	Lifetime Cancer Risk[d]	Dermal Cancer Risk[b]	Incidental Oral Cancer Risk[c]	Lifetime Cancer Risk[d]
Fruit Trees - 2 apps, 7 days apart							
Apple, pear - BC rate	Adults	3×10^{-7}	N/A	3×10^{-7}	5×10^{-9}	N/A	5×10^{-9}
	Youth (11<16 years)	1×10^{-8}			2×10^{-10}		
	Child (6<11 years)	2×10^{-8}			3×10^{-10}		
Apple, pear - Eastern Canada rate	Adults	3 × 10-8		4×10^{-8}	1×10^{-9}		1×10^{-9}
	Youth (11<16 years)	2 × 10-9			5×10^{-11}		
	Child (6<11 years)	2 × 10-9			6×10^{-11}		
Stone fruit	Adults	9 × 10-8		1×10^{-7}	3×10^{-9}		4×10^{-9}
	Youth (11<16 years)	4 × 10-9			2×10^{-10}		

Scenario	Lifestage[a]	TPM			CAZ		
		Dermal Cancer Risk[b]	Incidental Oral Cancer Risk[c]	Lifetime Cancer Risk[d]	Dermal Cancer Risk[b]	Incidental Oral Cancer Risk[c]	Lifetime Cancer Risk[d]
	Child (6<11 years)	5 × 10-9			2×10^{-10}		
Turf - 3 applications (2 dollar spot, 1 brown patch)							
Residential Turf	Adults	5×10^{-5}	N/A	6×10^{-5}	5×10^{-7}	N/A	6×10^{-7}
	Youth (11<16 years)	4×10^{-6}			4×10^{-8}		
	Child (1<2 years)	8×10^{-6}	8×10^{-8}		8×10^{-8}	9×10^{-10}	
Golfer	Adults	3×10^{-7}	N/A	4×10^{-7}	4×10^{-9}	N/A	4×10^{-9}
	Youth (11<16 years)	3×10^{-8}			3×10^{-10}		
	Child (6<11 years)	4×10^{-8}			4×10^{-10}		

Shaded cells indicate where the cancer risk is above the threshold of 1×10^{-6} and risks are not shown to be acceptable.
TPM = thiophanate-methyl; CAZ = carbendazim

a. For some scenarios, youth were not included in the non-cancer risk assessment, but were included in the cancer risk assessment to calculate a lifetime cancer risk.
b. Values are from Table 5 for thiophanate-methyl and Table 6 for carbendazim
c. Based on the hand-to-mouth scenario for children (1<2 years old).
d. All dermal and applicable incidental oral cancer risks were summed to determine a lifetime cancer risk. In addition, lifetime cancer risk was determined assuming lifestage durations of 63 years as an adult, 5 years as a youth and 5 years as a child.

Appendix IX Aggregate and Cumulative Assessment

Table 1 Residential Aggregate Non-Cancer Exposure and Risk Assessment for TPM

Scenario	Sub-population	Residential Dermal MOE[a]	Dietary Exposure[b] (mg/kg bw/day)	Oral MOE[c] (Target = 300)	Aggregate MOE[d] (Target = 3000)
Fruit Trees - 2 apps, 7 days apart					
Apple, pear- BC rate	Adults	1240	0.000033	303 000	1230
	Child (6<11 years)	1810	0.000060	167 000	1790
Apple, pear- Eastern Canada rate	Adults	5470	0.000033	303 000	5370
	Child (6<11 years)	7990	0.000060	167 000	7630
Stone fruit	Adults	1950	0.000033	303 000	1960
	Child (6<11 years)	2860	0.000060	167 000	2810
Turf - 3 applications (2 dollar spot, 1 brown patch)					
Residential Turf	Adults	Residential postapplication scenarios did not reach the target MOE for all sub-populations and therefore aggregate risk not assessed.			
	Child (1<2 years)				
Golfer	Adults	693	0.000033	303 000	692
	Youth (11<16 years)	595	0.000034	294 000	594
	Child (6<11 years)	507	0.000060	167 000	506

TPM= thiophanate-methyl; MOE = margin of exposure

a. Dermal MOEs from Residential assessment (see Table 1). Based on a NOAEL of 100 mg/kg bw/day from a 21-day dermal rabbit study.

b. Background chronic dietary exposure.

c. MOE = NOAEL/exposure. Based on a NOAEL of 10 mg/kg bw/day from an oral rabbit developmental toxicity study. Target MOE of 300.

d. Aggregate MOE = 1/[(1/dermal MOE)=(1/oral MOE). Target MOE = 300, as this is the target for both the dermal and oral risk assessments.

Table 2 Residential Aggregate Non-Cancer Exposure and Risk Assessment for CAZ

Scenario	Sub-population[a]	Residential Dermal Exposure[b] (mg/kg bw/day)	Dietary Exposure[c] (mg/kg bw/day)	Aggregate MOE[d] Target = 1000
Fruit Trees- 2 apps, 7 days apart				
Apple, pear - BC rate	Adults	0.0021	0.000440	3940
Apple, pear - Eastern Canada rate	Adults	0.0004	0.000440	11 800
Stone fruit	Adults	0.0011	0.000440	6350
Turf - 3 applications (2 dollar spot, 1 brown patch)				
Residential Turf	Residential postapplication scenarios did not reach the target MOE for all sub-populations and therefore aggregate risk not assessed.			

Golfer	Adults	0.0017	0.000440	4650
	Youth	0.0020	0.000321	4320

CAZ = carbendazim; MOE = margin of exposure.

a. Although there is potential dermal exposure to carbendazim for children less than 13 years of age, there was no relevant dermal endpoint identified for children. In addition, females aged 13-49 years were considered the most sensitive subpopulation. The risk assessment for females aged 13-49 years would address potential aggregate risk for all subpopulations. Therefore aggregate risk was determined for adults 16 years and older and youth 11-16 years only.

b. Dermal exposure from Table 2. Dermal exposure were determined for adults 16+ and youth aged 11<16 years. Based on body surface area and body weights dermal exposures are similar for males and females.

c. Background chronic dietary exposure. For adults, chronic dietary exposure based on females aged 13-49 years. For youth aged 11<16 years, chronic dietary exposure based on females aged 11<16 years.

d. MOE = NOAEL/(dermal exposure + dietary exposure). Based on a NOAEL of 10 mg/kg bw/day from an oral rabbit developmental toxicity study. Target MOE of 1000.

Table 3 Aggregate and Cumulative Cancer Risk Assessment for TPM and CAZ

Scenario	TPM			CAZ			TPM + CAZ
	Lifetime Cancer Risk			Lifetime Cancer Risk			Cumulative Lifetime Cancer Risk[d]
	Residential[a]	Dietary[b]	Aggregate[c]	Residential[a]	Dietary[b]	Aggregate[c]	
Fruit Trees- 2 apps, 7 days apart							
Apple, pear - BC rate	3×10^{-7}	2×10^{-7}	6×10^{-7}	5×10^{-9}	3×10^{-7}	3×10^{-7}	9×10^{-7}
Apple, pear - Eastern Canada rate	4×10^{-8}		3×10^{-7}	1×10^{-9}		3×10^{-7}	6×10^{-7}
Stone fruit	1×10^{-7}		3×10^{-7}	4×10^{-9}		3×10^{-7}	7×10^{-7}
Turf- 3 applications (2 dollar spot, 1 brown patch)							
Golfer	4×10^{-7}	2×10^{-7}	7×10^{-7}	4×10^{-9}	3×10^{-7}	3×10^{-7}	1×10^{-6}

TPM = thiophanate-methyl; CAZ = carbendazim

a. Lifetime cancer risk from residential uses. See Table 7 of this Appendix.

b. Lifetime cancer risk from dietary exposure (food and drinking water). See Table 4, Appendix IV.

c. Aggregate lifetime cancer risk from both residential and dietary exposure. Sum of residential and dietary cancer risks.

d. Cumulative lifetime cancer risk is the sum of aggregate cancer risks from both thiophanate-methyl and carbendazim.

Appendix X Environmental Assessment

Table 1 Aerobic Soil Biotransformation Half-lives for Thiophanate-methyl and Carbendazim

Soil Type	pH	DT_{50} (d)[1]	DT_{90} (d)	Model	Comments / Persistence Classification[2] (Reference, PMRA#)
Thiophanate-methyl					
Clay loam soil	7.2	< 1	< 1	Not reported	Major transformation product, Carbendazim: found at 38–83% of applied thiophanate-methyl within the first three weeks of the study. After 12 months, carbendazim was found at 22% (clay loam), 36% (sandy loam, pH 5.7) and 1% (sandy loam, pH 7.5). Bound residues increased with time to a maximum of 76% after 12 months in pH 7.5 soil. Non-persistent (1530457)
Sandy loam soil	5.7	< 1	< 1		
Sandy loam soil	7.5	< 1	< 1		
Silt loam soil	NR	0.61 d (n=3) (0.48 – 0.74 d)	25.7% (120 d)	Not reported	Mean DT_{50}, 0.61 d (n=3). Non-extractable residues after 100 days were 40 to 73% for all three soil types. Carbendazim was 63 to 76% of applied parent after 3-7 days. This study reports DT_{50}s for carbendazim of 39.8 days (range of 23.1 to 57.8 days) when thiophanate-methyl is the starting material. These data are included below for carbendazim. Non-persistent (2952361)
Clay loam soil	NR		7.6% (120 d)		
Sandy loam soil	NR		7.3% (120 d)		
Carbendazim					
Keyport silt loam	6.5	272	902	SFO	The starting material for this study was benomyl which degraded quickly (half-life < 19 hours) to carbendazim. The registrant-calculated half-life for carbendazim was > 320 days. Persistent (2952339)
Sand 1 Standardboden I	6.8	37	123	SFO	Slightly persistent (2952340)
Loamy Sand Standardboden II	5.2	44	146	SFO	
Sand 2 Neuhofen	6.8	36	118	SFO	Slightly persistent (2952340)
Schwan-heimer Sand (SS2.2)	4.7	26.7	100	SFO	Slightly persistent (2952340)
Silt loam	NA	57.8	NA	SFO	Slightly persistent (2952361)
Clay loam	NA	23.1	NA	SFO	
Sandy Loam	NA	38.5	NA	SFO	

1. The degradation half-lives were corrected to FOCUS reference moisture conditions at 10 kPa and 20 °C. Note: The 80th percentile of all eight DT_{50} values is 52.3 days, and this value was used for determining modelled EECs in water.
2. Persistence classification based on Goring et al. 1975.

NR = not reported
NA = not available
SFO = single first order

Table 2 Environmental Toxicity of Thiophanate-methyl and Carbendazim to Terrestrial Organisms

Organism	Study type	Species	Endpoint		Value	Comments	Reference (PMRA#)
Terrestrial Species							
Invertebrate	Acute	Honey bee (*Apis mellifera*)	TPM	48-h LD_{50} (contact)	> 100 µg a.i./bee	Relatively nontoxic	1530457
		Honey bee (*Apis mellifera*)	Topsin M 500 SC	LD_{50} (contact)	114.7 µg a.i./bee	Relatively nontoxic	2952341
		Honey bee (*Apis mellifera*)	TPM	10 d-LD_{50}	> 48.3 µg a.i./bee/day	Mortality	2952341
		Earthworm (*Eisenia fetida*)	TPM	14-d EC_{50}	162 mg a.i./kg soil	Mortality	1530417
				NOEC	0.60 kg a.i./ha	Reproduction	1530416, 1530417
			CAZ	LOEC	0.15 kg CAZ/ha	Reduction in body weight gain	
	Contact (glass plate)	Predatory mite, *Typhlodromus pyri*	Topsin M 500 SC	LR_{50}	> 1575 g a.i./ha	Mortality	2952341
				ER_{50}	> 1575 g a.i./ha	Reproduction	
	Contact (glass plate)	Parasitic wasp, *Aphidius rhopalosiphi*	Topsin M 500 SC	LR_{50}	> 1500 g a.i./ha	Mortality	2952341
				ER_{50}	175-525 g a.i/ha	Reproduction	
	Extended laboratory (barley plants)	Parasitic wasp, *Aphidius rhopalosiphi*	Topsin M 500 SC	48h-LR_{50}/ER_{50}	> 1500 g a.i./ha	Mortality and reproduction	2952341
Birds	Acute oral	Bobwhite quail (*Colinus virginianus*)	TPM	LD_{50}	> 4640 mg a.i./kg bw	Practically nontoxic	1530457
		Mallard duck (*Anas platyrhynchos*)	TPM	LD_{50}	> 4640 mg a.i./kg bw	Practically nontoxic	1530457
			CAZ	LD_{50}	> 2250 mg CAZ/kg bw/day	Practically nontoxic	2952341
	5-day dietary	Bobwhite quail (*Colinus virginianus*)	TPM	LC_{50}	> 10 000 mg a.i./kg diet equivalent to LD_{50} > 1061.8 mg a.i./kg bw/day[1]	Practically nontoxic	1530457
		Mallard duck (*Anas platyrhynchos*)	TPM	LC_{50}	> 10 000 mg a.i./kg diet equivalent to LD_{50} > 565.6 mg a.i./kg bw/day[1]	Practically nontoxic.	1530457
			CAZ	LD_{50}	LD_{50} 615 mg CAZ/kg bw/day	Moderately toxic	2952341
	Reproduction	Bobwhite quail (*Colinus virginianus*)	TPM	NOEC	> 500 mg a.i./kg diet equivalent to	No effects	1530457

