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Proposed Re-evaluation Decision PRVD2016-07

Thiram

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Table of Contents

Overview

What is the Proposed Re-evaluation Decision?

After a re-evaluation of the fungicide thiram, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing the cancellation of all thiram uses in Canada.

An evaluation of available scientific information found that, under the current conditions of use, thiram products pose potential risks of concern to human health and the environment. Based on the health and environmental assessments, risks of concern were identified for both workers and the general public in addition to birds, mammals and aquatic organisms.

This proposal affects all end-use products containing thiram registered in Canada. This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for thiram and presents the reasons for the proposed re-evaluation decision.

The information is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides additional technical information on the assessment of thiram.

PMRA will accept written comments on this proposal up to 60 days from the date of publication of this document. Please forward all comments to Publications (please see contact information indicated on the cover page of this document).

What Does Health Canada Consider When Making a Re-evaluation Decision?

PMRA's pesticide re-evaluation program considers potential risks as well as the value of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2001-03, PMRA Re-evaluation Program, presents the details of the re-evaluation activities and program structure. Re-evaluation draws on data from registrants, published scientific reports, information from other regulatory agencies and any other relevant information.

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

What is Thiram?

Thiram is a contact protectant fungicide registered in Canada for both food and nonfood uses. It is registered to control diseases as seed treatment (cereal, oilseed, pulse, vegetable, fruit and feed crops), foliar spray application on tree fruits (apple, peach and plum), strawberry and celery (plant beds), root dip of sweet potato, and as an animal repellent to protect dormant outdoor ornamentals and young fruit trees. Thiram is applied by growers, farm and nursery workers and professional applicators.

Health Considerations

Can Approved Uses of Thiram Affect Human Health?

Based on the human health risk assessment, all uses of thiram are proposed for cancellation.

Exposure to thiram may occur through diet, when handling the product or by entering treated sites. When assessing health risks, two key factors are considered: the levels at which no health effects occur and the levels to which people may be exposed.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose at which no effects are observed. Unless there is evidence to the contrary, it is assumed that effects observed in animals are relevant to humans and that humans are more sensitive to effects of a chemical than the most sensitive animal species. For thiram, toxicology endpoints from a developmental neurotoxicity study in rats were used for risk assessment. Based on the weight of evidence from the available studies, a cancer unit risk value was also established for thiram.

The risk assessment compares the estimated level of human exposure to the no-effect doses identified in the animal tests. The reference values used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). The estimated exposure to thiram from domestically produced and imported food commodities exceeded the acute, chronic and cancer reference values established from the toxicology database. Potential risks of concern were identified for workers handling thiram products during mixing/loading and application as well as from planting treated seeds and re-entering treated sites following application. Potential risks of concern were also identified for handlers of the domestic-class product as well as for individuals coming into contact with treated fruit trees in residential settings.

The thiram health risk assessment has considered the currently registered use pattern and label directions as well as additional mitigation measures to reduce exposure such as additional personal protective equipment, engineering controls, reduced application rates and cancellation of certain uses.

Environmental Considerations

What Happens When Thiram is Introduced Into the Environment?

The use of thiram poses potential risks to birds, mammals and aquatic organisms that cannot be fully mitigated.

Thiram can enter nontarget terrestrial and aquatic habitats through spray drift and can enter aquatic habitats through runoff. Thiram is soluble in water and does not vaporize when sprayed on crops and is not expected to enter the atmosphere and be transported long distances from where it is used. Thiram is non-persistent in soil and water, breaking down quickly and is not likely to accumulate in fish tissues. Thiram has the potential to move through the soil profile and contaminate groundwater in some types of soil.

When exposed to high enough concentrations, thiram is toxic to birds and mammals, which may be at risk if they consume food sources that have been sprayed with this pesticide. Aquatic organisms are also potentially at risk due to exposure to thiram. The environmental risk assessment considered the currently registered use pattern as well as mitigation in the form of spray buffer zones and label statements highlighting the risk of runoff, however, risks to birds and aquatic organisms cannot be fully mitigated.

Value Considerations

What is the Value of Thiram?

Thiram is important for the control of several fungal root diseases on many cereal, oilseed, pulse, vegetable, fruit and feed crops; for the control of several fungal diseases on apple, peach, plum, strawberry and celery; and as an animal repellent to protect dormant outdoor ornamentals and young fruit trees. It is a contact protectant fungicide with multi-site mode of action. It is most often used in coformulation with single-site fungicides for broader disease control, and resistance management, thereby prolonging the effective life of these fungicides which are highly prone to the development of resistance. According to proprietary pesticide usage data, thiram is most often applied as a seed treatment, with the highest use on canola, dry beans, rye, flax and wheat.

Proposed Measures to Minimize Risk

Based on the available data and current risk assessments, Health Canada is proposing cancellation of all uses of thiram. Consequently, all maximum residue limits are proposed for revocation.

Next Steps

The PMRA is inviting stakeholders to submit comments on this document, as well as detailed proposals to further refine the risk assessment and mitigate risks. The PMRA will accept comments and proposals for a period of 60 days from the date of publication of this document. Please forward all comments to Publications.

Before making a final decision on thiram, the PMRA will consider all comments or proposals received from the public in response to this consultation document. A science-based approach will be applied in making a final decision on thiram. The PMRA will then publish a re-evaluation decision document, which will include the decision and the reasons for it, a summary of the comments and proposals received on the proposed decision and the PMRA's response to these comments and/or proposals.

If no proposals to refine the risk assessment are received, or if those received are inadequate, then the PMRA will proceed to finalize the re-evaluation decision to cancel all thiram uses in Canada.

Science Evaluation

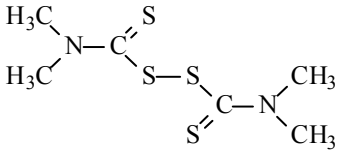
1.0 Introduction

Thiram is a contact, protectant fungicide with multi-site mode of action and belongs to Mode of Action (MoA) group M3. It is registered to control diseases as seed treatment (cereal, oilseed, pulse, vegetable, fruit and feed crops), foliar spray application on tree fruits (apple, peach and plum), strawberry and celery (plant beds), root dip of sweet potato, and as an animal repellent to protect dormant outdoor ornamentals and young fruit trees.

Currently, there are two technical grade active ingredients, one manufacturing concentrate, 16 commercial and one domestic end-use products registered in Canada. Most of the end-use products are coformulated with other fungicides and/or insecticides. The commercial end-use products are formulated as dust, suspensions, water-dispersible granules or wettable powders. The domestic end-use product is formulated as a suspension.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient

Common name	Thiram
Function	Fungicide
Chemical Family	Dithiocarbamate
Chemical name	
1 **International Union of Pure and Applied Chemistry (IUPAC)**	Tetramethylthiuram disulfide; bis(dimethylthiocarbamoyl) disulfide
2 **Chemical Abstracts Service (CAS)**	Tetramethylthioperoxydicarbonic diamide
CAS Registry Number	137-26-8
Molecular Formula	$C_6H_{12}N_2S_4$
Structural Formula	
Molecular Weight	240.4

Registration Number	Purity of the Technical Grade Active Ingredient
18422	98.0% nominal (95.06-99.70%)
18595	98.4% nominal (98-100%)

2.2 Identity of relevant impurities of human health or environmental concern

Based on the manufacturing process used, impurities of human health or environmental concern as identified in the Canada Gazette, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances, are not expected to be present in the product.

