Proposed Re-evaluation Decision PRVD2018-17

Mancozeb and its Associated End-use Products

Consultation Document

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Proposed Re-evaluation Decision

Under 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. The PMRA applies internationally accepted risk assessment methods as well as current risk management approaches and policies.

Mancozeb is a protectant contact fungicide with multi-site mode of action used to control a broad spectrum of plant diseases on a wide variety of food and feed crops, as well as uses in forests and woodlots, outdoor ornamentals and greenhouse food crops. Mancozeb belongs to the group of fungicides commonly known as ethylene bis (dithiocarbamates) (EBDCs), along with the active ingredients maneb, zineb, metiram and nabam. It should be noted that in Canada, nabam has no registered food uses and maneb and zineb have been voluntarily discontinued. The EBDCs decompose and/or metabolize to ethylene thiourea (ETU), whose cumulative risk profile is also being taken into account.

A Proposed Re-evaluation Decision document was first published on 30 July 2013 (PRVD2013-01). Subsequently, on 24 August 2018, the PMRA indicated that it will be re-issuing a Proposed Re-evaluation Decision document (PRVD) in respect of mancozeb and its associated end-use products to allow for an informed consultation to take place. Although PRVD2013-01 for mancozeb outlined dietary risks of concern, the associated risk management proposal (that is, the proposed regulatory decision) was inadvertently not included. The proposal should have stated, based on the dietary and environmental risk assessments, that all uses were proposed to be cancelled, except greenhouse tobacco, rather than stating that certain uses were proposed for continued registration with further risk-reduction measures proposed. When conducting the mandatory consultation during a re-evaluation, the *Pest Control Products Act* requires that a summary of any evaluation, the proposed decision and the reasons for it be set out in the consultation document (the PRVD).

As a result, the final decision document (RVD2018-21) has been withdrawn and there will be no changes to the labels or registration status of the existing products, pending the completion of this re-evaluation (i.e., until a new re-evaluation decision is issued (RVD)). In addition, the mancozeb-related information in the Proposed Maximum Residue Limit document for EBDC Fungicides (PMRL2018-27) was also withdrawn because it is based on the conclusions reached in RVD2018-21.

The present document is a re-issuance of PRVD2013-01 which now includes a complete summary of the evaluations undertaken up until that time, the proposed decision and the reasons for it. As such, this consultation document is based on the use pattern and the registration status of maconzeb at the time PRVD2013-01 was originally issued.

Outcome of Science Evaluation

An evaluation of available scientific information found that, under the current conditions of use:

- Dietary risks from food alone and drinking water alone were identified and not found to be acceptable when all the uses on the current labels, except greenhouse tobacco, were considered. Therefore, all uses, with the exception of greenhouse tobacco, are proposed for cancellation.

- Although not a food use, the forestry and woodlot uses are proposed for cancellation due to potential residues occurring in drinking water, for which risks from outdoor applications have been identified and not found to be acceptable, as noted above. Therefore, these uses are proposed for cancellation.

- Occupational risks (postapplication) were identified and not found to be acceptable for apples, pears, grapes and greenhouse tomatoes. Occupational mixer/loader/applicator risks were identified and not found to be acceptable for potato seed piece treatment, and seed treatment for barley, corn, flax, oat and wheat, except for on-farm slurry application. Therefore, these uses are proposed for cancellation.

- Postapplication risks for workers were found to be acceptable for most agricultural label uses when the proposed mitigation measures (restricted-entry intervals) are applied. However, for apples, pears and grapes and greenhouse tomatoes, some or all of the proposed restricted-entry intervals (REIs) are not believed to be agronomically feasible and these uses are therefore proposed for cancellation.

- The use on greenhouse tobacco would not result in dietary exposure and occupational risks were found to be acceptable with additional risk mitigation measures. Therefore, this use is proposed for continued registration.

- Environmental risks to birds and small wild mammals were identified for foliar sprays of mancozeb on all crops and were not found to be acceptable. Therefore, all foliar applications are proposed for cancellation.