Organism	Study type	Species	Endpoint		Value	Comments	Reference (PMRA#)
					NOEL >53.1 mg a.i./kg bw/day[2]		
			TPM	NOAEL	9.1 mg a.i./kg bw/day	-	2952341
		Mallard duck (*Anas platyrhynchos*)	TPM	NOEC	103 mg a.i./kg diet equivalent to NOEL of 5.83 mg a.i./kg bw/day[1]	Effects on eggs and body weight	1530457
				NOAEL	9.7 mg a.i./kg bw/day	-	2952341
			CAZ	NOEL	26.4 mg CAZ/kg bw/day	-	2952341
Mammals	Acute oral	Rat (*Rattus norvegicus*)	LD_{50}		> 5 000 mg a.i./kg bw	Practically nontoxic	1085860
		Rat (*Rattus norvegicus*)	LD_{50}		6640 mg a.i./kg bw (females)	Practically nontoxic	963010
	Two-generation reproduction (dietary exposure)	Rat (*Rattus norvegicus*)	$NOEC_{offspring\ toxicity}$		200 mg a.i./kg diet equivalent to $NOEL_{offspring\ toxicity}$ = 16 mg a.i./kg bw/day	Reductions in body weight of F_{2b} pups	1085872, 1085873
Terrestrial plants	Vegetative vigour	Cabbage, corn, cucumber, lettuce, oat, onion, radish, ryegrass, tomato, soybean (4 monocots, 6 dicots)	ER_{50}		> 1570 g a.i./ha	No effects	2952341
	Seedling emergence		ER_{50}		> 1680 g a.i./ha	No effects	2952341

TPM: thiophanate-methyl, CAZ: carbendazim superscript

1. The 5-d LD_{50s} and the NOEL were calculated using default adult mallard body weight (1082 g) and food ingestion rate (61.2 g dw food/day- FIR (g dry weight/day) = 0.648(BW in g)$^{0.651}$).
2. The NOEL was calculated using default adult bobwhite quail body weight (178 g) and food ingestion rate (18.9 g dw food/day - FIR (g dry weight/day) = 0.648(BW in g)$^{0.651}$)

Table 3 Environmental Toxicity of Thiophanate-methyl and Carbendazim to Aquatic Organisms

Organism	Study type	Species	Endpoint		Value	Comments [1]	Reference (PMRA#)
Freshwater							
Invertebrate	Acute	*Daphnia magna*	TPM	48-h LC_{50}	5.4 mg a.i./L	Moderately toxic	1530457
			CAZ	48-h LC_{50}	5.4 mg CAZ/L	Moderately toxic	1530457
			CAZ	48-h LC_{50}	0.15 mg CAZ/L	Highly toxic	2952341
	Chronic (life-cycle; semi-static	*Daphnia magna*	CAZ	21-d NOEC	0.003 mg CAZ/L	Survival	1530457
			TOPSI	21-d	0.0177 mg	Cumulative	1530460

Organism	Study type	Species	Endpoint		Value	Comments [1]	Reference (PMRA#)
	exposure)		N M WDG (CAZ)	NOEC	CAZ/L	number of offspring	
			CAZ	21-d NOEC	0.0015 mg CAZ/L	Reproduction	2952341
			TPM	21-d NOEC	0.16 mg a.i./L	-	2952341
Fish	Acute	Rainbow trout (*Oncorhynchus mykiss*)	TPM	96-h LC_{50}	8.3 mg a.i./L	Moderately toxic	1530457
		Bluegill sunfish (*Lepomis macrochirus*)	TPM	96-h LC_{50}	> 41 mg a.i./L	Slightly toxic	1530457
		Channel Catfish (*Ictalurus punctatus*)	CAZ	96-h LC_{50}	0.019 mg CAZ/L	Very highly toxic	2952341
		Rainbow trout (*Oncorhynchus mykiss*)	CAZ	96-h LC_{50}	0.54 mg CAZ/L[2]	Highly toxic	2952341
		Bluegill sunfish (*Lepomis macrochirus*)	CAZ	96-h LC_{50}	> 3.2 mg CAZ/L	Moderately toxic	2952341
		Common carp *(Cyprinus carpio)*	CAZ	96-h LC_{50}	0.44 mg CAZ/L	Highly toxic	2952341
		Brown trout (*Salmo trutta*)	CAZ	96-h LC_{50}	0.39 mg CAZ/L	Highly toxic	2960522
		Assessment endpoint for freshwater fish species, SSD (n=5)	CAZ	HC_5	0.013 mg CAZ/L	Very highly toxic	Calculated[3]
	Early Life Stage (flow-through exposure)	Rainbow trout (*Oncorhynchus mykiss*)	TPM	28-d NOEC	0.32 mg a.i./L	Mortality, lethargy and loss of equilibrium	1530423
	Early Life Stage (flow-through exposure)	Channel Catfish (*Ictalurus punctatus*)	CAZ	NOEC	0.002 mg CAZ/L	Larval survival	1530457
Amphibian	Acute	Green pond frog (*Rana hexadactyla*) - tadpole	Bavistin (50% CAZ)	96-h LC_{50}	16.02 mg CAZ/L	Slightly toxic	2960522
		African clawed frog (*Xenopus laevis*) - embryo	CAZ	LC_{50}	1.072 mg CAZ/L	Moderately toxic	2959051
				NOEC	0.191 mg CAZ/L	Body length, neurotoxicity	
Vascular aquatic plants		Duckweed (*Lemna gibba*)	TPM	EC_{50}	> 4.7 mg a.i./L	-	1530457
Algae	Acute	Green algae (*Selenastrum capricornutum)*	TPM	EC_{50}	> 0.95 mg a.i./L	-	1530457
		Blue-green algae (*Anabaena flos-aquae*)	TPM	EC_{50}	> 4.3 mg a.i./L	-	1530457
		Freshwater diatom	TPM	EC_{50}	0.93 mg	-	1530457

Organism	Study type	Species	Endpoint		Value	Comments [1]	Reference (PMRA#)
		(*Navicula pelliculosa*)			a.i./L		
Marine Organisms							
Estuarine/ marine fish	Acute	Sheepshead minnow (*Cyprinodon variegatus*)	TPM	96-h LC_{50}	40 mg a.i./L	Slightly toxic	1530457
Estuarine/ marine invertebrates	Acute	Eastern Oyster (*Crassostrea virginica*)	TPM	96-hr LC_{50}	2.2 mg a.i./L	Moderately toxic	1530457
	Acute	Mysid Shrimp (*Americamysis bahia*)	TPM	96-hr LC_{50}	1.1 mg a.i./L	Moderately toxic	1530457
	Chronic (life-cycle)	Mysid Shrimp (*Americamysis bahia)*	CAZ	NOEC	0.025 mg a.i./L	Survival	1530457
Algae	Acute	Marine diatom (*Skeletonema costatum*)	TPM	EC_{50}	1.7 mg a.i./L	-	1530457

1. USEPA classification, where applicable.
2. Geomean value from five tests on *O. mykiss*. The LC_{50} values ranged from 1.19 – 0.98 mg/L for this species.
3. The SSD was calculated using ETX 2.2 software and the following endpoints:
   - Channel catfish (*Ictalurus punctatus*) 96-hr LC_{50} = 0.019 mg CAZ/L
   - Brown trout (*Salmo trutta*) 96-hr LC_{50} = 0.39 mg CAZ/L
   - Common carp (*Cyprinus carpio*) 96-hr LC_{50} = 0.44 mg CAZ/L
   - Rainbow trout (*Oncorhynchus mykiss*) 96-hr LC_{50} = 0.54 mg CAZ/L
   - Bluegill sunfish (*Lepomis macrochirus*) 96-hr LC_{50} = >3.2 mg CAZ/L

Table 4 Earthworm Acute Risk Assessment for Thiophanate-methyl (TPM)

Appl. Rate × No. Appl. (kg a.i./ha)	Cum Appl. Rate kg (a.i./ha)	EEC (mg a.i./kg soil)	RQ = EEC/0.5 × EC_{50}	LOC exceeded (RQ=1)
Sugarbeet (0.392 × 2 at a 14-day interval)	0.392	0.174	< 0.1	No
Raspberry/strawberry (0.77 × 2 at a 7-day interval)	0.776	0.345	< 0.1	No
Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	12.283	5.459	< 0.1	No
Half-life of TPM in soil = 1 d. TPM 0.5 × EC_{50} = 81 mg a.i./kg soil. (PMRA# 1530417)				

Table 5 Earthworm Chronic Risk Assessment for Thiophanate-methyl (TPM) and Carbendazim (CAZ)

Organism	Appl. Rate × No. Appl. (kg a.i./ha)	Endpoint value	EEC	RQ	LOC exceeded (RQ=1)
Thiophanate-methyl					
Earthworm, *Eisenia fetida*	Sugarbeet (0.392 × 2 at a 14-day interval)	NOEC: 0.6 kg a.i./ha	In-field: 0.392 kg a.i./ha	0.7	No
			Off-field (0.392 kg a.i./ha × 6% drift[1]): 0.024 kg a.i./ha	< 0.1	No

Organism	Appl. Rate × No. Appl. (kg a.i./ha)	Endpoint value	EEC	RQ	LOC exceeded (RQ=1)
	Raspberry/ Strawberry (0.770 × 2 at a 7-day interval)	NOEC: 0.6 kg a.i./ha	In-field: 0.776 kg a.i./ha	1.3	Yes
			Off-field (0.776 kg a.i./ha × 6% drift[1]): 0.047 kg a.i./ha	< 0.1	No
			Off-field (0.776 kg a.i./ha × 74% drift[2]): 0.57 kg a.i./ha	0.95	No
			Off-field (0.776 kg a.i./ha × 59% drift[3]): 0.46 kg a.i./ha	0.77	No
	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	NOEC: 0.6 kg a.i./ha	In-field: 12.283 kg a.i./ha	20.5	Yes
			Off-field (12.283 kg a.i./ha × 6% drift[1]): 0.74 kg a.i./ha	1.2	Yes
Carbendazim					
Earthworm, *Eisenia fetida*	Sugarbeet (0.181 CAZ × 2 at a 14-day interval)	LOEC: 0.15 kg CAZ/ha	In-field: 0.331 kg CAZ/ha	2.2	Yes
			Off-field (0.331 kg CAZ/ha × 6% drift[1]): 0.02 kg CAZ/ha	0.13	No
	Raspberry/ Strawberry (0.355 CAZ × 2 at a 7-day interval)	LOEC: 0.15 kg CAZ/ha	In-field: 0.679 kg CAZ/ha	4.5	Yes
			Off-field (0.679 kg CAZ/ha × 6% drift[1]): 0.04 kg CAZ/ha	0.27	No
			Off-field (0.679 kg CAZ/ha × 74% drift[2]): 0.5 kg CAZ/ha	3.3	Yes
			Off-field (0.679 kg CAZ/ha × 59% drift[3]): 0.4 kg CAZ/ha	2.7	Yes
	Turf (1.938 CAZ × 2 + 5.653 CAZ × 1 at 7-day intervals)	LOEC: 0.15 kg CAZ/ha	In-field: 9.029 kg CAZ/ha	60.2	Yes
			Off-field (9.029 kg CAZ/ha × 6% drift[1]): 0.54 kg CAZ/ha	3.6	Yes

1. 6% drift from field sprayer application using minimum spray droplet size of 'medium'.
2. 74% drift from early season airblast application.
3. 59% drift from late season airblast application.

Table 6 Foliar Application: In-field and Off-field Exposure of Thiophanate-methyl on Plant Surfaces After Application at Highest Single Foliar Application Rate

Foliar Application Method	Drift Deposition Adjustment Factor (%)	Highest In-field Single Application Rate (g a.i./ha)	Maximum Off-field Spray Drift (g a.i./ha)
Aerial	26	50	13
Airblast (Early Season)	74	1575	1166
Airblast (Late Season)	59	1575	929
Ground Field Sprayer	11	12 250	1348

Table 7 Foliar Application: Acute Contact Risk to Bees Based on Screening Level Exposure Estimates for Thiophanate-methyl

Application Rate (EEC) (kg a.i./ha)	Koch and Weiber (adjustment factor) (µg a.i./bee per kg a.i./ha)	Exposure Estimate for Bees* (µg a.i./bee/day	Toxicity Endpoint µg a.i./bee/day)	RQ**	LOC exceeded
12.25	2.4	29.4	LD_{50}: > 100	< 0.29	No
*Exposure estimate for bees= application rate (kg a.i./ha) × adjustment factor **Exposure estimate for bees/toxicity endpoint Note: LOC for bee is set at 0.4.					