2.3 Physical and Chemical Properties of the Technical Grade Active Ingredient

Property	Result
Vapour pressure at 25°C	2.3 mPa
Ultraviolet (UV)/visible spectrum	Does not absorb at λ >350 nm
Solubility in water at room temperature	18 mg/L
n-Octanol/water partition coefficient	Log P = 1.73
Dissociation constant	pKa = 8.19

2.4 Description of Registered Thiram Uses

Thiram is registered in Canada as a seed treatment for the control of many fungal diseases on alfalfa, barley, beans (dry common), beans (snap common), beets, broccoli, bromegrass, Brussels sprouts, cabbage, canola, cantaloupe, carrot, cauliflower, corn (field, sweet), cucumber, eggplant, flax, grasses, lentils, lettuce, mustard (oilseed Juncea), oats, onions (dry bulb), peas, pepper, pumpkin, radish, rapeseed, rye, safflower, soybeans, spinach, squash, sugar beet, sweet potatoes, tomato, triticale, turnip, watermelon and wheat. Thiram is registered for use as a foliar spray for the control of specific diseases on apples, celery (in plant beds), peaches, plums and strawberries. It is also registered for use as an animal repellant on ornamental trees, including arrowwood (Viburnum), ash, basswood, buckthorn, buffaloberry, cherry, crab apple, cranberry, dogwood, dormant apple, elm, euonymus, hackberry, holly, honeysuckle, indigo bush, juneberry, lespedeza, lilac, locust, magnolia, maple, multiflora rose, olive, plum, poplar, prune, redbud, tulip and walnut. Registered use of thiram belongs to the following use-site-categories: seed and plant propagation materials food and feed, terrestrial feed crops, terrestrial food crops, ornamental outdoor and various indoor and outdoor sites.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Thiram is a member of the dimethyl dithiocarbamate group of fungicides, which includes the related active ingredients ziram and ferbam. The database for thiram is extensive including the standard battery of assays, as well as a wealth of oncogenicity, genotoxicity, developmental toxicity and neurotoxicity data. Published studies were also incorporated into the hazard assessment. Overall, the toxicology database for thiram was considered adequate to characterize the toxicity profile of this active ingredient. The evidence from the animal toxicology database suggested that the most sensitive endpoint of concern for thiram is neurotoxicity. The neurotoxicity profile of thiram indicated effects on both the central and the peripheral nervous systems which were mainly characterized by reduced learning and memory capacity, altered motor activity, ataxia and paralysis of the hind legs. Exposure to thiram can produce effects similar to those of disulfiram (Antabuse, the ethyl analogue of thiram) by inhibiting acetaldehyde dehydrogenase, an enzyme responsible for metabolizing alcohol. These effects include symptoms of nausea, vomiting, pounding headache, dizziness, faintness, mental confusion, chest and abdominal pain, dyspnea, sweating, and skin rash.

Thiram was readily absorbed (via the oral route), distributed, and extensively metabolized in the rats. Elimination occurred primarily through the expired air and the urine of rats following low acute or repeat dose administration. Available studies indicated that within 24 hours of administration of ^{14}C-thiram to rats, a high amount of radioactivity was eliminated as expired air in the form of volatile compounds which included carbon dioxide (CO_2), carbamyl sulfide (COS), and carbon disulfide (CS_2). The parent compound was not detected in the urine. Recovery of the radioactivity was low in the feces. There were no apparent sex-related differences in the distribution, metabolism or excretion of ^{14}C-thiram. The recovered concentration of ^{14}C-thiram in tissues was low (1-4% of the administered dose). Therefore, an appreciable accumulation of thiram is not anticipated after repeated exposures.

Following acute administration, thiram was of slight oral toxicity in rats, low dermal toxicity in rabbits, and low inhalation toxicity in rats. Thiram was moderately irritating to rabbit eyes, non-irritating to rabbit skin and was a skin sensitizer in guinea pigs.

In short- or long-term oral toxicity studies in which test animals were administered thiram, body weight and the nervous system were commonly affected. Additional target organs of toxicity were the stomach, pancreas, liver, thyroid, and mesenteric lymph nodes in the rat and the liver and blood in the dog.

In a short-term dietary study in rats, decreased body weight, increases in the incidence and severity of the lesions in the nonglandular stomach, and an increase in the incidence of the congested mesenteric lymph nodes were noted. Mucosal hyperplasia, submucosal inflammation and ulceration of the non-glandular stomach comprised the lesions noted in the stomach.

In short-term oral studies in dogs, toxicity was manifested as nausea, vomiting, decreased food consumption and body weight, anemia, elevated cholesterol, and increased absolute and relative liver weights. At longer duration of exposure or higher dose levels, these signs of toxicity were more severe. Additionally, hepatic lesions, which included necrosis and degeneration of the liver, increased in incidence and severity. Neurotoxic effects noted in the dogs included fits and clonic convulsions at the high doses. Other types of neurotoxicity assessment (for example, Functional Observational Battery, motor activity) were not conducted.

Thiram elicited a positive response in a series of *in vivo* (dominant lethal mutation assay in mouse) and *in vitro* (bacterial/Ames assays with and without metabolic activation) gene mutation assays, but was negative in a mammalian cell mutagenicity assay. In the two available chromosomal aberration assays with Chinese hamster ovary cells, thiram produced a negative response in the test conducted without an incubation period, and was positive in the test conducted with an incubation period at slightly higher doses. In the sister chromatid exchange assay with human lymphocytes, thiram induced increases in sister chromatid exchange over controls in the presence and absence of metabolic activation. In three available mouse micronucleus assays, positive responses were observed in two of the three assays. Overall, the weight of evidence from the battery of genotoxicity tests suggested that thiram was mutagenic (both *in vitro* and *in vivo*) and clastogenic.

In the two-year mouse oncogenicity study, thiram elicited retinal atrophy, decreased body weight, intracellular protein-like droplets in the urinary bladder, increased pigmentation of the spleen and lesions in the non-glandular stomach. There was no evidence of oncogenicity in this study.

In the supplementary two-year rat study, decreased body weight and food consumption were observed in both sexes at the high dose. In females, slight anaemia and increased incidences of atrophy of the calf muscles, myocardium, and sciatic nerves were also noted at the same dose.

A supplementary 80-week dietary study in rats showed increased incidence and severity of fatty infiltration of pancreas and increased incidence of squamous metaplasia of the thyroid. When neurotoxicity was assessed in the satellite group of female rats given the high dose diet in this study, animals exhibited ataxia and paralysis of the hind legs which were associated with demyelination and degeneration of axon cylinders, and the presence of macrophages in the sciatic nerve bundle. Other neurotoxic effects in this group included loss of motor function, degeneration of ventral horn in the lower lumber spine, and clasping of the hind feet when picked up by the tail.

In the two-year dietary rat study, the main target organs of toxicity were the liver and the thyroid. Pre-neoplastic and neoplastic lesions, which were evident in these organs, were characterized by thyroid C-cell hyperplasia, thyroid C-cell adenomas, liver bile duct hyperplasia, and hepatocellular adenomas. Other effects included reduced body weight and food consumption, and increased incidence of steatosis and/or fatty infiltration of the pancreas. In addition to these effects, males exhibited increased congestion of mesenteric lymph nodes and pancreatic acinar atrophy, while anaemia and cystic adrenals were observed in the high-dose females.