Proposed Regulatory Decision for Mancozeb

Under the authority of the *Pest Control Products Act*, Health Canada is proposing cancellation of all uses of mancozeb, except greenhouse tobacco, due to risks to human health and the environment that were not found to be acceptable.

During the phase-out period of all uses, except greenhouse tobacco, the following additional risk mitigation measures may be required, unless scientific data and/or changes to the use pattern are adequately address the human health and environmental risks identified above:

Human Health

- Packaging of all wettable powder products in water soluble packages.

- Additional protective equipment (respirator) and/or engineering controls (closed cab).
- Lengthened restricted-entry intervals are to be added to product labels.
- Additional label statement limiting applications of both mancozeb and metiram so that the total quantity of active does not exceed the specified maximum seasonal quantity for either mancozeb or metiram.

Environment

- Additional precautionary label statements to help reduce runoff and to protect non-target aquatic species.
- The use of spray buffer zones to protect for non-target aquatic habitats.
- Limit aerial applications to once per season.
- A statement advising that the use of mancozeb may result in leaching of ETU to groundwater particularly in areas where soils are permeable and/or the depth to the water table is shallow.

International Context

Canada is a member of the Organisation for Economic Co-operation and Development (OECD), which provides a forum for governments to work together to share experiences and seek solutions to common problems. As stated above, the following pertains to the registration status of maconzeb at the time PRVD2013-01 was originally issued.

Mancozeb is registered for use in the European Union and the United States. The European Union published a final review report for mancozeb in July 2009. The European Union concluded that the use of mancozeb on apple, potato, tomato and grape was acceptable based on available information at that time. The European Union requested additional confirmatory data. In the United States, mancozeb is registered for use on similar agricultural crops as in Canada, on turf, ornamentals and, seed and potato seed piece treatments. The American rates are lower than those in Canada and preharvest intervals are longer for many crops (apple, pear, grapes and potato). The United States Enviromental Protection Agency (USEPA) published a re-registration eligibility decision for mancozeb in September 2005. The USEPA concluded that re-registration of mancozeb was acceptable provided that additional risk mitigation measures were implemented. In addition, the USEPA requested additional confirmatory data.

Next Steps

The public, including manufacturers and stakeholders, are encouraged to submit comments during the 90-day public consultation period. If additional scientific data and/or changes to the use pattern are not adequate to address the risks identified above, all uses of mancozeb, except greenhouse tobacco, will be cancelled.

All comments received during the public consultation period will be taken into consideration in preparation of the re-evaluation decision document. 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 the PMRA's responses.

The implementation timeline for the cancellation or amendments to product labels will be determined at the final decision phase of this re-evaluation, taking into consideration the PMRA's cancellation and amendments policy (Regulatory Directive DIR2018-01, *Policy on Cancellations and Amendments Following a Re-evaluation and Special Review*).

Additional Information

No additional scientific data are required at this time. However, during the consultation period, the registrants may consider submission of further data or propose changes to the use pattern that could be used to address the human health and environmental risks identified. These data are identified in Section 8.2 of this Proposed Regulatory Decision.

Science Evaluation

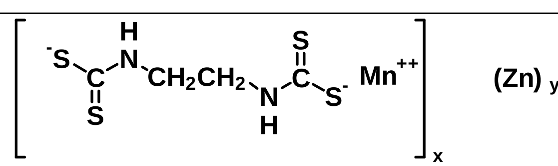
1.0 Introduction

Mancozeb is a broad spectrum, Resistance Management Group M3 (alkylenebis dithiocarbamate) fungicide having multi-site mode of action. It is a protectant fungicide that works by contact. Mancozeb reacts with, and inactivates, the sulfhydryl groups of amino acids and enzymes of fungal cells, resulting in disruption of lipid metabolism, respiration and production of ATP (British Crop Protection Council, 2004).