Table 8 Foliar Application: Acute and Chronic Dietary Risk to Adult Bees Based on Screening Level Exposure Estimates for Thiophanate-methyl

Application Rate (kg a.i./ha)	Adjustment Factor (µg a.i./bee per kg a.i./ha)	Exposure Estimate for Bees*(µg a.i./bee/day)	Toxicity Endpoint (µg a.i./bee/day)	RQ**	LOC exceeded
Adults (Acute)					
0.77	28.6	22	LD_{50}: 114.7	0.2	no
1.575	28.6	45	LD_{50}: 114.7	0.4	no
2.1	28.6	60	LD_{50}: 114.7	0.5	yes
12.25	28.6	351	LD_{50}: 114.7	3.1	yes
Adults (Chronic)					
0.77	28.6	22	LD_{50}: > 48.3	< 0.5	no
1.575	28.6	45	LD_{50}: > 48.3	< 0.9	no
2.1	28.6	60	LD_{50}: > 48.3	< 1.2	yes
12.25	28.6	351	LD_{50}: > 48.3	< 7.3	yes

*Exposure estimate for bees = application rate (kg a.i./ha) × adjustment factor (28.6 µg a.i./bee per kg a.i./ha for adults)
**Exposure estimate for bees/toxicity endpoint
Note: LOC for bees is set at 0.4 for acute endpoints and 1.0 for chronic endpoints.

Table 9 Foliar Application: Acute and Chronic Risk (Contact and/or Oral) to Bees From Spray Drift Based on Screening Level Exposure to Thiophanate-methyl

Bee Stage	Exposure	Adjustment Factor	Exposure Estimate for Bees * (µg a.i./bee/day)	Toxicity Endpoint (µg a.i./bee/day)	RQ**	LOC exceeded
Aerial Spray (26% drift): 0.013 kg a.i./ha (maximum off-field spray drift)						
Adult	Acute contact	2.4	0.0312	LD_{50}: > 100	<0.1	no
	Acute oral	28.6	0.372	LD_{50}: 114.7	<0.1	no
	Chronic oral	28.6	0.372	LD_{50}: > 48.3	<0.1	no
Airblast - early season (74% drift): 0.1166 kg a.i./ha(maximum off-field spray drift)						
Adult	Acute contact	2.4	0.28	LD_{50}: > 100	<0.1	no
	Acute oral	28.6	3.34	LD_{50}: 114.7	<0.1	no
	Chronic oral	28.6	3.34	LD_{50}: > 48.3	<0.1	no
Airblast - late season (59% drift): 0.0929 kg a.i./ha(maximum off-field spray drift)						
Adult	Acute contact	2.4	0.22	LD_{50}: > 100	<0.1	no
	Acute oral	28.6	2.66	LD_{50}: 114.7	<0.1	no
	Chronic oral	28.6	2.66	LD_{50}: > 48.3	<0.1	no
Ground Field Spray (11% drift): 0.0385 kg a.i./ha(maximum off-field spray drift)						
Adult	Acute contact	2.4	0.32	LD_{50}: > 100	<0.1	no
	Acute oral	28.6	3.86	LD_{50}: 114.7	<0.1	no
	Chronic oral	28.6	3.86	LD_{50}: > 48.3	<0.1	no

*Exposure estimate for bees = application rate (kg a.i./ha) × adjustment factor (µg a.i./bee per kg a.i./ha)
**Exposure estimate for bees/toxicity endpoint
Note: LOC for bees is set at 0.4 for acute endpoints and 1.0 for chronic endpoints.

Table 10 Seed Treatment: Acute and Chronic Dietary Risk to Adult Bees Based on Screening Level Exposure Estimates for Thiophanate-methyl

Exposure	EEC (µg a.i./g)	Exposure Estimate for Bees* (µg a.i./bee/day)	Toxicity Endpoint (µg a.i./bee/day)	RQ**	LOC exceeded
Adult acute oral	1	0.292	LD_{50}: 114.7	<0.1	no
Adult chronic oral	1	0.292	LD_{50}: > 48.3	<0.1	no
*Exposure Estimate for bees=0.292 × EEC for adults **Exposure estimate for bees/toxicity endpoint Note: LOC for bee is set at 0.4 for acute endpoints and 1 for chronic endpoints.					

Table 11 Soil Applications: Acute and Chronic Dietary Risk to Bees Based on Screening Level Exposure Estimates for Thiophanate-methyl

Application Rate kg a.i./ha	Briggs EEC µg a.i./g	Exposure Estimate for Bees* µg a.i./bee/day	Toxicity Endpoint (µg a.i./bee/day)	RQ**	LOC exceeded
Adults (Acute)					
0.0595	0.025	0.007	LD_{50}: 114.7	< 0.1	no
1.785	0.752	0.220	LD_{50}: 114.7	< 0.1	no
Adults (Chronic)					
0.0595	0.025	0.007	LD_{50}: > 48.3	< 0.1	no
1.785	0.752	0.220	LD_{50}: > 48.3	< 0.1	no
*Exposure estimate for bees=0.292 × Briggs EEC for adults **Exposure estimate for bees/toxicity endpoint Note: LOC for bee is set at 0.4 for acute endpoints and 1 for chronic endpoints. K_{oc} value = 71					

Table 12 Soil Applications: Acute and Chronic Dietary Risk to Bees Based on Screening Level Exposure Estimates for Thiophanate-methyl

Application Rate (kg a.i./ha)	Briggs EEC (µg a.i./g)	Exposure Estimate for Bees* (µg a.i./bee/day)	Toxicity Endpoint (µg a.i./bee/day)	RQ**	LOC exceeded
Adults (Acute)					
0.0595	0.004	0.001	LD_{50}: 114.7	< 0.1	no
1.785	0.130	0.038	LD_{50}: 114.7	< 0.1	no
Adults (Chronic)					
0.0595	0.004	0.001	LD_{50}: > 48.3	< 0.1	no
1.785	0.130	0.038	LD_{50}: > 48.3	< 0.1	no
*Exposure estimate for bees=0.292 × Briggs EEC for adults **Exposure estimate for bees/toxicity endpoint Note: LOC for bee is set at 0.4 for acute endpoints and 1 for chronic endpoints. K_{oc} value = 476					

Table 13 Summary of Potential Risk to Pollinators and Proposed Risk Mitigation for Foliar, Soil and Seed Treatment Uses

Application Method	Negligible Potential for Risk	Potential for Risk + Proposed Mitigation	
		Low-Moderate Pollinator Exposure	High Pollinator Exposure
Foliar	**No exposure:** - Turf (sod farms and golf courses) - Tobacco - White button mushroom **Based on risk assessment:** - Aspen, Poplar - Apple (Eastern Canada rate) - Pear (Eastern Canada rate) - Lowbush blueberry - Raspberry - Strawberry - Outdoor ornamentals - Roses	**Restrict applications during bloom to evening:** - White bean	**Restrict applications during bloom to evening:** - Apple (BC rate) - Pear (BC rate) - Cherry - Peach - Nectarine - Plum - Prune **Restrict applications during bloom to evening:** - Turf (where clover or other flowering bee attractive plants are present)
Seed Treatment	**Based on risk assessment:** - Dry common bean - Sweet corn - Potato	There are no seed treatment applications with low-moderate pollinator exposure with a potential risk.	There are no seed treatments with high pollinator exposure with a potential risk.
Soil	**Based on risk assessment:** - potted greenhouse ornamentals	There are no soil applications with low-moderate pollinator exposure with a potential risk.	There are no soil applications with high pollinator exposure with a potential risk.

Table 14 Screening Level Risk Assessment for Beneficial Arthropods for Representative Uses of Thiophanate-methyl

Organism	Exposure	Endpoint Value [1]	Use	EEC [2]	RQ [3]	LOC exceeded
Invertebrates						
Predatory mite (*Typhlodromus pyri*)	Contact (glass plate)	LR_{50} > 1575 g a.i./ha	Orchard (1575 g a.i./ha × 2 applications at a 7-day interval)	In-field: 2544.6 g a.i./ha	< 1.6	No
				Off-field: (In-field EEC × 0.74): 1883 g a.i./ha	< 1.2	No
			Turf (4200 g a.i./ha × 2 applications at a 7-day interval)	In-field: 6785.7 g a.i./ha	< 4.3	Yes
				Off-field: (In-field EEC × 0.11): 746.4 g a.i./ha	< 0.47	No
			Turf (12250 g a.i./ha × 1 fall application)	In-field: 12250 g a.i./ha	< 7.8	Yes
				Off-field: (In-field EEC × 0.11): 1225 g a.i./ha	< 0.78	No
Parasitic wasp (*Aphidius rhopalosiphi*)	Contact (glass plate)	LR_{50} > 1500 g a.i./ha	Orchard (1575 g a.i./ha × 2 applications at a 7-day interval)	In-field: 2544.6 g a.i./ha	< 1.7	No
				Off-field: (In-field EEC × 0.74): 1883 g a.i./ha	< 1.3	No
			Turf (4200 g a.i./ha × 2 applications at a 7-	In-field:	< 4.5	Yes

Organism	Exposure	Endpoint Value [1]	Use	EEC [2]	RQ [3]	LOC exceeded
			day interval)	6785.7 g a.i./ha		
				Off-field: (In-field EEC × 0.11): 746.4 g a.i./ha	< 0.50	No
			Turf (12250 g a.i./ha × 1 fall application)	In-field: 12250 g a.i./ha	< 8.2	Yes
				Off-field: (In-field EEC × 0.11): 1225 g a.i./ha	< 0.82	No

EEC = estimated environmental concentration, RQ = Risk Quotient; LOC = Level of Concern
[1] Arthropod data are based on tier 1 (glass plate) studies.
[2] in-field EEC = cumulative application rate; off-field EEC = cumulative application rate × drift factor. The cumulative application rate is based on a default half-life of 10 days for foliar dissipation. The off- field risk assessment is based on a drift of 11% for groundboom application and of 74% for airblast application.
[3] RQ = EEC / endpoint value; bolded values indicate that the RQ exceeds the LOC. LOC = 2 for glass plate studies using the standard beneficial arthropod test species, *Typhlodromus pyri* and *Aphidius rhopalosiphi* and unrefined EECs.

Table 15 Refined Risk Assessment for Beneficial Arthropods for Representative Uses of Thiophanate-methyl

Organism	Exposure	Endpoint Value [1]	Use	EEC [2]	RQ [3]	LOC exceeded
Invertebrates						
Predatory mite (*Typhlodromus pyri*)	Contact (glass plate)	LR_{50} > 1575 g a.i./ha	Turf (4200 g a.i./ha × 2 applications at a 7-day interval)	Refined In-field (in-field EEC × 0.4): 2714.3 g a.i./ha	< 1.7	Yes
			Turf (12250 g a.i./ha × 1 fall application)	Refined In-field (in-field EEC × 0.4): 4900 g a.i./ha	< 3.1	Yes
Parasitic wasp (*Aphidius rhopalosiphi*)	Contact (glass plate)	LR_{50} > 1500 g a.i./ha	Turf (4200 g a.i./ha × 2 applications at a 7-day interval)	Refined In-field (in-field EEC × 0.4): 2714.3 g a.i./ha	< 1.8	Yes
			Turf (12250 g a.i./ha × 1 fall application)	Refined In-field (in-field EEC × 0.4): 4900 g a.i./ha	< 3.3	Yes
	Extended laboratory - (barley seedlings)	LR_{50}/ER_{50} > 1500 g a.i./ha (mortality and reproduction)	Turf (4200 g a.i./ha × 2 applications at a 7-day interval)	Refined In-field (in-field EEC × 0.4): 2714.3 g a.i./ha	< 1.8	Yes
			Turf (12250 g a.i./ha × 1 fall application)	Refined In-field (in-field EEC × 0.4): 4900 g a.i./ha	< 3.3	Yes

EEC = estimated environmental concentration, RQ = Risk Quotient; LOC = Level of Concern
[1] Arthropod data are based on tier 1 (glass plate) and aged residue tests.
[2] refined in-field EEC = cumulative application rate × foliar deposition fraction for grasses. The cumulative application rate is based on a default half-life of 10 days for foliar dissipation.
[3] RQ = EEC / endpoint value; bolded cells indicate that the RQ exceeds the Level of Concern. Level of concern (LOC) = 1 for refined EECs.

Table 16 Endpoints for Use in Bird and Mammal Risk Assessment

Exposure	Species	Endpoint	Endpoint after UF [1]
Avian acute	Mallard duck (*Anas platyrhynchos*)	14-d LD_{50} > 4640 mg a.i./kg bw	> 464 mg a.i./kg bw/day
	Bobwhite quail	LD_{50} > 2250 mg CAZ/kg bw/day	> 225 mg CAZ/kg bw/day[2]
Avian dietary	Mallard duck (*Anas platyrhynchos*)	5-d LC_{50} > 10 000 mg a.i./kg diet	5-d LD_{50}[3] > 56.56 mg a.i./kg bw/day
Avian reproduction	Mallard duck (*Anas platyrhynchos*)	NOEC = 103 mg a.i./kg diet	NOEL[3] = 5.83 mg a.i./kg bw/day
Mammalian acute	Rat (*Rattus norvegicus*)	LD_{50} = 6640 mg a.i./kg bw	664 mg a.i./kg bw
Mammalian reproduction	Mouse (*Mus musculus*)	NOEL = 16 mg a.i./kg/day	16 mg a.i./kg/day

1. UF = uncertainty factor; the acute LD_{50} toxicity endpoint is divided by a factor of 10 to account for potential differences in species sensitivity as well as varying protection levels (for example, community, population, individual).
2. A screening level acute assessment was done for carbendazim as the endpoint is potentially more sensitive than the endpoint for thiophanate-methyl.
3. The 5-d LD_{50} and NOEL were calculated using default adult mallard body weight (1082 g) and food ingestion rate (61.2 g dw food/day; - FIR (g dry weight/day) = 0.648(BW in g)$^{0.651}$).