The carcinogenic potential of thiram was considered in this two-year dietary study in rats and within the context of all available toxicity data. In this study, statistically significant positive trends and a dose-dependent increase in the incidences of thyroid C-cell and hepatocellular adenomas in both sexes were noted; however, the incidences of these tumours were not statistically significant in the pairwise analysis. The incidences of thyroid C-cell adenomas in females and hepatocellular adenomas in males exceeded those of the historical control means starting at the mid-dose. At the high dose, these incidences reached the upper range of the historical control for these findings. In addition, a clear dose-related increase in the incidence of the pre-neoplastic lesion (for example, thyroid C-cell hyperplasia) in females was noted in this study. Further evidence of the carcinogenic potential of thiram was noted elsewhere in the database. For example, in the supplementary 80-week study in rats with the same strain, evidence of squamous metaplasia of thyroid was noted. In addition, evidence of similar thyroid and liver tumours were observed in a two-year rat study which was conducted with a test substance containing ziram (a structurally similar compound) and 6.5% thiram. And finally, the weight of evidence from the genotoxicity profile indicates that thiram is a mutagenic compound. It was concluded that the degree of concern for carcinogenic potential of thiram was high and a cancer unit risk was therefore calculated.

Two supplementary two-generation reproduction toxicity studies in rats and a number of nonguideline studies on sperm, fertility and reproduction in rats and mice were available in the thiram toxicology database. The first two-generation reproduction toxicity study resulted in poor reproductive performance across all groups including the control group rendering the study supplementary. A similar issue of poor reproductive performance was encountered in the follow-up two-generation reproduction toxicity study. Additionally, other reproductive parameters, including sperm analysis, were not conducted in the second study. Overall, poor fertility (≤ 80%) was observed in all treated and control groups in both two-generation reproduction toxicity studies. Treatment related effects in these two studies included reduced body weight, body weight gain, and food consumption. In the second study, decreased body weight was noted in the offspring generations at a dose that did cause any adverse effects in the parental generations. In the nonguideline reproduction toxicity studies, a NOAEL of 10 mg/kg bw/day was identified based on sperm abnormalities, testicular effects, and failure of male rats to mate successfully with females observed at the higher doses. Since the references doses selected for the risk assessment were several fold lower than this NOAEL, concern is accounted for with respect to the poor reproductive performance in the two-generation studies and an additional two-generation reproduction toxicity study is not required at this time.

Two standard developmental toxicity studies are available for thiram, including one in rats, and one in rabbits. In the rat developmental toxicity study, reduced body weight was observed in the treated dams and at higher doses in the treated pups. Other developmental effects, which were observed at a maternally toxic dose included increased incidences of large anterior fontanelle, incomplete ossification of numerous bones, and reduced length of the 13th rib. In the rabbit developmental toxicity study, doses up to 10 mg/kg bw/day did not elicit any developmental or maternal toxicity. Although the maximum tolerated dose was not reached in this study, treatment-related effects were observed in the preliminary range-finding study at 7.5 mg/kg

bw/day and above, and therefore, an additional rabbit developmental toxicity study is not required at this time.

In the acute neurotoxicity studies conducted with thiram, decreased motor activity levels and habituation, lethargy (including reduced body weight and lower temperature), reduced startle response and the absence of a tail-pinch response were observed a few hours post treatment. Females were more affected than males, exhibiting increased cage posture and forelimb grip strength, as well as reduced handling reactivity, number of rears, approach response, muscle tone, and air righting, at doses producing decreased body weight. Males also exhibited decreased arousal, decreased palpebral closure, increased urination and lacrimation.

In the short-term neurotoxicity study, reduced body weight and food consumption were observed. At the high-dose, decreased absolute brain weights, and decreased motor activity habituation were observed.

In the developmental neurotoxicity (DNT) study, reduced body weight and increased incidence of congested mesenteric lymph nodes were observed in the dams at the high dose. No other findings were observed in the dams at lower doses. Effects were noted in the offspring at the mid-dose including reduced body weight, increased mean activity counts, altered motor activity levels, reduced motor activity habituation, and increased time taken to complete the Morris water maze.

The signs of neurotoxicity in the DNT study at the high dose were more severe and occurred in the presence of maternal toxicity. Other effects at the high dose included a decrease in the number of males completing the Morris water maze, an increase in the size of hippocampus in male pups and an increase in the size of neocortex in female pups. The increased time taken to complete the Morris water maze indicated treatment-related effects on learning and memory as were the results from the brain morphometrics analyses (in other words, the increase in the size of hippocampus and neocortex). The brain morphometric analysis was not conducted in the mid- and low-dose groups.

The toxicology endpoints used in the human health risk assessment for thiram are summarized in Appendix I.

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 take into account completeness of the data with respect to 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 for the assessment of risk to infants and children, the database is considered adequate. Data available included nonguideline studies that assessed sperm anomalies, fertility and reproduction in rats and mice, two supplementary two-

generation reproduction toxicity studies in rats, two developmental toxicity studies (one in rats and one in rabbits), and one developmental neurotoxicity study in rats.

With respect to identified concerns relevant to the assessment of risk to infants and children, treatment-related effects in the pups were noted at maternally toxic doses in the developmental toxicity studies in rats and rabbits. However, a sensitivity of the young was observed in the two-generation reproduction toxicity and DNT studies. In the two-generation reproduction toxicity study, decreased body weight of the young was noted at a dose that did not cause adverse effects in the parental animals. In the DNT study, decreased body weight, altered motor activity, reduced motor activity habituation, and effects on learning and memory were noted at a dose that did not cause any maternal toxicity.

Effects on learning and memory in the young in the DNT study were considered serious and were consistent with the brain morphometric results at the high dose. This study lacked the brain morphometric examination for the pups at the mid- and low doses. Since the neurobehavioral effects in the young were also observed in the absence of maternal toxicity, a high degree of concern was identified. Therefore, the *Pest Control Products Act* factor was retained at 10-fold for both acute and repeated exposure scenarios when using the DNT study to establish the point of departure for risk assessment.

3.2 Occupational and Non-Occupational Risk Assessment

3.2.1 Toxicology Endpoint Selection for Occupational and Residential Risk Assessment

Occupational and bystander (all durations, dermal and inhalation routes)

For characterization of occupational and residential, dermal and inhalation, risks for all durations, an oral No Observed Adverse Effect Level (NOAEL) of 1.86 mg/kg bw/day from the developmental neurotoxicity study was selected as the most appropriate endpoint. At the Lowest Observed Adverse Effect Level (LOAEL) of 4.36 mg/kg bw/day, reduced body weight, altered motor activity, decreased motor activity habituation, and increase in time taken to complete the Morris maze were observed in the young animals in the absence of maternal toxicity. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The *Pest Control Products Act* factor was retained at 10-fold for risk assessments pertaining to residential scenarios. For occupational scenarios, an additional 10-fold factor was considered for protecting any potentially sensitive populations including pregnant workers. Therefore, the target Margin of Exposure is 1000-fold for occupational and residential assessments.

Unit Risk for Cancer Assessment

A linear low dose extrapolation (q_1*) assessment was conducted for thyroid C-cell adenomas in females and hepatocellular adenomas in males observed in a two-year dietary study in rats. The calculated q_1* value for both tumour incidences was 3.5×10^{-2} (mg/kg bw/day)$^{-1}$.

Absorption Factors

For extrapolation of an oral endpoint for dermal risk assessment, a dermal absorption factor of 50% was established based on the physical/chemical properties of the active ingredient (solubility, physical state, molecular size). For inhalation risk assessment, 100% inhalation absorption was assumed.

3.2.2 Occupational Exposure and Risk Assessment

Workers can be exposed to thiram while mixing/loading and applying products containing this active ingredient, planting treated seeds, or when entering treated sites to conduct postapplication activities.