Following the re-evaluation announcement for mancozeb by the PMRA in the Re-evaluation Note REV2005-04, *PMRA Re-evaluation Program (April 2005 to June 2009)*, the technical registrants and primary data providers in Canada indicated that they intended to provide continued support for all uses included on the labels of Commercial Class end-use products.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient

Common name		mancozeb
Function		fungicide
Chemical Family		ethylenedithiocarbamate
Chemical name		
1	**International Union of Pure and Applied Chemistry (IUPAC)**	manganese ethylenebis(dithiocarbamate) (polymeric) complex with zinc salt
2	**Chemical Abstracts Service (CAS)**	[[1,2-ethanediylbis[carbamodithioato]](2-)]manganese mixture with [[1,2-ethanediylbis[carbamodithioato]](2-)]zinc
CAS Registry Number		8018-01-7
Molecular Formula		$(C_4H_6MnN_2S_4)_xZn_y$, where x:y = 10:1
Structural Formula		
Molecular Weight		271.2 g/mol

Purity of the Technical Grade Active Ingredient

Registration #	Purity (% w/w)
19788	93
20734	83.2
25166	87

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 products.

2.2 Physical and Chemical Properties of the Technical Grade Active Ingredient

Property	Result[a]
Vapour pressure at 20°C	$< 1.33 \times 10^{-2}$ mPa
Ultraviolet (UV)/visible spectrum	Not expected to absorb at λ >300 nm
Solubility in water at 25°C	6.2 ppm (pH 7.5)
n-Octanol/water partition coefficient	logP = 0.26
Dissociation constant	N/A - No dissociable groups present

[a] Values from e-Pesticide Manual, version 3.1 (2004)

2.3 Description of Registered Mancozeb Uses

Appendix I list all mancozeb products that are registered under the authority of the *Pest Control Products Act*. Appendix II lists all Commercial Class uses of mancozeb in currently registered end-use products. All uses were supported by the technical registrants at the time of re-evaluation initiation and were therefore considered in the health and environmental risk assessments of mancozeb with one exception. The use of mancozeb in a tank mix with Benlate (benomyl) on the label for Manzate 200 WP Fungicide (Registration No. 10526) was not assessed since benomyl is no longer registered in Canada.

3.0 Impact on Human and Animal Health

Toxicology studies in laboratory animals describe potential health effects resulting from various levels of exposure to a chemical and identify dose levels where 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.

3.1 Toxicology Summary

Mancozeb

The toxicology database for mancozeb consisted of acute, short-term, long-term, reproductive, developmental, and genotoxicity studies (Appendix III, Table 1). The available toxicity data (Appendix III, Table 3) were used to select endpoints for risk assessment for dietary and non-dietary routes of exposure. Published toxicity studies have also been incorporated into the risk assessment. Refinements to the current risk estimates may be possible with the submission of additional toxicity data.

Depending on the animal species, the absorption of mancozeb was moderate to rapid. In the mouse, it was extensively metabolized with predominant distribution to the thyroid. In the rat, absorption was moderate, metabolism was extensive and distribution was primarily to the thyroid and liver. Metabolites found in the mouse and rat include ethylene diamine (EDA), N-acetyl-EDA, ethanolamine, oxalic acid, ethylene urea (EU), ethylene thiourea (ETU) and ethylene bis(isothiocyanate sulphide) (EBIS). Ethyl-thiourea-N-thiocarbamide (ETT) was found in the mouse, but not the rat. Mancozeb was rapidly excreted (>90% by 24 hours) in the mouse, with total radiolabeled recovery of 26–44% in urine, 48–64% in feces, 0–4% in exhaled air and 1.4% remaining in the carcass. In the rat, elimination was biphasic with most of an oral dose being eliminated by 24 hours. Recovery was evenly divided between the urine and faeces, with 2–8% in bile.