Table 17 Screening Level Risk Assessment for Thiophanate-methyl for Birds and Mammals at the Highest Single Foliar Application Rate on Turf

Exposure	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw)	RQ
Small Bird (0.02 kg)				
Acute	> 464	Insectivore	342	< 0.7
Reproduction	5.83	Insectivore	342	**59**
Medium Sized Bird (0.1 kg)				
Acute	> 464	Insectivore	267	< 0.6
Reproduction	5.83	Insectivore	267	**46**
Large Sized Bird (1 kg)				
Acute	> 464	Herbivore (short grass)	172	< 0.5
Reproduction	5.83	Herbivore (short grass)	172	**30**
Small Mammal (0.015 kg)				
Acute	664	Insectivore	196.63	0.30
Reproduction	16	Insectivore	196.63	**12.3**
Medium Sized Mammal (0.035 kg)				
Acute	664	Herbivore (short grass)	381.36	0.6
Reproduction	16	Herbivore (short grass)	381.36	**23.8**
Large Sized Mammal (1 kg)				
Acute	664	Herbivore (short grass)	203.77	0.3
Reproduction	16	Herbivore (short grass)	203.77	**12.7**

* Bold values indicate that the LOC is exceeded with RQ > 1

Table 18 Screening Level Risk Assessment for Carbendazim for Birds at the Highest Single Foliar Application Rate on Turf

Exposure	Toxicity (mg CAZ/kg bw/d)	Feeding Guild (food item)	EDE (mg CAZ/kg bw)	RQ
Small Bird (0.02 kg)				
Acute	> 225	Insectivore	126	< 0.6
Medium Sized Bird (0.1 kg)				
Acute	> 225	Insectivore	98	< 0.4
Large Sized Bird (1 kg)				
Acute	> 225	Herbivore (short grass)	63	< 0.3

Table 19 Avian Risk Assessment Using Maximum and Mean Thiophanate-methyl Residue Values

			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off-Field		On-field		Off-Field	
Exposure	**Toxicity (mg a.i./kg bw/d)**	**Food Guild (food item)**	**EDE (mg a.i./kg bw)**	**RQ ***	**EDE (mg a.i./kg bw)**	**RQ ***	**EDE (mg a.i./kg bw)**	**RQ ***	**EDE (mg a.i./kg bw)**	**RQ ***
Apples/Pears – 437.5 g a.i./ha × 2 at a 7-d interval [1]										
Small Bird (0.02 kg)										
Reproduction	5.8	Insectivore	58	**9.9**	43	**7.3**	40	**6.8**	29	**5.1**
	5.8	Granivore (grain and seeds)	9.0	**1.5**	6.6	**1.1**	4.3	0.7	3.1	0.5
	5.8	Frugivore (fruit)	18	**3.1**	13	**2.3**	8.5	**1.5**	6.3	**1.1**
Medium Sized Bird (0.1 kg)										
Reproduction	5.8	Insectivore	45	**7.7**	33	**5.7**	31	**5.3**	23	**3.9**
	5.8	Granivore (grain and seeds)	7.0	**1.2**	5.1	0.9	3.3	0.6	2.5	0.4
	5.8	Frugivore (fruit)	14	**2.4**	10	**1.8**	6.6	**1.1**	4.9	0.8
Large Sized Bird (1 kg)										
Reproduction	5.8	Insectivore	13	**2.3**	9.7	**1.7**	9.1	**1.6**	6.7	**1.2**
	5.8	Granivore (grain and seeds)	2.0	0.3	1.5	0.3	1.0	0.2	0.7	0.1
	5.8	Frugivore (fruit)	4.1	0.7	3.0	0.5	2.0	0.3	1.4	0.3
	5.8	Herbivore (short grass)	29	**5.0**	21	**3.7**	10	**1.8**	7.6	**1.3**
	5.8	Herbivore (long grass)	18	**3.0**	13	**2.2**	5.8	0.9	4.2	0.7
	5.8	Herbivore (Broadleaf plants)	27	**4.6**	20	**3.4**	8.9	**1.5**	6.6	**1.1**
Apples/Pears – 1575 g a.i./ha × 2 at a 7-d interval [1]										
Small Bird (0.02 kg)										
Reproduction	5.8	Insectivore	207	**36**	153	**26**	143	**25**	106	**18.1**
	5.8	Granivore (grain and seeds)	32	**5.5**	24	**4.1**	15	**2.6**	11	**1.9**
	5.8	Frugivore (fruit)	64	**11**	47	**8.1**	31	**5.3**	23	**3.9**
Medium Sized Bird (0.1 kg)										
Reproduction	5.8	Insectivore	162	**28**	119	**20.5**	1121	**19**	83	**14.2**
	5.8	Granivore (grain and seeds)	25	**4.3**	19	**3.2**	12	**2.1**	8.8	**1.5**
	5.8	Frugivore (fruit)	50	**8.6**	37	**6.4**	24	**4.1**	18	**3.0**
Large Sized Bird (1 kg)										
Reproduction	5.8	Insectivore	47	**8.1**	35	**6.0**	33	**5.6**	24	**4.1**
	5.8	Granivore (grain and seeds)	7.3	**1.3**	5.4	0.9	3.5	0.6	2.5	0.4
	5.8	Frugivore (fruit)	15	**2.5**	11	**1.9**	7.0	**1.2**	5.6	**0.9**
	5.8	Herbivore (short grass)	104	**18**	77	**13.3**	37	**6.4**	27	**4.7**
	5.8	Herbivore (long grass)	64	**11**	47	**8.1**	21	**3.6**	15	**2.6**
	5.8	Herbivore (Broadleaf plants)	97	**17**	71	**12.3**	32	**5.5**	24	**4.1**
Turf - 4200 g a.i./ha [2]										
Small Bird (0.02 kg)										
Reproduction	5.8	Insectivore	342	**59**	21	**3.5**	236	**41**	14	**2.4**
	5.8	Granivore (grain and seeds)	53	**9.1**	3.2	0.5	25	**4.3**	1.5	0.3
	5.8	Frugivore (fruit)	106	**18**	6.4	**1.1**	50	**8.7**	3.0	0.5

			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off-Field		On-field		Off-Field	
Exposure	**Toxicity (mg a.i./kg bw/d)**	**Food Guild (food item)**	**EDE (mg a.i./kg bw)**	**RQ ***	**EDE (mg a.i./kg bw)**	**RQ ***	**EDE (mg a.i./kg bw)**	**RQ ***	**EDE (mg a.i./kg bw)**	**RQ ***
Medium Sized Bird (0.1 kg)										
Reproduction	5.8	Insectivore	267	**46**	16	**2.7**	184	**32**	11	**1.9**
	5.8	Granivore (grain and seeds)	41	**7.1**	2.5	0.4	20	**3.4**	1.2	0.2
	5.8	Frugivore (fruit)	83	**14**	4.9	0.9	39	**6.8**	2.4	0.4
Large Sized Bird (1 kg)										
Reproduction	5.8	Insectivore	78	**13**	4.7	0.8	54	**9.2**	3.2	0.6
	5.8	Granivore (grain and seeds)	12	**2.1**	0.7	0.1	5.8	**1.0**	0.3	<0.1
	5.8	Frugivore (fruit)	24	**4.1**	1.5	0.2	12	**2.0**	0.7	0.1
	5.8	Herbivore (short grass)	172	**30**	10	**1.8**	61	**11**	3.7	0.6
	5.8	Herbivore (long grass)	105	**18**	6.3	**1.1**	34	**5.9**	2.1	0.4
	5.8	Herbivore (Broadleaf plants)	159	**27**	9.6	**1.6**	53	**9.1**	3.2	0.5

***** Bold values indicate that the LOC is exceeded with RQ > 1

1. The cumulative application rate for apples/pears is based on a default half-life of 10 days for foliar dissipation. This value is based on the foliar dissipation of a variety of active ingredients reported by Willis and McDowell (1987); with 93% of the foliar dissipation half-life less than 10 days, this value is considered to be a reasonable conservative estimate of typical foliar half-lives.
2. For on-field feeding, insects and short grass are the only relevant food items for birds and mammals feeding for turf use (for example, greens and fairways).

Table 20 Mammalian Risk Assessment Using Maximum and Mean Thiophanate-methyl Residue Values

			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off-Field		On-field		Off-Field	
Exposure	**Toxicity (mg a.i./kg bw/d)**	**Food Guild (food item)**	**EDE (mg a.i./kg bw)**	**RQ***	**EDE (mg a.i./kg bw)**	**RQ***	**EDE (mg a.i./kg bw)**	**RQ***	**EDE (mg a.i./kg bw)**	**RQ***
Apples/Pears – 437.5 g a.i./ha × 2 at a 7-d interval [1]										
Small Sized Mammals (0.015 kg)										
Reproduction	54	Insectivore	33	0.6	24	0.5	23	0.4	17	0.3
	54	Granivore (grain and seeds)	5.1	<0.1	3.8	<0.1	2.4	<0.1	1.8	<0.1
	54	Frugivore (fruit)	10	0.2	7.6	0.1	4.9	<0.1	3.6	<0.1
Medium Sized Mammal (0.035 kg)										
Reproduction	54	Insectivore	29	0.5	21	0.4	20	0.4	15	0.3
	54	Granivore (grain and seeds)	4.5	<0.1	3.3	<0.1	2.1	<0.1	1.6	<0.1
	54	Frugivore (fruit)	9.0	0.2	6.6	0.1	4.3	<0.1	3.2	<0.1
	54	Herbivore (short grass)	64	**1.2**	47	0.9	23	0.4	17	0.3
	54	Herbivore (long grass)	39	0.7	29	0.5	13	0.2	9.5	0.2
	54	Herbivore (Broadleaf plants)	59	**1.1**	44	0.8	20	0.4	15	0.3
Large Sized Mammal (1 kg)										
Reproduction	54	Insectivore	16	0.3	11	0.2	11	0.2	7.9	0.1
	54	Granivore (grain and seeds)	2.4	<0.1	1.8	<0.1	1.1	<0.1	0.9	<0.1
	54	Frugivore (fruit)	4.8	<0.1	3.6	<0.1	2.3	<0.1	1.7	<0.1

			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off-Field		On-field		Off-Field	
Exposure	**Toxicity (mg a.i./kg bw/d)**	**Food Guild (food item)**	**EDE (mg a.i./kg bw)**	**RQ***	**EDE (mg a.i./kg bw)**	**RQ***	**EDE (mg a.i./kg bw)**	**RQ***	**EDE (mg a.i./kg bw)**	**RQ***
	54	Herbivore (short grass)	34	0.6	25	0.5	12	0.2	9.0	0.2
	54	Herbivore (long grass)	21	0.4	15	0.3	6.8	0.1	5.1	0.1
	54	Herbivore (Broadleaf plants)	32	0.6	23	0.4	10	0.2	7.8	0.1
Apples/Pears – 1575 g a.i./ha × 2 at a 7-d interval [1]										
Small Sized Mammals (0.015 kg)										
Reproduction	54	Insectivore	119.1	**2.2**	88.2	**1.6**	82.3	**1.5**	60.9	**1.1**
	54	Granivore (grain and seeds)	18.4	0.3	13.6	0.3	8.8	0.2	6.5	0.1
	54	Frugivore (fruit)	36.9	0.7	27.3	0.5	17.6	0.3	13.0	0.2
Medium Sized Mammal (0.035 kg)										
Reproduction	54	Insectivore	104.4	**1.9**	77.3	1.4	72.1	**1.3**	53.4	**1.0**
	54	Granivore (grain and seeds)	16.2	0.3	12.0	0.2	7.7	0.1	5.7	0.1
	54	Frugivore (fruit)	32.3	0.6	23.9	0.4	15.4	0.3	11.4	0.2
	54	Herbivore (short grass)	231.0	**4.3**	171	**3.2**	82.1	**1.5**	60.7	**1.1**
	54	Herbivore (long grass)	141.1	**2.6**	104.4	**1.9**	46.1	0.9	34.1	0.6
	54	Herbivore (Broadleaf plants)	213.8	**4.0**	158.2	**2.9**	70.7	**1.3**	52.3	**1.0**
Large Sized Mammal (1 kg)										
Reproduction	54	Insectivore	55.8	**1.0**	41.3	0.8	38.5	0.7	28.5	0.5
	54	Granivore (grain and seeds)	8.6	0.2	6.4	0.1	4.1	0.1	3.0	0.1
	54	Frugivore (fruit)	17.3	0.3	12.8	0.2	8.2	0.2	6.1	0.1
	54	Herbivore (short grass)	123.5	**2.3**	91.4	**1.7**	43.8	0.8	32.4	0.6
	54	Herbivore (long grass)	75.4	**1.4**	55.8	**1.0**	24.6	0.5	18.2	0.3
	54	Herbivore (Broadleaf plants)	114.2	**2.1**	84.5	**1.6**	37.8	0.7	27.9	0.5
Turf use - 4200 g a.i./ha [2]										
Small Sized Mammals (0.02 kg)										
Reproduction	54	Insectivore	197	**3.6**	12	0.2	136	**2.5**	8.2	0.15
	54	Granivore (grain and seeds)	30	0.6	1.8	<0.1	15	0.3	0.9	<0.1
	54	Frugivore (fruit)	61	**1.1**	3.7	<0.1	29	0.5	1.7	<0.1
Medium Sized Mammals (0.035 kg)										
Reproduction	54	Insectivore	172	**3.2**	10	0.2	119	**2.2**	7.1	0.1
	54	Granivore (grain and seeds)	27	0.5	1.6	<0.1	13	0.2	0.8	<0.1
	54	Frugivore (fruit)	53	0.9	3.2	<0.1	25	0.4	1.5	<0.1
	54	Herbivore (short grass)	381	**7.1**	23	0.4	135	**2.5**	8.1	0.2
	54	Herbivore (long grass)	233	**4.3**	14	0.3	76	**1.4**	4.6	<0.1
	54	Herbivore (Broadleaf plants)	353	**6.5**	21	0.4	117	**2.2**	7.0	0.1
Large Sized Mammals (1 kg)										
Reproduction	54	Insectivore	92	**1.7**	5.5	0.1	64	**1.2**	3.82	<0.1
	54	Granivore (grain and seeds)	14	0.2	0.9	<0.1	6.8	0.1	0.41	<0.1
	54	Frugivore (fruit)	29	0.5	1.7	<0.1	14	0.3	0.82	<0.1
	54	Herbivore (short grass)	204	**3.8**	12	0.2	72	**1.3**	4.34	<0.1
	54	Herbivore (long grass)	124	**2.3**	7.5	0.1	41	0.7	2.44	<0.1
	54	Herbivore (Broadleaf plants)	189	**3.5**	11	0.2	62	**1.2**	3.74	<0.1