3.2.2.1 Mixer, Loader and Applicator Exposure and Risk Assessment for Foliar, Root-dip and Animal Repellant Uses

The following handler exposure scenarios were considered based on the supported thiram use pattern:

- Mixing/loading of wettable powder (WP) or water dispersible granule (WDG) formulations and applying as a liquid spray using groundboom equipment (celery, strawberry);
- Mixing/loading of WP or WDG formulations and applying as a liquid spray using airblast equipment (apple, peach, plum);
- Mixing/loading of WP or WDG formulations and dip application (sweet potato), and
- Mixing/loading and applying of liquid animal repellent using a paintbrush, a manually-pressurized handgun, or a backpack sprayer.

For all assessed mixer/loader/applicator (M/L/A) scenarios, occupational exposure was considered to be of short-/intermediate-term duration.

Combined (dermal and inhalation) exposure estimates for workers mixing/loading and applying thiram using groundboom, airblast, or hand-held equipment (for animal repellent) were calculated using unit exposure values for mixers/loaders and applicators from the Canadian Pesticide Handlers Exposure Database (PHED) Version 1.1 and the Agriculture Handler Exposure Task Force (AHETF). For workers involved in dip application, exposure estimates were calculated using surrogate data from the published literature.

Default area treated per day (ATPD) values were assumed for the airblast and groundboom strawberry assessments. For the groundboom celery assessment, ATPD assumptions were based on crop specific production statistics from Statistics Canada. For the animal repellent assessment, volumes handled per day were assumed based on the United States Environmental Protection Agency (USEPA) Residential Standard Operating Procedures (SOPs) for gardens and trees applications. Additional assumptions for risk assessment included the maximum application rates and a worker body weight of 80 kg. Lifetime average daily dose values were calculated by amortizing exposure over the lifetime assuming workers would work 30 days per year for 40 years with a life expectancy of 78 years.

Personal protective equipment (PPE) to be used by occupational handlers is not specified on all thiram product labels. For the purpose of the mixer/loader/applicator risk assessment, exposure estimates were determined for workers wearing different levels of PPE. In addition to standard equipment, the use of engineering controls such as closed mixing/loading systems and enclosed cab application equipment was also considered in the risk assessment.

Combined (dermal and inhalation) mixer/loader/applicator risks of concern were identified for all assessed thiram groundboom, airblast, root-dip and animal repellent uses even when assuming the highest level of PPE and use of engineering controls. Establishing limits to the amount of thiram handled (for example, reduced application rate or limits to the area treated per day) were not considered adequate to address potential risk concerns.

3.2.2.2 Commercial Seed Treatment Exposure and Risk Assessment

Thiram is registered as a seed treatment for use in commercial treatment facilities. Workers may be exposed to thiram from various occupational activities associated with the treatment of the seed as well as from planting treated seeds. Exposure from treating and planting was not combined as it was not expected that a single individual would perform both tasks.

Exposure to workers treating cereal, oilseed and pulse seeds was assessed for mixer/loader, coater, bagger, cleaner and foreman activities based on exposure values from surrogate studies of commercial seed treatment. Commercial seed treatment throughput varies widely by facility. For the thiram risk assessment, it was assumed that 40 000 – 216 000 kg of seed would be treated per 8 hour day and that treating would last for 60 days per year.

Exposure to workers planting commercially treated cereal, oilseed and pulse seeds was assessed based on maximum application rates and surrogate studies of planting treated seeds. Seeding rate varies depending on equipment used and seed type. For the thiram risk assessment, it was assumed that 1 350 – 5 400 kg of treated seed would be planted per day for 10 days per year.

The assessments assumed maximum application rates and a worker body weight of 80 kg. Lifetime average daily dose values were calculated by amortizing exposure over the lifetime assuming workers would work 40 years with a life expectancy of 78 years.

Potential risks of concern were identified for workers involved in commercial seed treatment assuming PPE consisting of coveralls, chemical resistant gloves, respirator and use of closed transfer systems during application. Further, risks of concern were identified for workers involved in planting treated seed assuming chemical resistant gloves, coveralls and use of closed cab planting equipment.

3.2.2.3 On-farm Seed Treatment Exposure and Risk Assessment

Thiram is also registered for on-farm seed treatment as a dry or slurry application (typically performed at the time of planting). Workers may be exposed to thiram from both the treatment and planting of the seed. As it is expected the same person may treat and plant the seed, the

exposure was combined for the on-farm risk assessment.

Exposure from on-farm treating/planning of cereal, oilseed, pulse, vegetable and forage seeds was assessed based on maximum application rates, a worker-body weight of 80 kg and surrogate exposure studies. Lifetime average daily dose values were calculated by amortizing exposure over the lifetime assuming workers would treat/plant 10 days per year for 40 years with a life expectancy of 78 years. For the thiram risk assessment, it was assumed that 54 – 5 400 kg of seed would be treated and planted per day. Potential risks of concern were identified for workers wearing coveralls, chemical resistant gloves and using closed cab planting equipment.

3.2.2.4 Postapplication Occupational Exposure and Risk Assessment

The postapplication occupational risk assessment considers exposures to workers who enter treated sites to conduct agronomic activities involving foliar contact (such as handharvesting, thinning, or scouting).

For workers entering treated fields to conduct agronomic activities, dermal exposure is considered to be the primary route of exposure. Considering low volatility of this active ingredient and assuming at least 12 hours have passed before re-entry, inhalation exposure to thiram is not expected for postapplication workers re-entering treated sites.

Postapplication exposure of workers to thiram residues on fruits and vegetables is expected to be short-/intermediate-term based on the application timing and re-entry activities. The potential for postapplication exposure from animal repellent use was considered low given that products will be applied in the late fall to dormant shrubs and trees and no postapplication activities would occur following the application. Postapplication exposure from planted treated seed and bulbs is not expected.

Potential exposure of postapplication workers was estimated following a single application at the maximum registered rate using activity-specific transfer coefficients and dislodgeable foliar residue values. The dislodgeable foliar residue refers to the amount of residue that can be dislodged or transferred from a surface, such as leaves of a plant. In the thiram risk assessment this was assumed to be 25% of the application rate. A transfer coefficient is a measure of the relationship between exposure and the dislodgeable foliar residue for individuals engaged in a specific activity, and is calculated from data generated in field exposure studies (Agricultural Re-entry Task Force, ARTF). The transfer coefficients are specific to a given crop and activity combination and reflect standard agricultural work clothing worn by adult workers.

Potential risks of concern were identified for workers re-entering treated areas on the day of application for all assessed crop/activity combinations following a single application. Assuming a residue dissipation of 10% per day, restricted entry intervals (REIs) of minimum 33 days would be required. The REIs are not expected to be agronomically feasible given need to re-enter fields sooner. Given that potential risks of concern were identified following a single application of thiram, postapplication risks following multiple applications of this active ingredient have not been assessed.

3.2.3 Residential Handler Exposure and Risk Assessment

Thiram is registered as a domestic product in Canada for use as an animal repellent to protect dormant ornamentals, shrubs, nursery stock, young fruit trees, evergreens, hedges and perennials. The end-use product is formulated as a solution and can be applied by a homeowner undiluted using a paintbrush or diluted (in equal parts with water) using knapsack sprayer or manual pressurized handgun sprayer.

Residential exposure of a homeowner applying the animal repellent product is expected to be short-term duration given that the product is applied once per season. The current domestic-class product label does not specify any PPE to be used by residential handlers. Considering that the product is applied in the late fall to dormant plants, a homeowner is assumed to wear a single layer of clothing (long pants, long shirt).