For the purposes of risk assessment, the extent of in vivo metabolic conversion of parent EBDC pesticide to ETU was determined to be 7.5% on a weight basis (United States Environmental Protection Agency (USEPA) 1989). This value represents an average value for all EBDC pesticides (mancozeb, metiram, maneb, zineb, nabam). Based on urinary and biliary excretion of ETU in rat metabolism studies, about 20% of an administered EBDC dose is converted to ETU on a molar basis. In order to express the in vivo dose of ETU on a mg/kg bw basis, a molecular weight correction factor was applied. The molecular weight correction factor, 0.38, was calculated as the ratio of the ETU molecular weight (102 g/mole) and the average of all parent EBDC molecular weights (270 g/mole). Therefore, a 100 mg dose of an EBDC given to a rat would yield an in vivo ETU dose of 7.5 mg.

Mancozeb was of low acute oral and inhalation toxicity in the rat and low dermal toxicity to the rabbit. It was a severe eye irritant and slight skin irritant to rabbits. In guinea pigs, mancozeb was a skin sensitizer.

A 28-day dermal toxicity study in the rat had no adverse dermal or systemic effects at the highest dose tested. After a 28 or 90 day inhalation exposure, the primary effect in the rat was decreased body weight.

On day one in an acute neurotoxicity study there was a decrease in total session motor activity in comparison to controls in all dose groups and a NOAEL could not be established. Degeneration of an individual nerve fibre with myelin ovoid formation was seen in the proximal sciatic nerve of one male in the high dose group and in the tibial nerve of two males in this dose group. These lesions were similar to those seen in a 90-day neurotoxicity study with mancozeb (below) and were attributed to treatment.

In a 90-day rat neurotoxicity study, both sexes had demyelination, myelin phagocytosis, Schwann cell proliferation, and muscle atrophy of the hindlimbs. In published studies, mancozeb and maneb have been shown to cause a decrease in dopamine and GABA uptake (Dominico et al., 2006 and 2007). These effects were not noted with nabam and thus, the effects were attributed to the metal component of mancozeb (manganese and zinc). In published studies, mancozeb was reported to be a pro-oxidant neurotoxicant, increasing intracellular reactive oxygen species.

In 90-day oral toxicity studies, the primary target in mice and rats was the thyroid. The animals had decreased T4 (thyroxine), increased TSH (thyroid stimulating hormone) and increased absolute and relative thyroid weight and follicular cell hyperplasia. Female rats, at the highest dose tested, also had increased centrilobular hepatocyte hypertrophy.

The dog was the most sensitive species tested, yielding lower NOAELs than the rat and mouse. In 90-day and 1-year dog toxicity studies, the primary targets were body weight, blood, and thymus; and at the highest dose tested, the thyroid. The blood effects included a decrease in red blood cells, hematocrit and hemoglobin. The thymic effects included an increase in cortical lymphoid depletion, and decreased size, suggesting possible immunotoxicity. This is supported by published epidemiology studies in Italian vine workers (Colosio et al., 1996 and 2007) which indicate that prolonged low level exposure to mancozeb may cause immunotoxicity. Due to concern for the immunotoxic potential of mancozeb, a guideline immunotoxicity study may address this concern (See Section 8.2 Additional Data).

With respect to systemic toxicity after chronic dietary exposure, the primary effects noted in the chronic mouse studies were decreased body weight, body-weight gain, T3 (triiodothyronine) and T4. One mouse toxicity study also showed an increase in benign liver tumours (males), but this was not seen in a second study conducted using similar dose levels. In a chronic rat toxicity study, the primary effects were mild bilateral retinopathy and loss of photoreceptor cells at the two highest doses tested in females, but only at the highest dose tested in males. This effect was observed after one year of exposure. Two separate epidemiology studies that were conducted in 2000 and 2005, on data generated from the ongoing Agricultural Health Study in Iowa and North Carolina, USA, support the relevance of the animal findings to the human risk assessment. Kamel et al (2000) conducted a case-control study to examine the relationship between pesticide exposure and retinal degeneration in farmers. Maneb exposure had significantly increased risks of retinal degeneration (OR (odds ratio) = 2.3, 95% CI (confidence interval): 1.3, 4.3). A significantly increased risk of retinal degeneration was also reported for exposure to fungicides in general (OR=1.8, 95%CI: 1.3, 2.6). A second case-control study was conducted to examine the association between fungicide exposure and retinal degeneration among wives of farmer pesticide applicators (Kirrane et al., 2005).