* Bold values indicate that the LOC is exceeded with RQ > 1

1. The cumulative application rate for apples/pears is based on a default half-life of 10 days for foliar dissipation. This value is based on the foliar dissipation of a variety of active ingredients reported by Willis and McDowell (1987); with 93% of the foliar dissipation half-life less than 10 days, this value is considered to be a reasonable conservative estimate of typical foliar half-lives.

For on-field feeding, insects and short grass are the only relevant food items for birds and mammals feeding for turf use (for example, greens and fairways).

Table 21 Seed Treatment Screening Level Risk Assessment of Thiophanate-methyl for Birds and Mammals

Birds			
Size (g)	**EDE (mg a.i./kg bw/day)**	**Acute LD_{50}/10: >464 mg a.i/kg bw/day RQ***	**Reproduction NOEL: 5.82 mg a.i./kg bw/day RQ***
20	185	< 0.4	**32**
100	145	< 0.3	**25**
1000	42	< 0.1	**7.3**
Mammals			
Size (g)	**EDE (mg a.i./kg bw/day)**	**Acute LD_{50}/10: 664 mg a.i/kg bw/day RQ***	**Reproduction NOEL: 54 mg a.i./kg bw/day RQ***
15	106	0.2	**2.0**
35	91	0.1	**1.7**
1000	50	0.1	0.9

* Bold values indicate that the LOC is exceeded with RQ > 1
dry bean – 729.4 mg a.i./kg seed

Table 22 Seed Treatment Screening Level Risk Assessment of Carbendazim for Birds

Birds		
Size (g)	**EDE (mg CAZ/kg bw/day)**	**Acute LD_{50}/10: > 225 mg CAZ/kg bw/day RQ**
20	85	< 0.4
100	67	< 0.3
1000	20	< 0.1

dry bean – 336.59 mg carbendazim /kg seed

Table 23 The Number of Seeds Treated With Thiophanate-methyl Required to Reach the Bird Reproductive Endpoint and Foraging Area Required to Reach the Endpoints

Crop (EEC: mg a.i./kg seed)	**Size (g)**	**Reproduction**	
		# seeds to reach endpoint (min to max.)[a]	**Area Required [b] (m^2)**
Birds			
Dry bean (729.4) Standard drilling - spring	20	0.5 – 0.8	0.4 – 2.5
	100	2.4 – 4.0	1.8 – 13
	1000	24 – 40	18 – 126
Sweet corn (711.6) Precision drilling	20	0.7 – 1.3	11 – 125
	100	3.3 – 6.6	54 – 624
	1000	33 – 66	541 – 6242
Mammals			
Dry bean (729.4) Standard drilling - spring	15	3.3 – 5.6	4.1 – 11
	35	7.7 – 13	9.4 – 25
Sweet corn (711.6) Precision drilling	15	4.6 – 9.1	152 – 434
	35	11 – 21	351 – 1012

a. minimum to maximum number of seeds to reach endpoint based on seed size range (maximum to minimum)

b. minimum and maximum area required based on minimum and maximum seeding rate

Table 24 Screening Level Risk Assessment of Thiophanate-methyl and Carbendazim for Aquatic Organisms Based on the Highest Cumulative Application Rate for Turf

Organism	Exposure	Endpoint value (mg a.i./L) adjusted using uncertainty factors		EEC[1] (mg a.i./L)	RQ	LOC exceeded
Freshwater species						
Invertebrate, *Daphnia magna*	Acute	TPM	$LC_{50}/2 = 2.7$	1.54	0.6	No
		CAZ	$LC_{50}/2 = 0.075$	0.91	12	Yes
	Chronic	TPM	NOEC = 0.16	1.54	9.6	Yes
		CAZ	NOEC = 0.0015	0.91	605	Yes
Fish	Acute	TPM	$LC_{50}/10 = 0.83$	1.54	1.9	Yes
		CAZ	$HC_5 = 0.013$	0.91	70	Yes
	Early Life-Stage	TPM	NOEC = 0.32	1.54	4.8	Yes
		CAZ	NOEC = 0.002	0.91	454	Yes
Amphibians (using fish data as a surrogate)	Acute	TPM	$LC_{50}/10 = 0.83$	8.19	9.9	Yes
	Early Life-Stage	TPM	NOEC = 0.32	8.19	26	Yes
		CAZ	NOEC = 0.002	4.84	2420	Yes
Amphibians	Acute	CAZ	$LC_{50}/10 = 0.1072$	4.84	45	Yes
Vascular plants	Dissolved	TPM	$EC_{50}/2 = > 2.35$	1.54	< 0.7	No
Algae	Acute	TPM	$EC_{50}/2 = 0.47$	1.54	3.3	Yes
Estuarine/Marine Species						
Fish	Acute	TPM	$LC_{50}/10 = 4$	1.54	0.4	No
Crustaceans	Acute	TPM	$LC_{50}/2 = 0.55$	1.54	2.8	Yes
	Chronic (life-cycle)	CAZ	NOEC = 0.025	0.91	36	Yes
Mollusks	Acute	TPM	$LC_{50}/2 = 1.1$	1.54	1.4	Yes
Algae	Acute	TPM	$LC_{50}/2 = 0.85$	1.54	1.8	Yes

1. EECs for fish and aquatic invertebrates are based on a waterbody depth of 80 cm; 15 cm of water for amphibians.

1.547 × 2 + 4.511 × 1 at 7-day intervals

Table 25 Risk Quotients for Freshwater Aquatic Organisms as Determined for Runoff of Thiophanate-methyl

Organism (exposure)	Crop (application rate, kg a.i./ha; interval)	Toxicity Value (mg a.i./L)	EEC (mg a.i./L)	RQ	LOC exceeded
Freshwater Species					
Daphnia magna (Acute, 48-hours)	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	$LC_{50}/2 = 2.7$	0.069	< 0.1	No
	White Bean (1.575 × 2 at a 7-day interval)	$LC_{50}/2 = 2.7$	0.063	< 0.1	No
	Apple/Pear*	$LC_{50}/2 = 2.7$	0.008	< 0.1	No
Daphnia magna (Chronic, 21-days)	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	NOEC = 0.16	0.011	< 0.1	No
	White Bean (1.575 × 2 at a 7-day interval)	NOEC = 0.16	0.007	< 0.1	No
	Apple/Pear*	NOEC = 0.16	0.001	< 0.1	No
Rainbow trout, *Oncorhynchus mykiss* (Acute, 96-hours)	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	$LC_{50}/10 = 0.83$	0.04	< 0.1	No
	White Bean (1.575 × 2 at a 7-day interval)	$LC_{50}/10 = 0.83$	0.029	< 0.1	No

Organism (exposure)	Crop (application rate, kg a.i./ha; interval)	Toxicity Value (mg a.i./L)	EEC (mg a.i./L)	RQ	LOC exceeded
	Apple/Pear*	$LC_{50}/10 = 0.83$	0.003	< 0.1	No
Rainbow trout, *Oncorhynchus mykiss* (Early Life Stage, 28-days)	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	NOEC = 0.32	0.011	< 0.1	No
	White Bean (1.575 × 2 at a 7-day interval)	NOEC = 0.32	0.007	< 0.1	No
	Apple/Pear*	NOEC = 0.32	0.001	< 0.1	No
Amphibians (Acute, 96-hours using fish data as a surrogate)	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	$LC_{50}/10 = 0.83$	0.197	0.2	No
	White Bean (1.575 × 2 at a 7-day interval)	$LC_{50}/10 = 0.83$	0.142	0.2	No
	Apple/Pear*	$LC_{50}/10 = 0.83$	0.017	< 0.1	No
Amphibians (Early Life Stage, 28-days using fish data as a surrogate)	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	NOEC = 0.32	0.05	0.2	No
	White Bean (1.575 × 2 at a 7-day interval)	NOEC = 0.32	0.032	0.1	No
	Apple/Pear*	NOEC = 0.32	0.004	< 0.1	No
Freshwater diatom, *Navicula pelliculosa* (5-day)	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	$EC_{50}/2 = 0.47$	0.04	< 0.1	No
	White Bean (1.575 × 2 at a 7-day interval)	$EC_{50}/2 = 0.47$	0.029	< 0.1	No
	Apple/Pear*	$EC_{50}/2 = 0.47$	0.003	< 0.1	No

* Although the rate for use on apples/pears in B.C. (1.575 ×2 at a 7-day interval) is higher than the rate in Eastern Canada (0.4375 × 2 at a 7-day interval), the runoff EECs from modelling were higher for ON/QC scenarios and are therefore reported here. These EECs cover off the higher use rate on apples/pears in B.C.

Table 26 Risk Quotients for Estuarine/Marine Aquatic Organisms as Determined for Runoff of Thiophanate-methyl

Organism (exposure)	Crop (application rate, kg a.i./ha; interval)	Toxicity Value (mg a.i./L)	EEC (mg a.i./L)	RQ	LOC exceeded
Mysid shrimp, *Americamysis bahia* (Acute, 96-hours)	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	$LC_{50}/2 = 0.55$	0.04	< 0.1	No
	White Bean (1.575 × 2 at a 7-day interval)	$LC_{50}/2 = 0.55$	0.029	< 0.1	No
	Apple/Pear*	$LC_{50}/2 = 0.55$	0.003	< 0.1	No
Eastern Oyster, *Crassostrea virginica* (Acute, 96-hours)	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	$LC_{50}/2 = 1.1$	0.04	< 0.1	No
	White Bean (1.575 × 2 at a 7-day interval)	$LC_{50}/2 = 1.1$	0.029	< 0.1	No
	Apple/Pear*	$LC_{50}/2 = 1.1$	0.003	< 0.1	No
Marine diatom, *Skeletonema costatum* (Acute)	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	$LC_{50}/2 = 0.85$	0.04	< 0.1	No
	White Bean (1.575 × 2 at a 7-day interval)	$LC_{50}/2 = 0.85$	0.029	< 0.1	No
	Apple/Pear*	$LC_{50}/2 = 0.85$	0.003	< 0.1	No

* Although the rate for use on apples/pears in B.C. (1.575 × 2 at a 7-day interval) is higher than the rate in Eastern Canada (0.4375 × 2 at a 7-day interval), the runoff EECs from modelling were higher for ON/QC scenarios and are therefore reported here. These EECs cover off the higher use rate on apples/pears in B.C.