Daily exposure estimates were calculated using unit exposure values from the PHED and assuming the maximum application rate. Volumes handled per day were assumed based on the USEPA Residential SOP for gardens and trees applications. Risks of concern were identified for a homeowner applying thiram animal repellent products.

3.2.4 Residential Postapplication Exposure and Risk Assessment

Residential postapplication exposure may occur following application of commercial class thiram products to fruit trees in residential areas or areas accessible to the general public (for example, residential orchards and gardens). In contrast to professional workers who generally perform one task on one crop throughout the day (for example, harvesting of apples), individuals in residential settings are likely to conduct various activities related to tree maintenance on the same day. Further, the dermal contact is expected to occur as early as on the day of pesticide application and individuals are expected to wear shorts and short-sleeved shirts.

Dermal exposure is considered to be the primary route of postapplication exposure in the residential setting. Considering low volatility of this active ingredient, inhalation exposure to thiram is not expected for the general public re-entering treated sites.

Dermal exposure estimates for individuals in residential settings conducting postapplication activities related to tree maintenance were calculated using default peak dislodgeable foliar residue values (25% of application rate) and activity specific transfer coefficients (2012 USEPA Residential SOPs). Lifetime average daily dose values were calculated assuming exposure duration of 1 day per year and a 78-year lifespan.

Potential risks of concern were identified from residential postapplication exposure following application of commercial class thiram products to fruit trees in residential areas for all population groups (including for children, youths and adults).

The potential for exposure of the general public to thiram following late fall application to dormant plants as an animal repellent is considered to be low based on the timing of application. On this basis, postapplication residential risk from application as an animal repellent is not of concern.

3.3 Dietary Risk Assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet. Exposure to thiram from imported foods is also included in the assessment.

These dietary assessments are age-specific and incorporate the different eating habits of the population at various stages of life. Science Policy Notice SPN2003-03, Assessing Exposure from Pesticides in Food - A User's Guide, presents detailed acute, chronic and cancer dietary risk assessments procedures used by the PMRA.

The thiram dietary risk assessment considered exposure from all food sources that could potentially contain thiram. Residue estimates for plant and animal commodities were based on field trial data. When field trial data were not available, the Canadian Maximum Residue Limit (MRL) was used to estimate residues in crops. Surveillance data suitable for the purpose of dietary risk evaluation from the Canadian Food Inspection Agency National Chemical Residue Monitoring Program and the United States Department of Agriculture Pesticide Data Program were not available for thiram. Processing factors, percent of crop treated and food supply information were also used to refine the assessment.

Acute, chronic and cancer dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (Version 2.16) which uses food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.3.1 Toxicology Endpoint Selection for Acute Dietary Risk Assessment

Acute Reference Dose (ARfD)

For characterization of acute dietary risk, the oral NOAEL of 1.86 mg/kg bw/day from the developmental neurotoxicity study was selected as the most appropriate endpoint. At the LOAEL of 4.36 mg/kg bw/day, altered motor activity, decreased motor activity habituation, and effects on learning and memory were observed in the young animals in the absence of maternal toxicity. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As per the *Pest Control Products Act* section, the *Pest Control Products Act* factor was retained at 10-fold. The composite assessment factor is 1000-fold and is considered protective of any potentially sensitive subpopulations.

$$\textbf{ARfD} = \frac{\textbf{1.86 mg/kg bw/day}}{\textbf{1000}} = \textbf{0.00186 mg/kg bw}$$

3.3.2 Acute Dietary Exposure and Risk

Acute dietary risk is calculated considering the highest ingestion of thiram that would be likely on any one day, and using food consumption and food residue values. A statistical analysis compiles all possible combinations of consumption and residue levels to estimate a distribution of the amount that might be consumed in a day. A value representing the high end (99.9th percentile) of this distribution 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.

The probabilistic assessment results show that based on the current use-pattern the acute dietary (food only) exposure to thiram (at the 99.9th percentile) results in potential risks of concern for all population subgroups. Several mitigation approaches were explored to decrease the acute dietary exposure (for example, removal of high-residue or high-consumption commodities). Despite the approach taken to limit the dietary exposure, dietary risks of concern remain. Therefore, all registered uses of thiram are proposed for cancellation and all established MRLs are proposed for revocation.

3.3.3 Toxicology Endpoint Selection for Chronic/Cancer Dietary Risk Assessment

Acceptable Daily Intake (ADI)

To estimate dietary risk from repeated exposure, the oral NOAEL of 1.86 mg/kg bw/day from the thiram developmental neurotoxicity study was selected as the most appropriate endpoint. At the LOAEL of 4.36 mg/kg bw/day, altered motor activity, decreased motor activity habituation, and effects on learning and memory were observed in the young animals in the absence of maternal toxicity. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The *Pest Control Products Act* factor was retained at 10-fold. The composite assessment factor is 1000-fold and is considered protective of any potentially sensitive subpopulations.

$$\textbf{ADI} = \frac{\textbf{1.86 mg/kg bw/day}}{\textbf{1000}} = \textbf{0.00186 mg/kg bw/day}$$

Unit Risk for Cancer Assessment

A linear low dose extrapolation (q_1*) assessment was conducted for thyroid C-cell adenomas in females and hepatocellular adenomas in males observed in a 2-year dietary study in rats. The calculated q_1* value for both tumour incidences was 3.50×10^{-2} (mg/kg bw/day)$^{-1}$.

3.3.4 Chronic/Cancer Dietary Exposure and Risk

The chronic dietary exposure was calculated by using the average consumption of different foods and the residue values on those foods. This expected intake of residues was then compared to the ADI for determining chronic risk; or multiplied by the q_1* to determine the cancer risk.

The chronic assessment results show that based on the current thiram use-pattern the chronic dietary (food only) risk is of concern for certain population subgroups. Cancer dietary (food only) risk is also of concern for the general population. As with the acute assessment, several mitigation approaches were explored to decrease the chronic/cancer dietary exposure. Despite this, dietary risks are of concern. Therefore, all registered uses of thiram are proposed for cancellation and all established MRLs are proposed for revocation.

3.4 Exposure from Drinking Water

3.4.1 Concentrations in Drinking Water

Concentrations of thiram in Canadian drinking water sources were modelled using PRZM/EXAMS for surface water and LEACHM for groundwater. The modelling results indicate that thiram has the potential to leach into groundwater and run-off to surface water.

It is expected that exposure to thiram via drinking water would contribute to the overall dietary exposure. However, given the acute/chronic/cancer risks of concern for thiram from food sources alone, a refined thiram drinking water exposure and risk assessment has not been conducted at this time.

3.5 Aggregate Risk Assessment

An aggregate exposure and risk assessment for the general public combining the different routes of exposure to thiram has not been conducted at this time since individual exposure components (residential and dietary exposures) result in potential risks of concern individually.

3.6 Human Health Conclusion

The current assessment has considered the currently registered thiram use pattern and label directions as well as additional mitigation measures such as additional PPE, engineering controls, reduced application rates and removal of certain uses. Potential risks of concern have been identified for most of the assessed human health scenarios (including occupational, residential and dietary scenarios) despite consideration of additional measures to reduce exposure:

- Occupational mixer/loader/applicator risks were identified for all groundboom, airblast, root dip and animal repellent uses.
- Occupational risks were identified for all seed treatment uses.
- Occupational postapplication risks were identified on the day of application for all foliar uses. Required REIs are not expected to be agronomically feasible.
- Residential hander risks were identified for homeowners applying the animal repellent product.
- Residential postapplication risks were identified following application of thiram to residential orchards/gardens.
- Acute, chronic and cancer dietary exposure (food only) results in potential risks of concern based on the current use pattern.