Risk estimates were not statistically significant for specific fungicides, but elevated odds ratios were reported for maneb/mancozeb (OR=1.4, 95% CI: 0.6, 3.0). These studies support a relationship between fungicide (including mancozeb and maneb) exposure and human retinopathy.

One of two chronic mouse toxicity studies with mancozeb showed an increase in benign thyroid tumours with no progression to carcinomas. In the chronic rat study, there was an increase in thyroid adenomas and carcinomas at the highest dose tested. The thyroid tumours evident with mancozeb treatment, like its metabolite ETU, follow a clear mode and mechanism of action. Mancozeb, as well as ETU, inhibit thyroid peroxidase, leading to chronic thyroid hormone deficiency (decreased T4). This in turn stimulates the hypothalamus and pituitary gland, causing the production of more TSH. This hormonal imbalance leads to thyroid growth, hyperplasia and subsequent follicular cell neoplasia. Frequently, pituitary gland neoplasia also occurs, which was evident with ETU, but not mancozeb. Mancozeb has shown positive and negative findings in both in vitro and in vivo genotoxicity studies. Similar to ETU, mancozeb appears to have some genotoxic potential.

Since ETU is a common metabolite and degradate for all EBDCs, the ETU cancer risk assessment has been deemed appropriate for use in the mancozeb cancer risk assessment. For additional details, see the following ETU assessment. This approach was considered protective of the benign liver tumours observed with mancozeb in male mice.

Two guideline reproductive toxicity studies were conducted, one with penncozeb and one with mancozeb. In the penncozeb study, decreased body weight was noted in the adults, as well as offspring on PND 21. At the highest dose tested, in the presence of parental toxicity, the pups had delayed eye opening in both generations and decreased body weight. In the mancozeb study, there was no reproductive or offspring toxicity observed at any dose level. The parental generations had decreased body weight, increased relative liver weight and relative and absolute thyroid weight, and males had hypertrophy and/or vacuolation of pituitary cells.

A published, non-guideline reproductive toxicity study in mice assessed the gradation and temporality of mancozeb effects during the first 8 days of pregnancy (Bindali et al., 2001). A decrease in diestrus, with concomitant increase in the estrus phase was noted in the graded response portion of the study. However, the primary effect was inhibition of implantation with dosing through gestation days 3, 5 and 8 (graded and temporal studies combined). There was no effect on thyroid weight.

No sensitivity of the young was noted in the developmental rat and rabbit toxicity studies via gavage, or in a developmental study in rats via inhalation exposure. In rats, the primary maternal effect after oral exposure was decreased body weight and body-weight gain. At the highest dose tested, there were two abortions and pups had increased incidences of dilated brain ventricles, incomplete skull ossification, hydrocephaly, forelimb flexure, cryptorchidism, resorptions and decreased fetal body weight. These effects in rats are consistent with rat developmental effects evident after ETU administration, and may address this concern for a developmental neurotoxicity (DNT) study with ETU (see Section 8.2, Additional Data Requirements). The primary effect in two rabbit studies was an increase in abortions and decreased maternal body weight, increased maternal mortality, alopecia and ataxia. In a published rat developmental inhalation study, dams at the highest dose tested had decreased body-weight gain, hindlimb weakness, slower righting reflexes and increased resorptions. The hindlimb weakness correlates with the effects observed in the short-term neurotoxicity study. Pups at the high dose had increased wavy ribs and external petechial hemorrhage. Although there are triggers for requiring a DNT study with mancozeb, concern for developmental neurotoxicity may be addressed with the DNT identified for ETU (see Section 8.2, Additional Data Requirements). It is also possible that there is developmental neurotoxicity potential from mancozeb that is secondary to thyroid toxicity. Thus a developmental thyroid assay using mancozeb, may suffice in characterizing the developmental neurotoxicity potential of mancozeb. Database uncertainty factors are incorporated into the risk assessment to address these concerns, as well as concerns with the potential for immunotoxicity.