Table 27 Risk Quotients for Freshwater and Estuarine/Marine Aquatic Organisms as Determined for Runoff of Carbendazim

Organism (exposure)	Crop (application rate, kg CAZ/ha; interval)	Toxicity Value (mg CAZ/L)	EEC (mg CAZ/L)	RQ	LOC exceeded
Freshwater Species					
Daphnia magna (Chronic, 21-days)	Turf (1.547 × 2 + 4.511 × 1 at 7-day intervals)	NOEC = 0.0015	0.043	28.7	Yes
	White Bean (0.580 × 2 at a 7-day interval)	NOEC = 0.0015	0.038	25.3	Yes
	Apple/Pear*	NOEC = 0.0015	0.006	4.0	Yes
Acute Assessment endpoint for freshwater fish species, SSD (n=5)	Turf (1.547 × 2 + 4.511 × 1 at 7-day intervals)	LC_{50}/10 = 0.013	0.048	3.7	Yes
	White Bean (0.580 × 2 at a 7-day interval)	LC_{50}/10 = 0.013	0.043	3.3	Yes
	Apple/Pear*	LC_{50}/10 = 0.013	0.007	0.5	No
Channel Catfish, *Ictalurus punctatus* (Chronic, Early Life Stage)	Turf (1.547 × 2 + 4.511 × 1 at 7-day intervals)	NOEC = 0.002	0.043	21.5	Yes
	White Bean (0.580 × 2 at a 7-day interval)	NOEC = 0.002	0.038	19.0	Yes
	Apple/Pear*	NOEC = 0.002	0.006	3.0	Yes
Amphibians (Acute, 96-hours)	Turf (1.547 × 2 + 4.511 × 1 at 7-day intervals)	LC_{50}/10 = 0.1072	0.178	1.7	Yes
	White Bean (0.580 × 2 at a 7-day interval)	LC_{50}/10 = 0.1072	0.163	1.5	Yes
	Apple/Pear*	LC_{50}/10 = 0.1072	0.025	0.2	No
Amphibians (Early Life Stage - using fish data as surrogate)	Turf (1.547 × 2 + 4.511 × 1 at 7-day intervals)	NOEC = 0.002	0.126	63	Yes
	White Bean (0.580 × 2 at a 7-day interval)	NOEC = 0.002	0.11	55	Yes
	Apple/Pear*	NOEC = 0.002	0.02	10	Yes
Estuarine/marine Species					
Mysid shrimp, *Americamysis bahia* (Chronic, Life-Cycle)	Turf (1.547 × 2 + 4.511 × 1 at 7-day intervals)	NOEC = 0.025	0.043	1.7	Yes
	White Bean (0.580 × 2 at a 7-day interval)	NOEC = 0.025	0.038	1.5	Yes
	Apple/Pear*	NOEC = 0.025	0.006	0.2	No

* Even though the rate for use on apples/pears in B.C. (0.58 × 2 at a 7-day interval) is higher than the rate in Eastern Canada (0.161 × 2 at a 7-day interval), the runoff EECs from modelling were higher for ON/QC scenarios and are therefore reported here. These EECs cover off the higher use rate on apples/pears in B.C.

Table 28 Risk Quotients for Freshwater Aquatic Organisms Determined for Drift of Thiophanate-methyl

(early and late season airblast application on apples/pears, field sprayer application on turf and white beans, and aerial application on white beans using ASAE medium droplet size)

Organism (exposure)	Crop (application, kg a.i./ha; level)	Toxicity Value (mg a.i./L)	Drift EEC (mg a.i./L)	RQ	LOC exceeded
Freshwater Species					
Daphnia magna (Chronic, 21days)	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	NOEC = 0.16	Field sprayer (6% drift): 0.092	0.6	No
	White Bean (1.575 × 2 at a 7-day interval)	NOEC = 0.16	Field sprayer (6% drift): 0.012	0.1	No
	Eastern Canada Apple/Pear (0.4375 × 2 at a 7-day interval)	NOEC = 0.16	Early season airblast appl. (74% drift): 0.0407	0.3	No
			Late season airblast appl. (59% drift): 0.0325	0.2	No
Rainbow trout, *Oncorhynchus mykiss* (Acute, 96-hours)	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	LC_{50}/10 = 0.83	Field sprayer (6% drift): 0.092	0.1	No
	White Bean (1.575 × 2 at a 7-day interval)	LC_{50}/10 = 0.83	Field sprayer (6% drift): 0.012	<0.1	No
			Aerial (23% drift): 0.046	0.1	No
	Eastern Canada Apple/Pear (0.4375 × 2 at a 7-day interval)	LC_{50}/10 = 0.83	Early season airblast appl. (74% drift): 0.0407	0.05	No
			Late season airblast appl. (59% drift): 0.0325	<0.1	No
Rainbow trout, *Oncorhynchus mykiss* (Early Life Stage, 28-days)	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	NOEC = 0.32	Field sprayer (6% drift): 0.092	0.1	No
	White Bean (1.575 × 2 at a 7-day interval)	NOEC = 0.32	Field sprayer (6% drift): 0.012	<0.1	No
			Aerial (23% drift): 0.046	0.1	No
	Eastern Canada Apple/Pear (0.4375 × 2 at a 7-day interval)	NOEC = 0.32	Early season airblast appl. (74% drift): 0.0407	0.13	No
			Late season airblast appl. (59% drift): 0.0325	0.1	No
Amphibians (Acute, 96-hours using fish data as a surrogate)	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	LC_{50}/10 = 0.83	Field sprayer (6% drift): 0.5	0.6	No
	White Bean (1.575 × 2 at a 7-day interval)	LC_{50}/10 = 0.83	Field sprayer (6% drift): 0.1	0.1	No
			Aerial (23% drift): 0.2	0.3	No
	Eastern Canada Apple/Pear (0.4375 × 2 at a 7-day interval)	LC_{50}/10 = 0.83	Early season airblast appl. (74% drift): 0.2176	0.3	No
			Late season airblast appl. (59% drift): 0.1735	0.2	No
Amphibians (Early Life Stage, 28-days using fish data as a surrogate)	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	NOEC = 0.32	Field sprayer (6% drift): 0.5	1.5	Yes
	White Bean (1.575 × 2 at a 7-day interval)	NOEC = 0.32	Field sprayer (6% drift): 0.1	0.2	No
			Aerial (23% drift): 0.2	0.8	No
	Eastern Canada Apple/Pear (0.4375 × 2 at a 7-day interval)	NOEC = 0.32	Early season airblast appl. (74% drift): 0.2176	0.7	No
			Late season airblast appl. (59% drift): 0.1735	0.5	No
Freshwater diatom, *Navicula*	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	EC_{50}/2 = 0.47	Field sprayer (6% drift): 0.092	0.2	No

Organism (exposure)	Crop (application, kg a.i./ha; level)	Toxicity Value (mg a.i./L)	Drift EEC (mg a.i./L)	RQ	LOC exceeded
pelliculosa (5-day)	White Bean (1.575 × 2 at a 7-day interval)	$EC_{50}/2 = 0.47$	Field sprayer (6% drift): 0.012	<0.1	No
			Aerial (23% drift): 0.046	0.1	No
	Eastern Canada Apple/Pear (0.4375 × 2 at a 7-day interval)	$EC_{50}/2 = 0.47$	Early season airblast appl. (74% drift): 0.0407	0.1	No
			Late season airblast appl. (59% drift): 0.0325	0.1	No

Table 29 Risk Quotients for Estuarine/Marine Aquatic Organisms Determined for Drift of Thiophanate-methyl from Early and Late Season[1]

Organism (exposure)	Crop (kg a.i./ha)	Endpoint (mg a.i./L)	EEC (mg a.i./L)	RQ	LOC exceeded
Estuarine/marine species					
Mysid shrimp, *Americamysis bahia* (Acute, 96-hours)	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	$LC_{50}/2 = 0.55$	Field sprayer (6% drift): 0.092	0.2	No
	White Bean (1.575 × 2 at a 7-day interval)	$LC_{50}/2 = 0.55$	Field sprayer (6% drift): 0.012	< 0.1	No
			Aerial (23% drift): 0.046	0.1	No
	Eastern Canada Apple/Pear (0.4375 × 2 at a 7-day interval)	$LC_{50}/2 = 0.55$	Early season airblast appl. (74% drift): 0.0407	0.1	No
			Late season airblast appl. (59% drift): 0.0325	0.1	No
Eastern Oyster, *Crassostrea virginica* (Acute, 96-hours)	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	$LC_{50}/2 = 1.1$	Field sprayer (6% drift): 0.092	0.1	No
	White Bean (1.575 × 2 at a 7-day interval)	$LC_{50}/2 = 1.1$	Field sprayer (6% drift): 0.012	< 0.1	No
			Aerial (23% drift): 0.046	< 0.1	No
	Eastern Canada Apple/Pear (0.4375 × 2 at a 7-day interval)	$LC_{50}/2 = 1.1$	Early season airblast appl. (74% drift): 0.0407	< 0.1	No
			Late season airblast appl. (59% drift): 0.0325	< 0.1	No
Marine diatom, *Skeletonema costatum* (Acute)	Turf (4.2 × 2 + 12.25 × 1 at 7-day intervals)	$LC_{50}/2 = 0.85$	Field sprayer (6% drift): 0.092	0.1	No
	White Bean (1.575 × 2 at a 7-day interval)	$LC_{50}/2 = 0.85$	Field sprayer (6% drift): 0.012	< 0.1	No
			Aerial (23% drift): 0.046	0.1	No
	Eastern Canada Apple/Pear (0.4375 × 2 at a 7-day interval)	$LC_{50}/2 = 0.85$	Early season airblast appl. (74% drift): 0.0407	< 0.1	No
			Late season airblast appl. (59% drift): 0.0325	< 0.1	No

[1] airblast application on apples/pears, field sprayer application on turf and white beans, and aerial application on white beans using ASAE medium droplet size

Table 30 Risk Quotients for Freshwater and Estuarine/Marine Aquatic Organisms Determined for Drift of Carbendazim from Early and Late Season [1]

Organism (exposure)	Crop kg CAZ/ha)	Endpoint (mg CAZ/L)	EEC (mg CAZ/L)	RQ	LOC exceeded
Freshwater Species					
Daphnia magna (Acute, 48 hours)	Turf (1.547 × 2 + 4.511 × 1 at 7-day intervals)	$EC_{50}/2 = 0.075$	Field sprayer (6% drift): 0.054	0.7	No
	White Bean (0.580 × 2 at a 7-day interval)	$EC_{50}/2 = 0.075$	Field sprayer (6% drift): 0.008	0.1	No
			Aerial (23% drift): 0.032	0.4	No
	Eastern Canada Apple/Pear (0.161 × 2 at 7-day intervals)	$EC_{50}/2 = 0.075$	Early season airblast appl. (74% drift): 0.0289	0.4	No
			Late season airblast appl. (59% drift): 0.023	0.3	No
Daphnia magna (Chronic, 21-days)	Turf (1.547 × 2 + 4.511 × 1 at 7-day intervals)	NOEC = 0.0015	Field sprayer (6% drift): 0.054	36.3	Yes
	White Bean (0.580 × 2 at a 7-day interval)	NOEC = 0.0015	Field sprayer (6% drift): 0.008	5.6	Yes
			Aerial (23% drift): 0.032	21.3	Yes
	Eastern Canada Apple/Pear (0.161 × 2 at 7-day intervals)	NOEC = 0.0015	Early season airblast appl. (74% drift): 0.0289	19.2	Yes
			Late season airblast appl. (59% drift): 0.023	15.3	Yes
Acute Assessment endpoint for freshwater fish species, SSD (n=5)	Turf (1.547 × 2 + 4.511 × 1 at 7-day intervals)	$LC_{50}/10 = 0.013$	Field sprayer (6% drift): 0.054	4.2	Yes
	White Bean (0.580 × 2 at a 7-day interval)	$LC_{50}/10 = 0.013$	Field sprayer (6% drift): 0.008	0.6	No
			Aerial (23% drift): 0.032	2.5	Yes
	Eastern Canada Apple/Pear (0.161 × 2 at 7-day intervals)	$LC_{50}/10 = 0.013$	Early season airblast appl. (74% drift): 0.0289	2.2	Yes
			Late season airblast appl. (59% drift): 0.023	1.8	Yes
Channel Catfish, *Ictalurus punctatus* (Chronic, Early Life Stage)	Turf (1.547 × 2 + 4.511 × 1 at 7-day intervals)	NOEC = 0.002	Field sprayer (6% drift): 0.054	27.2	Yes
	White Bean (0.580 × 2 at a 7-day interval)	NOEC = 0.002	Field sprayer (6% drift): 0.008	4.2	Yes
			Aerial (23% drift): 0.032	16	Yes
	Eastern Canada Apple/Pear (0.161 × 2 at 7-day intervals)	NOEC = 0.002	Early season airblast appl. (74% drift): 0.0289	14.4	Yes
			Late season airblast appl. (59% drift): 0.023	11.5	Yes
Amphibians (Acute, 96-hours)	Turf (1.547 × 2 + 4.511 × 1 at 7-day intervals)	$LC_{50}/10 = 0.1072$	Field sprayer (6% drift): 0.3	2.7	Yes
	White Bean (0.580 × 2 at a 7-day interval)	$LC_{50}/10 = 0.1072$	Field sprayer (6% drift): 0.04	0.4	No
			Aerial (23% drift): 0.2	1.6	Yes
	Eastern Canada Apple/Pear (0.161 × 2 at 7-day intervals)	$LC_{50}/10 = 0.1072$	Early season airblast appl. (74% drift): 0.1532	1.4	Yes
			Late season airblast appl. (59% drift): 0.1221	1.1	Yes