In most cases, the risks were identified in both the noncancer and cancer risk assessments.

No further refinements to the risk assessment were considered at this time. Given the toxicological properties of thiram, it is not expected that further refinements to the exposure assessments would change the overall risk conclusions.

4.0 Incident Reports

Since 26 April 2007, registrants have been required by law to report pesticide incidents to the PMRA that are related to their products. In addition, the general public, medical community, government and nongovernmental organizations are able to report pesticide incidents directly to the PMRA. Incidents were searched and reviewed for the active ingredient thiram. As of 10 June 2015, a total of ten human and eight domestic animal incidents involving this active ingredient (alone or in combination with other active ingredients) have been reported to the PMRA; all but one occurred in Canada. Of these, the symptoms reported in seven human and all eight domestic animal incidents were considered to have at least some degree of association with exposure to the pesticide.

All of the human incidents were minor or moderate in severity. Of those incidents that were considered at least possibly related to the reported exposure, the reported symptoms included eye irritation (three individuals), vomiting (one individual) and skin irritation (three individuals).

There were one major, four moderate, and three minor domestic animal incidents reported. Animals generally experienced symptoms after eating the product or seed treated with the product. Gastrointestinal symptoms were reported for all affected animals, followed by nervous and muscular symptoms.

These incident reports were considered in this evaluation and did not affect the risk assessment.

5.0 Value

Thiram is important for the control of several fungal diseases as seed treatment (cereal, oilseed, pulse, vegetable, fruit and feed crops), foliar spray application on tree fruits (apple, peach and plum), strawberry and celery (plant beds), root dip of sweet potato, and as an animal repellent to protect dormant ornamentals and young fruit trees. Based upon the proprietary pesticide usage data, thiram is most often applied as a seed treatment, with the highest use on canola, dry beans, rye, flax and wheat. Due to its multi-site mode of action and low risk for resistance development, thiram is used with other fungicides in an integrated pest management (IPM) program for disease and resistance management.

6.0 Environment

6.1 Fate and Behaviour in the Environment

Thiram is soluble in water (30 mg ai/L), has a low vapour pressure (2.3 mPa) and is not expected to volatilize. Thiram degrades rapidly due to phototransformation in soil (half-life 1.2–4.8 days)

and in water (half-life 8.8–10.2 hours). Hydrolysis is an important route of transformation in neutral and alkaline water (half-life 3.5–17.8 days at pH 7 and 6.9 hours, 6.9 days at pH 9) but is much slower in acidic environments (half-life 68.5–169 days at pH 5). Aerobic biotransformation studies indicate that thiram transforms rapidly in soils (DT_{50} 1.4–3.1 days). Thiram transforms rapidly in aerobic aquatic environments (DT_{50} 1.2–2.2 days) as well as anaerobic aquatic environments (DT_{50} 4.2 days). The major transformation products of thiram are CO_2 and CS_2, which are both volatile, and therefore not expected to persist in soil or water. Under both aerobic and anaerobic conditions in soil and water, biotransformation of thiram is mainly biphasic, with rapid initial degradation in the first few days, followed by much slower degradation.

Thiram has the potential to leach to groundwater in some types of soil to which it is not tightly bound. The Freundlich K_{ads} values indicate that thiram ranges from immobile to slightly mobile in soils (K_{ads} 54–263) (K_d 3.74–78.3). The degree of sorption to soil was not found to be related to the amount of organic matter present, or the soil pH. Leaching studies are not available for thiram. In a soil column leaching study of another active (ziram), where thiram was a major transformation product, thiram was not detected in leachate.

Terrestrial field studies are not available for Canadian environments or equivalent ecoregions. In terrestrial field studies conducted in California, applications of thiram dissipated, with half-lives of 27.4 days and 14.4 days for bare ground and turf plots of sandy loam soil, respectively. In North Carolina, the dissipation half-life was 36 days and 62.5 days for a bare ground plot of a sand soil and a turf plot of loamy sand soil, respectively. Dissipation was biphasic in both plots.

6.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on nontarget species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) 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).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to nontarget 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 risk

quotient is then compared to the level of concern (LOC). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (drift to nontarget habitats and runoff) 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.

6.2.1 Risks to Terrestrial Organisms

For the assessment of risk, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following treatment with thiram.

Thiram does not pose a risk to terrestrial invertebrates. The risk assessment showed that the risk from thiram to bees and earthworms was negligible.

Birds and mammals were both found to be at potential risk from consumption of food sources sprayed with thiram in-field, as well as food sources exposed to thiram from spray drift off-field. The highest risk to birds and mammals was for reproductive effects, with risks identified for herbivores and small insectivores. Seed treated with thiram was found to pose a reproductive risk to birds but not to mammals.

Pesticide Spray – Birds

Most of the in-field and off-site (spray drift) screening level acute oral, dietary and reproductive risk quotients for birds exceeded the LOC (level of concern), particularly at the higher application rates. The risk assessment for foliar spray applications was conducted for each of five crops (celery, strawberries, peaches, apples, and plums) and considers both the in-field exposure and off-site exposure. Since foliar dissipation DT_{50} data were not available, a default half-life of 10 d was used to calculate the foliar EDE's (estimated daily exposure) for spray applications of thiram. In addition, the mean nomogram residues were used to calculate the EDE's which is considered to be a refined level risk assessment. For the refined assessment of birds, reproductive risk quotients still exceeded the LOC for in-field risk for birds. Risk quotients were particularly large for reproductive effects for all sizes of birds. The largest reproductive RQ was 2667.1 for small insectivores following application to celery. Acute oral and dietary risk quotients were 1 to 2 orders of magnitude lower than the reproductive level risk quotients, but still exceeded the LOC in many instances. The risk quotients are calculated assuming birds feed exclusively on food sources contaminated with thiram. The off-field spray drift exceeded the LOC by a wide margin for reproductive effects at all of the application rates. Acute and dietary risk quotients for off-field spray drift also exceeded the LOC at the higher application rates (celery, peaches and plums). The largest off-field risk quotient was 293.4 for reproductive effects on small

insectivores. For the risk quotients that exceeded the LOC, the percentage of the diet required to reach the LOC ranged from 0.04% for small insectivores (reproductive effects, celery), up to 100% of the diet for dietary (large herbivores, plums) . This was particularly evident with small insectivores where 0.04% of the diet contaminated with thiram was required to reach the LOC, which is equivalent to 0.6 minutes of feeding on food. These risks to birds cannot be fully mitigated.

Treated Seed – Birds

In addition, a risk assessment was conducted for bird exposure to treated wheat, corn and canola seed. The risk from thiram is a function of the amount of pesticide on the seed, the body weight of the bird, the food ingestion rate and the number of seeds available for consumption. At the screening level, it was assumed that the entire diet consisted of treated seeds and all of the treated seed that is applied is available for consumption. The toxicity endpoints are converted to the number of seeds needed to be consumed per day to reach the threshold dose for each toxicity endpoint. The exposure is calculated as the number of seeds normally consumed per day for each size of bird. At the screening level, almost all of the risk quotients exceeded the LOC for wheat, corn and canola. However, with the exception of reproductive toxicity, the risk quotients are not particularly large. The risk quotients are larger for reproductive effects owing to the sensitive endpoint. The acute oral, acute dietary and reproductive risk quotients are approximately 1.5–2 times larger for canola than for wheat or corn. The largest reproductive risk quotient is 953.9 for small birds consuming canola. The risks from consuming treated seed is only applicable for the first few days after planting of the treated seed, before transformation of the compound occurs and before the seed germinates.