Epidemiology and Non-Hodgkin's Lymphoma

In a nested case-control study (Mills et al., 2005), lymphohematopoietic cancers in 131 farm workers were examined. There was no increase in lymphocytic leukemia or non-Hodgkin`s Lymphoma. Workers exposed to a high level of mancozeb had a statistically significant increase in granulocytic leukemia (OR: 3.35; CI: 1.09-10.31; n=20). However, sample sizes were very small and pesticide exposure information was limited. Information on potential confounding factors such as smoking, diet, alcohol consumption, and family history was not collected and thus, odds ratios were not adjusted. Correlations between different pesticides were not examined. Given these limitations, this study does not provide convincing evidence of a relationship between mancozeb exposure and lymphohematopoietic cancers.

Potential associations have been reported between the EBDC maneb (no longer registered in Canada), and Parkinson's Disease (PD), also referred to as Parkinson's-like Disease or Parkinsonism. Nabam is the disodium salt of ethylene bis(dithiocarbamate), maneb is manganese ethylene bis(dithiocarbamate) and mancozeb is manganese ethylenebis(dithiocarbamate) (polymeric) complex with zinc salt. The neurological effects noted with maneb may be related to manganese as high levels of manganese can cause 'manganism', a disease similar to PD. In animal studies, co-administration of maneb and paraquat increased neurological effects in rats (Thiruchelvam et al. 2000, 2002, 2003, 2005; Barlow et al, 2003, Cicchetti et al, 2005, Cory-Slechta et al., 2004, 2005). Costello et al (2009) conducted a case-control study to examine the relationship between PD and residential exposure to paraquat and maneb in California, United States. Combined exposure to maneb and paraquat between 1974 and 1999 was associated with an increased risk of PD (OR=1.75, 95% 1.13, 2.73). However, this increase was mainly attributable to exposures between 1974 and 1989 (OR=2.14, 95% CI: 1.24, 3.68), as exposures between 1990 and 1999 were not associated with an increased risk of PD (OR=0.93, 95% CI: 0.45, 1.94). Exposure to paraquat alone was not associated with an increased risk of PD and too few cases of maneb-only exposures were available to conduct a meaningful analysis. When stratified by age, PD risk was greatest among subjects with disease onset before 60 years of age.

The reported findings suggest that combined exposure to paraquat and maneb may increase the risk of PD; however, this combination of exposures is no longer expected as maneb has been withdrawn by the registrant for use in Canada. Currently, epidemiological evidence does not establish a clear cause and effect relationship between a particular pesticide exposure and PD.

ETU

The toxicological database for ETU contains numerous published and unpublished studies, including metabolism, acute, short-term, long-term, reproductive, developmental, and genotoxicity studies (Appendix III, Table 2). However, for the purpose of this re-evaluation, the reproduction studies were considered supplemental and the database was lacking a developmental neurotoxicity study with comparative (adult vs young) thyroid assay. Both unpublished and published data have been considered in the toxicity assessment (Appendix III, Table 4).

ETU was rapidly absorbed by the digestive tract, and relatively slowly absorbed via the skin. Regardless of absorption pathway, ETU primarily accumulated in the thyroid, followed by the kidney, liver and brain. It had an elimination half-life of approximately 28 hours in the monkey, 9–10 hours in the rat and 5 hours in the mouse. Excretion was complete and occurred primarily in the urine (50–80%, depending on the species). Metabolism was more rapid in the mouse than in the rat, but more extensive in the rat with metabolites consisting of EU and other polar compounds.