Organism (exposure)	Crop kg CAZ/ha)	Endpoint (mg CAZ/L)	EEC (mg CAZ/L)	RQ	LOC exceeded
Amphibians (Early Life Stage- using fish data as a surrogate)	Turf (1.547 × 2 + 4.511 × 1 at 7-day intervals)	NOEC = 0.002	Field sprayer (6% drift): 0.3	145	Yes
	White Bean (0.580 × 2 at a 7-day interval)	NOEC = 0.002	Field sprayer (6% drift): 0.04	22.3	Yes
			Aerial (23% drift): 0.2	86	Yes
	Eastern Canada Apple/Pear (0.161 × 2 at 7-day intervals)	NOEC = 0.002	Early season airblast appl. (74% drift): 0.1532	77	Yes
			Late season airblast appl. (59% drift): 0.1221	61	Yes
Estuarine/marine Species (Only acute endpoints are used in the risk assessment for estuarine marine species)					
Mysid shrimp, *Americamysis bahia* (Acute, 96-hours)	Turf (1.547 × 2 + 4.511 × 1 at 7-day intervals)	$LC_{50}/2$ = 0.55 mg a.i./L converted to 0.31mg CAZ/L	Field sprayer (6% drift): 0.054	0.2	No
	White Bean (0.580 × 2 at a 7-day interval)	$LC_{50}/2$ = 0.55 mg a.i./L converted to 0.31mg CAZ/L	Field sprayer (6% drift): 0.008	<0.1	No
			Aerial (23% drift): 0.032	0.1	No
	Eastern Canada Apple/Pear (0.161 × 2 at 7-day intervals)	$LC_{50}/2$ = 0.55 mg a.i./L converted to 0.31mg CAZ/L	Early season airblast appl. (74% drift): 0.0289	0.1	No
			Late season airblast appl. (59% drift): 0.023	0.1	No

[1] airblast application on apples/pears, field sprayer application on turf and white beans, and aerial application on white beans using ASAE medium droplet size

Table 31 Inputs for the Aquatic Buffer Zone Models

Model Input Data for Aquatic Buffer Zones	
Half-life for aquatic buffer zones	61 days
Most sensitive fish endpoint for amphibian risk assessment, 15 cm	Channel catfish, NOEC = 0.002 mg carbendazim/L
Most sensitive freshwater species, 80 cm	*Daphnia magna*, NOEC = 0.0015 mg carbendazim/L
Most sensitive estuarine/marine species	Mysid shrimp, 1/2 LC_{50} = 0.55 mg thiophanate-methyl/L = 0.31 mg carbendazim/L equivalents (based on molecular weight ratio of 0.558 thiophanate-methyl / carbendazim)

Appendix XI Proposed Label Amendments for End-Use Products Containing Thiophanate-Methyl

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the label statements provided below.

1. For all Thiophanate-Methyl End-use Products:

1.1. General Label Improvements

- On the front panel for all end use products, replace ‘guarantee’ with ‘active ingredient.’

- The following label statements are to be added to the PRECAUTIONS of all commercial-class end-use product labels (this is not required for seed treatment labels):

“Apply only when the potential for drift beyond the area to be treated is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment, and sprayer settings.”

1.2. Resistance Management Recommendations for all commercial class products:

- As per Regulatory Directive DIR2013-04, Pesticide Resistance Management Labelling Based on Target Site/Mode of Action, verify the resistance management statement on each commercial class end use product label is updated to reflect current wording. Resistance management statements should be modified to reflect the use site.

1.3. The scientific (Latin) pathogen names must be indicated for all diseases.

2. Label Amendments relating to Health Risk Assessment

2.1. Uses Proposed for Cancellation

Use instructions for the following crops/uses must be removed from the product labels.

- Aerial application of the wettable powder product
- All turf uses, except on golf courses and sod farms for the liquid and water-soluble packaging products.
- All turf uses, white bean, sugarbeet, aspen and poplar for the wettable powder product.
- Greenhouse tobacco seedlings (foliar spray and foliar drench application)
- Greenhouse ornamentals grown for cut flowers (foliar application)
- Outdoor ornamentals grown for cut flowers
- Apples and pears grown in British Columbia due to the high application rate (this use in Eastern Canada has acceptable risks due to the lower application rate).

- Peach, nectarine, plum, prune, cherry
- Commercial seed treatment of bean seeds using wettable powder products.
- On-farm dry application to bean seeds using wettable powder products.
- potato seed piece treatment

2.2. Personal Protective Equipment

2.2.1. Liquid Commercial-Class Products for Uses Other Than Seed Treatment

For commercial-class liquid agricultural products not for use as a seed treatment (for example, product with registration #32093), label statements must be amended (or added) to include the following directions under PRECAUTIONS, unless the current label mitigation is more restrictive:

> "Wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks during mixing, loading, application, clean-up and repair. In addition, wear chemical-resistant headgear during open cab airblast application. Chemical-resistant headgear includes Sou'Wester hat, chemical-resistant rain hat or large brimmed waterproof hat and hood with sufficient neck protection. Gloves are not required during application within a closed cab or cockpit."
>
> "If mixing and loading more than 260 kg a.i. in a day, a closed mixing/loading system is required."
>
> "For groundboom application, if applying more than 260 kg a.i. in a day, a closed cab tractor is required."

2.2.2. Water Soluble Package Commercial-Class Products for Uses Other Than Seed Treatment

For commercial-class agricultural products in water soluble packaging, not for use as a seed treatment (for example, product with registration #27297), label statements must be amended (or added) to include the following directions under **PRECAUTIONS**, unless the current label mitigation is more restrictive:

> "Wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks during mixing, loading, application, clean-up and repair. In addition, wear chemical-resistant headgear during open cab airblast application. Chemical-resistant headgear includes Sou'Wester hat, chemical-resistant rain hat or large brimmed waterproof hat and hood with sufficient neck protection. Gloves are not required during application within a closed cab or cockpit."

2.2.3. Wettable Powder Commercial-Class Products for Uses Other Than Seed Treatment

For commercial-class wettable powder agricultural products, not for use as a seed treatment (for example, product with registration #25343), label statements must be amended (or added) to include the following directions under PRECAUTIONS, unless the current label mitigation is more restrictive:

> "Wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks during mixing, loading, application, clean-up and repair. In addition, wear chemical-resistant headgear during open cab airblast application. Chemical-resistant headgear includes Sou'Wester hat, chemical-resistant rain hat or large brimmed waterproof hat and hood with sufficient neck protection. Gloves are not required during application within a closed cab or cockpit."
>
> "For mushroom spawn treatment or mushroom casing drench, wear a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides, or a NIOSH-approved canister approved for pesticides during mixing, loading and application activities."
>
> Under the Directions For Use: For Control of Trichoderma Green Mould on White Button Mushrooms, under Specific Limitations for Mechanical Spreading of Treated Spawn and Drench Application to the Casings, add bullet:
>
> "Wear a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides, or a NIOSH-approved canister approved for pesticides during mixing, loading and application activities for mushroom spawn treatment or mushroom casing drench."

2.3. Use Directions and Restricted-entry Interval

The use directions in terms of maximum number of applications and minimum interval between applications must be updated and revised on all labels at the appropriate section. Refer to Table 1 for those use directions.

In addition, in the Precautions Section and in other parts of the label where it is mentioned, the restricted-entry intervals (REI) must be added or revised on the thiophanate-methyl agricultural labels (these are not required for seed treatment labels). These REIs are also presented in Table 1.

The REI text on the label should be modified as follows:

- "**DO NOT** enter or allow worker entry into treated areas during the restricted-entry intervals (REI(s)) specified in the following table."
- Include a table on each label that include activities and REIs from Table 1 for the crops registered on that label, as per the following example. **Ensure that only registered crops from the following table are included in your particular product label.**

Example of Restricted-entry Interval Table

Crop	Postapplication Activity	Restricted-entry Interval [a]
Example crop #1	Corresponding activity for crop 1 from Table 1	Corresponding REI from Table 1
Example crop #2	Corresponding activity for crop 2 from Table 1	Corresponding REI from Table 1
	Corresponding activity for crop 2 from Table 1	Corresponding REI from Table 1

[a] If the REI for hand harvesting and the pre-harvest interval (PHI) are different, follow the longer of the two intervals. If the crop is harvested mechanically, with no contact with treated foliage or crop, follow the PHI. If the REI is 12 hours and a PHI is not specified, entry is not permitted until after 12 hours.

Table 1 Proposed Restricted-entry Intervals and Use Pattern for Thiophanate-methyl

Crop	Activity	Proposed REI	Maximum number of applications, minimum interval between applications [a]
Greenhouse ornamentals, including ornamentals grown for cut flowers (soil drench application)	All activities	12 hours	2 applications/season, 15 day interval
Greenhouse potted ornamentals (not including ornamentals grown for cut flowers) (foliar application)	All activities	12 hours	2 applications/season, 7 day interval
Outdoor ornamentals (not including ornamentals grown for cut flowers)	All activities	12 hours	2 applications/year, 10 day interval
White Button Mushrooms (spawn and casing treatment)	All activities	12 hours	Current label statements are to remain on the labels.
Apple, pear (Eastern Canada application rate)	All activities	12 hours	2 applications/year, 7 day interval
Strawberry	All activities	12 hours	
Raspberry	Hand harvesting, tying/training (full foliage), handline irrigation	1 day	
	All other activities	12 hours	
Low bush blueberry	Handline irrigation	1 day	2 applications/year, 10 day interval
	All other activities	12 hours	
White bean	Scouting, handline irrigation	2 days	2 applications/year, 7 day interval
	All other activities	12 hours	
Sugarbeet	All activities	12 hours	2 applications/year, 14 day interval
Aspen, poplar	All activities	12 hours	2 applications/year, 10 day interval
Sod Farms [b]	All activities	12 hours	4 applications/year (1 for pink snow mould, 1 for brown patch at the higher rate or 2 at the lower rate, 2 for dollar spot), 7 day interval
Golf Courses [b]	All activities	Until sprays have dried [c]	

Form= formulation; REI = restricted-entry interval

[a] This proposed use pattern is based on what was supported by the registrant.

[b] All other turf uses are to be removed from the label.
[c] This is standard minimum REI for golf courses.

2.4 Directions for Use

Under '**Directions For Use**', under "Greenhouse Potted Ornamentals," where there are label directions for drench application ("Stem, Crown, and Root Rots…"):

- Replace 'drench' with 'soil drench'
- Add the following statement
  "DO NOT allow pesticide solution to contact foliage."

Under '**Directions For Use**', under "Greenhouse Potted Ornamentals," add the following statement:

"DO NOT apply as a foliar spray to ornamentals grown for cut flowers"

- Add the term "Outdoors" to ornamentals that are not grown in the greenhouse.
- For outdoor ornamental uses, add the following restriction: "DO NOT use on ornamentals grown for cut flowers."

Under '**Directions For Use**', under "Turf", add the following statement:

"DO NOT apply to turf in residential areas including lawns, gardens, parks, playing fields, cemeteries and schools."

Under '**Directions For Use**', under "Turf", Remove:

"*Product name* can be applied to golf course greens, tees, fairways and other turf areas"

And Replace with:

"*Product name* can be applied to golf course greens, tees, fairways and sod farms only. DO NOT apply to turf in other residential areas including lawns, gardens, parks, playing fields, cemeteries and schools."

Under '**Directions For Use**', under "Roses, Ornamental Plants" add the following statement:

"DO NOT use on roses and ornamental plants grown for cut flowers"

For golf course and sod farm, a maximum rate per year must be indicated (20.65 kg a.i./ha per year) along with a maximum number of applications to target each disease: dollar spot (2), brown patch (1 at maximum rate or 2 at minimum rate) and pink snow mould (1). Remove the label claim for powdery mildew.

2.4. Proposed Mitigation Measures for Seed Treatment End-Use Products

The label statements and modifications required for the remaining registered seed treatment uses of thiophanate-methyl, based on the occupational risk assessment are outlined in Table 2 below. Note: more restrictive protective equipment currently required on product labels, such as goggles and respiratory protection, are to be maintained in the product-specific statements, where present.