A refined risk assessment was carried out assuming only 3.3% of planted seeds are available to birds. The refined risk quotients were less than the LOC for acute oral and acute dietary effects but greater than the LOC for reproductive effects. It is evident that small, medium and large sized birds can consume enough seeds (0.02–48.9 seeds) in a single feeding session over a small area to reach a dose capable of having reproductive effects. These risks to birds cannot be fully mitigated.

Pesticide Spray – Mammals

For mammals, the risk assessment indicates that most of the in-field and off-site (spray drift) acute oral and the reproductive risk quotients exceed the LOC, particularly at the higher application rates (celery, peaches and plums). The largest exceedances occurred with herbivores. The risk assessment was carried out using a default DT_{50} for thiram on vegetation of 10 days, as well as the use of mean nomogram residues to calculate the exposure. The risk quotients are calculated assuming mammals feed exclusively on food sources exposed to thiram. Most of the acute oral and reproductive risk quotients exceed the LOC for on-field risk. The largest exceedances occurred with medium sized herbivores (consuming short grass) for reproductive effects (risk quotient 151.5). In addition, there were many exceedances of the LOC for off-site (spray drift) exposure at the higher application rates (celery, peaches and plums) in particular for herbivores. The largest off-site risk quotient was 111.8 for reproductive effects on medium sized

herbivores (consuming short grass). For the risk quotients exceeding the LOC for mammals, the percentage of the diet required to reach the LOC for acute oral and reproductive effects ranged from 0.7% (reproduction, medium sized herbivores consuming short grass) to 99% of the diet (medium sized insectivores and granivores, peaches). For 0.7% of the diet to reach the LOC, this is equivalent to about 5.4 minutes of feeding on contaminated food to reach the LOC. These risks to mammals cannot be fully mitigated.

Seed Treatment – Mammals

For seed treatments, almost all of the risk quotients exceeded the LOC for mammals for wheat, corn and canola. The acute oral risk quotients are not particularly large, whereas the risk quotients are larger for reproductive effects. The largest reproductive risk quotient is 27.1 for small mammals consuming canola . The acute and reproductive risk quotients are approximately 1.5 to 2 times larger for canola than for wheat or corn. The risks from consuming treated seed are only applicable during the first few days after treated seed planting, before transformation of the compound and seed germination.

A refined risk assessment was carried out assuming only 3.3% of planted seeds are available to mammals. All of the refined risk quotients were less than the LOC for both acute oral and reproductive effects.

6.2.2 Risks to Aquatic Organisms

Available aquatic toxicity data on thiram consisted of eight freshwater species (one invertebrate, five fish, and two algae) and three estuarine/marine species (two invertebrates and one fish). There was no chronic toxicity data available for estuarine/marine invertebrates or fish.

At the screening level, risk quotients for freshwater invertebrates exceeded the acute and chronic LOC's by a wide margin for direct application and for spray drift. For spray drift, the largest risk quotient was 765.0 for chronic effects (peaches). A refined risk assessment using PRZM/EXAMS modeling data for runoff indicated that the LOC's were still exceeded for freshwater invertebrates. The largest refined risk quotient for acute effects from runoff was 54.5 and the largest chronic risk quotient was 115, both for runoff from a Quebec celery scenario.

At the screening level, risk quotients for freshwater fish exceeded the acute and chronic LOC's by a wide margin both for direct application to water as well as for spray drift. For spray drift the largest risk quotient was 2390.6 for chronic effects (peaches). A refined risk assessment using PRZM/EXAMS modeling data for runoff indicated that the LOC's were still exceeded for freshwater fish. At the refined level, the largest acute risk quotient from was 76.2 and the largest chronic risk quotient was 140.6, both for a Quebec celery scenario.

Thiram toxicity data for freshwater fish were used as a surrogate for amphibians in the risk assessment. At the screening level, risk quotients for amphibians exceeded the acute and chronic LOC's by a very large margin for direct application to water and for spray drift. For spray drift the largest risk quotient was 2390.6 for chronic effects (peaches). A refined risk assessment for

runoff indicated that the LOC's were still exceeded. The largest risk quotient for acute effects from runoff was 130.3 and the largest chronic risk quotient was 278.1, both for a Quebec celery scenario.

At the screening level, risk quotients for freshwater algae exceeded the LOC for direct application and for spray drift. For spray drift the largest risk quotient was 425.0 for peaches. A refined risk assessment indicated that the risk quotients for runoff did not exceed the LOC for runoff except for the Quebec celery scenario (risk quotient 4.3).

At the screening level, acute risk quotients for estuarine/marine invertebrates and fish exceeded the LOC for direct application and for spray drift. For spray drift the largest acute risk quotient was 14.2 (peaches). A refined risk assessment using PRZM/EXAMS modeling data for runoff indicated that the LOC was exceeded only for the Quebec celery runoff scenario (risk quotient 4.3).

6.3 Environmental Conclusion

Thiram presents potential risks to certain terrestrial organisms (mammals and birds) from consuming food sources contaminated by direct spray application and spray drift, as well as from consuming treated seed. These significant risks to birds and mammals cannot be fully mitigated. Thiram also presents risks to some aquatic organisms from runoff and spray drift.

7.0 Pest Control Product Policy Considerations

7.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, those that meet all four criteria outlined in the policy, for example, persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*.

During the review process, thiram and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[2] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Thiram does not meet Track 1 criteria and is not considered a Track 1 substance.
- Thiram does not form any transformation products that meet all Track 1 criteria.

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

7.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical are compared against the list in the *Canada Gazette.* The list is used as described in the PMRA Notice of Intent NOI2005-01[3] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[4] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade thiram does not contain any contaminants of health or environmental concern identified in the *Canada Gazette.*

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02 (PMRA Formulants Policy).

8.0 Proposed Regulatory Decision

After a re-evaluation of thiram, Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing cancellation of all thiram uses in Canada. Furthermore, all established maximum residue limits (MRLs) for thiram are proposed for revocation.

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

[4] DIR2006-02, *Formulants Policy and Implementation Guidance Document*.

List of Abbreviations

ADI	Acceptable Daily Intake
AHETF	Agricultural Handlers Exposure Task Force
ARfD	Acute Reference Dose
ARTF	Agricultural Re-entry Task Force
ATPD	Area treated per day
CAF	Composite Assessment Factor
DNT	Developmental Neurotoxicity
EXAMS	Exposure Analysis Modeling System
LOAEL	Lowest Observed Adverse Effect Level
LEACHM	Leaching Estimation and Chemistry Model
MoA	Mode of Action
MOE	Margin of exposure
MRL	Maximum Residue Limit
NOAEL	No Observed Adverse Effect Level
PHED	Pesticide Handlers Exposure Database
PPE	Personal protective equipment
PRZM	Pesticide Root Zone Model
REI	Restricted Entry Interval
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
WDG	Water dispersible granule
WP	Wettable powder