During gestation, ETU in amniotic fluid, placenta and fetal carcass correlated with maternal blood levels. In postpartum animals, ETU levels in maternal liver and milk were 10-fold and twofold greater than maternal blood, respectively. Levels in maternal milk were 13-fold greater than in neonatal animals. Following oral exposure, blood levels peaked in maternal mice and rats after 1.3 and 1.4 hours, respectively and in the fetus after 2 hours. The main route of excretion was urine, with 74% of administered dose in the mouse and 70% of administered dose in the rat. In the mouse, 40% of ETU was metabolized, versus 95% in the rat. Oral administration in mice induced cytochrome P-450 (aniline hydroxylase: CYP2E1), but this activity was reduced in rats. This metabolic difference may be the reason that fetal rats demonstrate severe toxicity while the fetal mouse demonstrates mild toxicity, at comparable dose levels.

In published studies and assessments, ETU was of low acute oral toxicity in non-pregnant and pregnant mice (tested on gestation day 9) and pregnant hamster (tested on gestation day 11) and of low to moderate toxicity in non- pregnant and pregnant rats (tested on gestation day 13), respectively. ETU was of low acute dermal toxicity in the rabbit and low acute inhalation toxicity in the rat. It was non-irritating to rabbit eye and skin and was a skin sensitizer in guinea pigs.

The primary effects of ETU in mice and rats after short-term oral exposure were observed in the thyroid (decreased T_4, increased TSH, increased weight and hyperplasia) and liver (increased weight, cytoplasmic vacuolation and hyperplasia). Although mice exhibited thyroid effects, these occurred at higher dose levels than in the rat. However, mice were more sensitive to the liver effects than the rat. In 90-day and 1-year dog studies, body weight and blood effects, indicative of hemolytic anaemia (decreased haemoglobin, packed cell volume, red blood cells and increased reticulocytes), occurred at lower or at the same dose levels causing thyroid toxicity. Short-term dermal and inhalation toxicity studies were not available.

The National Toxicology Program (NTP) conducted reproductive/chronic/oncogenicity studies in the mouse and rat, combining both perinatal and adult exposures to ETU. Similar to the short-term studies, the thyroid, liver and pituitary were primary targets after exposure to ETU. Although the weight-of-evidence suggested that ETU was weakly genotoxic, thyroid tumours in both the mouse and rat had a clear mode and mechanism of action. ETU inhibits thyroid peroxidase, leading to chronic thyroid hormone deficiency (decreased T_4). This in turn stimulates the hypothalamus and pituitary, causing the production of more thyroid stimulating hormone (TSH). This hormonal imbalance leads to thyroid growth, hyperplasia and subsequent follicular cell neoplasia. Frequently, pituitary gland neoplasia also occurs, which was evident with ETU exposure in the mouse. Similar to the short-term studies, the mouse was more sensitive to liver effects than the rat in long-term studies. In the NTP study, mice exhibited an increase in liver adenomas and carcinomas, showing a clear dose-response in females. These adenomas/carcinomas occurred at comparable or lower doses than the thyroid and pituitary tumours. Since there is no current evidence supporting a threshold for induction of liver tumours, a cancer unit risk (q_1^*) of 0.0601 (mg/kg bw/day)$^{-1}$ based on liver tumours was generated for the cancer risk assessment of ETU and all EBDCs.

There were two supplemental reproduction studies in the ETU database. In one study, dose levels in mg/kg bw/day could not be calculated because of stability problems with the test material and unknown feed consumption. In addition, the study did not account for all of the pups. In the second study, there were low pup numbers. Both of these studies identified the thyroid as the primary target in adult rats and mice and decreased survival in both rat and mouse pups.

Developmental toxicity occurred via both the oral and dermal routes of exposure, with rats being the most sensitive species. After dermal exposure on gestation days 12 to 13, all fetal rats had marked skeletal malformations, at non-maternally toxic doses. The developmental effects by both the oral and dermal routes of exposure included cryptorchidism, exencephaly, ectopic kidneys, agenesis of kidneys, hydronephrosis, edematous fat pads, less than 13 ribs, fused lumbar, sacral or caudal vertebrae, oligodactyly, syndactyly, webbed digits, anal atresia and malformation of the central nervous system.