Table 2 Proposed Label Modifications for Currently Registered Thiophanate-Methyl Seed Treatment End-Use Products

Reg #	Form	Currently Registered		Required Action/Mitigation
		Scenario	Crop	
31761	Liquid	Commercial and on-farm seed treatment	Sweet corn, dry common bean	Under '**PRECAUTIONS' -** the product label must be amended as follows: Remove: "Wear a long-sleeved shirt, long pants, chemical resistant gloves, protective eyewear and a respirator fitted to exclude dust. When handling or planting treated seed, wear a long-sleeved shirt, long pants, chemical resistant gloves, protective eyewear and a respirator fitted to exclude dust." Add: "Use closed transfer for commercial seed treatment (facilities and mobile treaters). Closed transfer includes closed mixing, loading, calibrating and closed treatment equipment. No open transfer is permitted for commercial seed treatment. " "When treating, handling, or planting treated seed, wear a long-sleeved shirt, long pants, shoes plus socks, protective eyewear, chemical-resistant gloves, and NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit-tested. Closed cab tractors must be used for planting treated seeds. Respirators and chemical-resistant gloves are not required to be worn within the closed cab as long as the cab is equipped with equivalent respiratory protection (dust/mist filtering and/or vapour/gas purification system)." From the 'All treated seed…' paragraph under precautions, remove: "Wear a long-sleeved shirt, long pants, chemical resistant gloves, and a respirator fitted to exclude dust when handling treated seed." Add: • "For all activities involving handling of treated seeds (including planting), wear a long-sleeved shirt, long pants, shoes plus socks, protective eyewear, chemical-resistant gloves, and NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit-tested. Closed cab tractors must be used for planting treated seeds. Respirators and chemical-resistant gloves are not required to be worn within the closed cab as long as the cab is equipped with equivalent respiratory protection (dust/mist filtering and/or vapour/gas purification system)."
26987	WP	Commercial and on-farm seed treatment	Sweet corn, dry common bean	The front panel of the product label must be amended as follows: Add: "For on-farm seed treatment only. No commercial seed treatment (in facilities or with mobile treaters) is permitted." Under '**PRECAUTIONS' -** the product label must be amended as follows: Remove: "Wear a long-sleeved shirt, long pants, chemical resistant gloves, protective eyewear and a respirator fitted to exclude dust. When handling or planting treated seed, wear a long-sleeved shirt, long pants, chemical resistant gloves, protective eyewear and a respirator fitted to exclude dust." Add: "When treating, handling, or planting treated seed, wear a long-sleeved shirt, long pants, shoes plus socks, protective eyewear, chemical-resistant

Reg #	Form	Currently Registered		Required Action/Mitigation
		Scenario	Crop	
				gloves, and NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit-tested. Closed cab tractors must be used for planting treated seeds. Respirators and chemical-resistant gloves are not required to be worn within the closed cab as long as the cab is equipped with equivalent respiratory protection (dust/mist filtering and/or vapour/gas purification system)."
				Under '**PRECAUTIONS'-** the product label must be amended as follows, as commercial treatment is proposed to be cancelled: From the 'All bags containing treated seed …' paragraph under precautions, remove: "WEAR A LONG-SLEEVED SHIRT, LONG PANTS, CHEMICAL RESISTANT GLOVES AND A RESPIRATOR FITTED TO EXCLUDE DUST WHEN HANDLING TREATED SEED.' Add: "For all activities involving handling of treated seeds (including planting), wear a long-sleeved shirt, long pants, shoes plus socks, protective eyewear, chemical-resistant gloves, and NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit-tested. Closed cab tractors must be used for planting treated seeds. Respirators and chemical-resistant gloves are not required to be worn within the closed cab as long as the cab is equipped with equivalent respiratory protection (dust/mist filtering and/or vapour/gas purification system)."
				Under '**'Directions for Use'-** the product label must be amended as follows: Replace: "Dry Common Beans (*Phaseolus vulgaris*) For Slurry Machines:…" With: "…Dry Common Beans (*Phaseolus vulgaris*) For Slurry Machines (on-farm treatment only):…" Add: "For on-farm use only. **DO NOT** use for commercial seed treatment (in facilities or with mobile treaters)."
				Under '**'Directions for Use'-** the product label must be amended as follows: Remove: **"For Hand Mixing:** For each 25 kg of seed use 130 g in 350 mL of water. Mix well to keep powder suspended in water, pour over the seed and mix with a paddle or shovel until evenly coated. Do not use bare hands for mixing. Dry the seed before seeding or bagging."

Reg# = registration #; Form = formulation; WP = wettable powder

3. Label Amendments relating to Environmental Risk Assessment

3.1. Under "Environmental Precautions":

Toxic to aquatic organisms. Observe buffer zones specified under DIRECTIONS FOR USE.

Toxic to birds and small wild mammals. Any spilled or exposed seeds must be incorporated into the soil or otherwise cleaned-up from the soil surface.

Toxic to bees. Minimize spray drift to reduce harmful effects on bees in habitats close to the application site. Avoid application during the crop blooming period. If applications must be made during the crop blooming period, restrict applications to the evening when most bees are not foraging. Avoid applications when bees are foraging in the treatment area in ground cover containing blooming weeds. To further minimize exposure to pollinators, refer to the complete guidance "Protecting Pollinators during Pesticide Spraying – Best Management Practices" on the Health Canada website (***www.canada.ca/pollinators***).

Toxic to earthworms.

By-products from this product are toxic to aquatic organisms. Do not store waste piles of treated mushroom compost in an area which will allow runoff into surface waters.

To reduce runoff from treated areas into aquatic habitats avoid application to areas with a moderate to steep slope, compacted soil, or clay.
Avoid application when heavy rain is forecast.
Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

3.2. Under 'Directions for Use':

To protect pollinators, follow the instructions regarding bees in the Environmental Precautions section

As this product is not registered for the control of pests in aquatic systems, DO NOT use to control aquatic pests.

DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.

DO NOT allow effluent or runoff from greenhouses or mushroom houses containing this product to enter lakes, streams, ponds or other waters.

3.3. The following statement is required on all agricultural or commercial products, unless aerial application (blueberries, white beans) is permitted:

DO NOT apply using aerial application equipment.

3.4. For blueberries and white beans:

Aerial application: DO NOT apply during periods of dead calm. Avoid application of this product when winds are gusty. DO NOT apply when wind speed is greater than 16 km/h at flying height at the site of application. DO NOT apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Reduce drift caused by turbulent wingtip vortices. Nozzle distribution along the spray boom length MUST NOT exceed 65% of the wing- or rotorspan.

3.5. For all agricultural or commercial products:

Field sprayer application: DO NOT apply during periods of dead calm. Avoid application of this product when winds are gusty. DO NOT apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Boom height must be 60 cm or less above the crop or ground.

Airblast application: DO NOT apply during periods of dead calm. Avoid application of this product when winds are gusty. DO NOT direct spray above plants to be treated. Turn off outward pointing nozzles at row ends and outer rows. DO NOT apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side.

3.6. Buffer zones:

Spot treatments using hand-held equipment DO NOT require a buffer zone.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands), sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats.

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:			
			Freshwater Habitat of Depths:		Estuarine/Marine Habitat of Depths:	
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m
Field sprayer	Sugarbeet		4	1	0	0
	Lowbush blueberry, aspen, poplar, roses, ornamental plants, strawberry, raspberry		5	1	0	0
	White bean		10	2	0	0
	Turf		55	10	1	0
Airblast	Roses, ornamental plants	Early growth stage	35	15	0	0
		Late growth stage	25	5	0	0
	Lowbush blueberry, aspen, poplar, raspberry	Early growth stage	40	15	0	0
		Late growth stage	30	10	0	0
	Cherry, prune, peach, nectarine, plum	Early growth stage	45	20	0	0
		Late growth stage	35	10	0	0
	Apple, pear	Early growth stage	45	25	0	0
		Late growth stage	35	15	0	0

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:			
			Freshwater Habitat of Depths:		Estuarine/Marine Habitat of Depths:	
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m
	Apple, pear (for products requiring tank mixing with captan: Reg. Nos. 12279, 25343, 27297, 31784, 32096)	Early growth stage	35	10	0	0
		Late growth stage	25	5	0	0
Aerial	White bean	Fixed wing	600	25	0	0
		Rotary wing	550	25	0	0
	Lowbush blueberry	Fixed wing	175	15	0	0
		Rotary wing	150	10	0	0

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site.

3.7. Under “Use Restrictions”:

Toxic to birds and small wild mammals. Any spilled or exposed seeds must be incorporated into the soil or otherwise cleaned-up from the soil surface.

3.8. Under “Storage”:

To prevent contamination store this product away from food or feed.

3.9. Statements in the “Disposal” section should conform to DIR99-04 Disposal Statements for Control Product Labels.

References

Toxicological Assessment

A. Studies/Information Provided by Applicant/Registrant

PMRA document number	Reference
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1157209	1990, Oncogenicity Studies with Benomyl and MBC in Mice-Supplemental Peer Review, DACO 4.4.3
1407065	2003, Five-Day Toxicity Study of Mergal BCM in Rats. and Amendment, DACO 4.7
1783049	2007, 28 Day Dermal Toxicity Study of Carbendazim (CAS No. 10605-21-7) Administered to Male and Female CD (Sprague-Dawley) Rats, DACO 4.3.5 part 1
1783050	2007, 28 Day Dermal Toxicity Study of Carbendazim (CAS No. 10605-21-7) Administered to Male and Female CD (Sprague-Dawley) Rats, DACO 4.3.5 part 2
1783054	2007, 28 Day Dermal Toxicity Study of Carbendazim (CAS No. 10605-21-7) Administered to Male and Female CD (Sprague-Dawley) Rats, DACO 4.3.5 part 3
1783063	2008. Benchmark Dose Modeling for Reproductive Endpoints from Dermal Toxicity Study for Carbendazim (47371601), DACO 4.3.8
2490664	2014, An F1-Extended Two-Generation Reproductive Toxicity Study with Carbendazim in the Wistar Rat, DACO 4.8
2721396	1993, Historical Control and Method Validation Studies in Rats for the Acute and Subchronic Neurotoxicity Screening Battery, DACO 4.5.1
2721397	2001, Historical Control and Method Validation Studies for a Developmental Neurotoxicity Screening Battery Auditory Startle Habituation and Cognitive Function (Passive Avoidance and Water Maze Conditioning), DACO 4.5.1
2721398	2002, Motor Activity Assessment - Historical Control and Method Validation Study Using Triadimefon and Chlorpromazine in Wistar Rats, DACO 4.5.1
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B. Additional Information Considered

i) Published Information

PMRA Document Number	Reference
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2952523	2001, Revised Occupational and Residential Exposure Assessment and Recommendations for the Risk Assessment Document for Carbendazim (MBC). USEPA, DACO 12.5
2965082	1973, Carbendazim WHO Pesticides Residue Series 3. JMPR 1973, DACO 12.5
2977622	1995, Thiophanate-Methyl. JMPR. P. 351-373, DACO 12.5
2976565	1992, Thiophanate-Methyl. Ministry of Agriculture, Fisheries and Food (MAFF), DACO 12.5
2946557	1997, Monograph Carbendazim. White Draft. GRMG, DACO 12.5
2976563	2003, Addendum 5 to the Monograph of 13 November 1997, Carbendazim, DACO 12.5

Dietary Assessment

A. Studies/Information Provided by Applicant/Registrant

PMRA Document Number	Reference
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1530420	1992, Addendum 1 to Metabolism of the Fungicide 14C-Thiophanate-methyl in Lactating Goats, DACO: 6.2
1530421	1993, Isolation, Characterization, and Identification of Unknown Metabolite(s) from Goats Liver Treated with 14C-Thiophanate Methyl, DACO: 6.2
1530422	1992, 14C-Thiophanate Methyl Nature of the Residue in Laying Hens, DACO: 6.2
1530432	2003, Stability of Thiophanate-methyl in Soybean Seed During Frozen Storage Pending Analysis, DACO: 7.3
1530433	2000, Thiophanate Methyl Frozen Storage Stability of Residues in/on Whole Apples, DACO: 7.3
1530434	1996, Residue Stability Study Of MBC (Methyl-2-Benzimidazole Carbamate) IN SNAP Beans, Apples, Wheat Grain, Spinach, Sugar Beet Roots, And Tomatoes, DACO: 7.3
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1530438	2002, Stability of Thiophanate-Methyl in Cucumbers During Frozen Storage Pending Analysis, DACO: 7.3
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1530412	1997, Magnitude of the Residue of Thiophanate-Methyl in Milk and Tissue of Lactating Dairy Cattle, DACO: 7.5.1
2432575	2002, Comparison of Thiophanate-Methyl Residues from Crop Field Trials Conducted with Various Formulations, DACO: 7.4.1
2437646	1996, Thiophanate Methyl and Its Metabolites: Magnitude Of The Residue in Snap Bean, DACO: 7.4.1
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1075678	2004, Thiophanate-methyl and Carbendazim in/on Tobacco., DACO: 7.7
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Occupational and Residential Assessment

A. Studies/Information Provided by Applicant/Registrant

PMRA Document Number	Reference
2930750	2015, 14C-Thiophanate methyl: Dermal (6-hour Occlusive) Skin Absorption Study in Wistar Rats, DACO: 5.8
2930751	1981, Precutaneous Absorption of 14C-Thiophanate-methyl in Rats, DACO: 5.8
2930753	1981, Precutaneous Absorption of 14C-Thiophanate-methyl in Rats - Supplemental report to RD-8108, DACO: 5.8
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B. Studies/Information Provided by Task Forces

PMRA Document Number	Reference
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2313626	2006, Admire 240F - Determination of Dermal and Inhalation Exposure of Workers During On-Farm Seed Piece Treatment of Potatoes, DACO: 5.4

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C. Additional Information Considered

i) Unpublished Information

PMRA Document Number	Reference
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2313625	2013, Gaucho 480 SC – Worker Exposure During On-farm and Commercial Seed Treatment of Cereals, DACO: 5.3,5.4
2557310	2015, Observational Study to Determine Dermal and Inhalation Post-Application Exposure of Workers to Difenoconazole During Handling and Planting of Treated Potato Seed Pieces, DACO: 5.6

ii) Published Information

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PMRA Document Number	Reference
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