Appendix I Toxicology Endpoints for Health Risk Assessment for Thiram

	RfD (mg/kg bw/day)	**Study NOAEL**	**CAF or Target MOE and Rationale**[1]
ARfD (All Populations)	0.00186	NOAEL = 1.86 mg/kg bw/day Rat developmental neurotoxicity study (Altered motor activity, decreased motor activity habituation, and increase in time taken to complete the Morris maze)	CAF = 1000 PCPA = 10-fold
ADI (All Populations)	0.00186	NOAEL = 1.86 mg/kg bw/day Rat developmental neurotoxicity study (Reduced body weight, altered motor activity, decreased motor activity habituation, and increase in time taken to complete the Morris maze)	CAF = 1000 PCPA = 10-fold
Residential (all durations and all routes)		NOAEL = 1.86 mg/kg bw/day Rat developmental neurotoxicity study (Reduced body weight, altered motor activity, decreased motor activity habituation, and increase in time taken to complete the Morris maze)	MOE = 1000 PCPA = 10-fold
Occupational (all durations and all routes)		NOAEL = 1.86 mg/kg bw/day Rat developmental neurotoxicity study (Reduced body weight, altered motor activity, decreased motor activity habituation, and increase in time taken to complete the Morris maze)	MOE = 1000
Cancer Assessment	$q_1^* = 3.50\times10^{-2}$ $(mg/kg\ bw/day)^{-1}$	Based on thyroid C cell adenomas in females and hepatocellular adenomas in males	

[1] CAF (Composite assessment factor) refers to the total of uncertainty and *Pest Control Products Act* (PCPA) factors for dietary and residential risk assessments; MOE refers to target margin of exposure for dermal and inhalation assessments

Appendix II Toxicity to Non-Target Species

Organism	Study type	Species	Test material	Endpoint	Value* (effect)	Effect of concern	Reference
Terrestrial Species							
Invertebrate	Acute contact	Honey bee (*Apis mellifera*)	Thiram	48 h LD_{50}	>7.9 µg ai /bee	Mortality	PMRA 1752918
				48 h LD_{50}	73.72 µg ai /bee	Mortality	PMRA 1752918
				48 h LD_{50}	>100 µg ai /bee	Mortality	PMRA 1830692
	Acute contact	Earthworm (*Eisenia foetida*)	Thiram	LD_{50}	**540 g ai/ha**	Mortality	PMRA 1830692
Birds	Acute oral	Mallard (*Anas platyrhynchos*)	Thiram	LD_{50}	> 2800 mg ai/kg bw	Mortality	PMRA 1752918
		Ring Necked Pheasant (*Phasianus colchicus*)		LD_{50}	**673 mg ai/kg bw**	Mortality	PMRA 1752918
		Red-winged blackbird (*Agelaius phoeniceus*)		LD_{50}	> 100 mg ai/kg bw	Mortality	PMRA 1752918
		Starling (*Sturnus vulgatis*)		LD_{50}	> 100 mg ai/kg bw	Mortality	PMRA 1752918
	Dietary	Bobwhite Quail (*Coturnix virginianus*).	Thiram	LC_{50}	**3950 mg ai/kg diet**	Mortality	PMRA 1752918
		Mallard (*Anas platyrhynchos*)		LC_{50}	5000 mg ai/kg diet	Mortality	PMRA 1752918
		Ring Necked Pheasant (*Phasianus colchicus*)		LC_{50}	>5000 mg ai/kg diet	Mortality	PMRA 1752918
		Japanese quail (*Coturnix c. japonia*)		LC_{50}	>5000 mg ai/kg diet	Mortality	PMRA 1752918
	Reproduction	Bobwhite Quail (*Coturnix virginianus*).	Thiram	NOEC	500 mg ai/kg diet	Mortality	PMRA 1752918 & 1830692
		Mallard (*Anas platyrhynchos*)		NOEC	**9.6 mg ai/kg diet**	Mortality	PMRA 1752918
		Mallard (*Anas platyrhynchos*)		NOEC	<50 mg ai/kg diet	Mortality	PMRA 1752918
Mammals	Acute oral	Rat	Thiram	LD_{50}	2600 mg ai/kg bw	Mortality	PMRA 1752918

Organism	Study type	Species	Test material	Endpoint	Value* (effect)	Effect of concern	Reference
Terrestrial Species							
				LD_{50}	**620 mg ai/kg bw**	Mortality	Data from Health Evaluation Directorate
	Reproduction	Rat	Thiram	NOEL	**11 mg ai/kg bw /day**	Reproduction	Data from Health Evaluation Directorate
				NOEL	1.9 mg ai/kg bw /day	Reproduction	PMRA 1752918
Aquatic Species							
Freshwater Invertebrates	Acute	*Daphnia magna*	Thiram	48-h LC_{50}	**0.011 mg a.i./L**	Immobility	PMRA 1752918 & or 1830692
	Acute	*Daphnia magna*		48-h EC_{50}	0.21 mg a.i./L	Immobility	PMRA 1752918 & or 1830692
	Chronic	*Daphnia magna*	Thiram	21 d NOEC	**0.001mg ai /L**	Growth and reproduction	PMRA 1752918 & or 1830692
Estuarine/ marine Invertebrates	Acute	Mysid shrimp (*Mysidopsis bahia*)	Thiram	96-h LC_{50}	**0.0036 mg a.i./L**	Mortality	PMRA 1752918 & or 1830692
		Eastern oyster (*Crassostrea gigas*)		96-h EC_{50}	0.0047 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
	Chronic		Thiram		No data		
Freshwater Fish	Acute	Rainbow trout (*Oncorhynchus mykiss*)	Thiram	96-h LC_{50}	0.50 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
				96-h LC_{50}	0.046 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
				96-h LC_{50}	0.13 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
				96-h LC_{50}	0.28 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
		Bluegill sunfish (*Lepomis macrochirus*)		96-h LC_{50}	**0.042 mg a.i./L**	Mortality	PMRA 1752918 & or 1830692
				96-h LC_{50}	0.28 mg a.i./L	Mortality	PMRA 1752918 & or 1830692

Organism	Study type	Species	Test material	Endpoint	Value* (effect)	Effect of concern	Reference
Terrestrial Species							
				96-h LC_{50}	0.13 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
		Fathead minnow (*Pimephales promelas*)		96-h LC_{50}	0.27 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
		Cyprinodon variegatus		96-h LC_{50}	0.54 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
	Chronic (Early Life Stage)	Rainbow trout (*Oncorhynchus mykiss*)	Thiram	60-d NOEC	0.00064 mg ai/L	Mortality	PMRA 1752918 & or 1830692
				60-d NOEC	**0.00032 mg ai/L**	Mortality	PMRA 1752918 & or 1830692
Estuarine/ marine Fish	Acute	Sheepshead minnows (*Cyprinodon variegatus*)	Thiram	96-h LC_{50}	**0.54 mg ai/L**	Mortality	PMRA 1752918 & or 1830692
	Chronic		Thiram		No data		
Freshwater Plants & Algae	Acute	Algae *(Chlorella pyrenoido)*	Thiram	96 h EC_{50}	1.0 mg ai/L	Biomass	PMRA 1752918 & or 1830692
		Green alga (*Selenastrum capricornutum*)		48 h EC_{50}	**0.14 mg ai/L**	Biomass	PMRA 1752918 & or 1830692
		Green alga (*Selenastrum capricornutum*)		120 h EC_{50}	0.065 mg ai/L	Biomass	PMRA 1752918 & or 1830692
		Duckweed (*Lemna gibba)*		96 h EC_{50}	1.6 mg ai/L	Biomass	PMRA 1752918 & or 1830692
* Values used in risk assessment highlighted in bold font							

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A. LIST OF STUDIES/INFORMATION SUBMITTED BY REGISTRANT

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