Although thyroid toxicity is often associated with developmental effects, this potential mode of action is not applicable to the acute exposures that resulted in the above-noted malformations, indicating that ETU was a direct developmental toxin in the rat. In published studies, no developmental effects were noted in hamsters or guinea pigs. In mice, the only developmental effect observed was an increase in supernumerary ribs. Cats exhibited malformations in their offspring, at maternally toxic doses. Rats may have a differential sensitivity because of the way ETU is metabolized, compared to the mouse, rabbit, hamster, guinea pig and cat.

Manganese

Approximately 20% of mancozeb is elemental manganese. Manganese is an essential element in all animal species. However, over-exposure to manganese is associated with adverse neurological, reproductive and cardiopulmonary effects. These adverse effects are dependent on the route of exposure, the chemical form, the age of an individual at the time of exposure and an individual's nutritional status (such as the iron level). Regardless of the route of exposure, the nervous system is the primary target. Chronic exposure to high doses of manganese (well above the ADI) may result in 'manganism', a progressive condition marked by altered gait, fine tremor hyperactivity, abnormal movements, muscular rigidity, limb flexion and psychiatric disturbances. Since neurological effects noted in the mancozeb database may be related to the manganese, the exposure and risk assessment considered the potential manganese exposure from mancozeb. In general, the risk assessment for mancozeb is protective for manganese.

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. This pest control products act factor should take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, as well as potential pre-and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

Mancozeb

The toxicity database for mancozeb was extensive, consisting of two rat and one mouse reproductive toxicity studies, as well as developmental oral toxicity studies in rats, two in rabbits and a rat inhalation developmental toxicity study. Both published and unpublished studies were included in the assessment.

In a published, non-guideline reproductive toxicity study, mice had an increased incidence of failure to implant, starting on gestation day 3, in the presence of hormonal effects in the mothers. No sensitivity of the young was noted in the oral developmental studies in rats or rabbits. However, rats and rabbits did have increased abortions and resorptions in the presence of maternal toxicity. In a published rat developmental inhalation toxicity study, dams had a decrease in body-weight gain, hindlimb weakness and slower righting reflexes. At the same dose, there was an increase in resorptions as well as in increase in fetuses with wavy ribs and external petechial hemorrhage. There were indications that mancozeb and/or ETU, may be developmental neurotoxins. Currently, the mancozeb and ETU databases lack developmental neurotoxicity studies. It is possible that developmental neurotoxicity could result secondarily from mancozeb induced thyroid toxicity. Thus a developmental thyroid assay using mancozeb, may suffice in characterizing this concern. Due to concerns for the developmental neurotoxicity potential of mancozeb, a database uncertainty factor was used in the risk assessment.

While the available database for determining the sensitivity of the young was extensive, there are some uncertainties with regard to potential developmental neurotoxicity, and as noted above, these have been accounted for by application of a database uncertainty factor. The inhibition of implantation in mice and resorptions/abortions in rats and rabbits at the LOAEL were considered serious endpoints, although the level of concern was tempered by the presence of maternal toxicity. Therefore, the pest control products act factor was reduced to threefold for exposure scenarios using the rat reproductive or developmental toxicity studies for risk assessments. For risk assessments involving children, the risk was considered well characterized and the Pest control products act factor was reduced to onefold.

ETU

While there are no pesticide registrations for ETU, it is a metabolite of EBDC fungicides. The ETU database contains both unpublished and published studies, but lacks an adequate rat reproduction study and a rat DNT study, with a comparative thyroid assay. The registrant should consider submitting these studies during the consultation period.

With respect to pre- and postnatal toxicity, sensitivity of the young was observed in numerous rat developmental studies. Multiple and serious head, central nervous system and skeletal malformations were noted after 1–2 doses via both the dermal and oral routes of exposure. The effects occur at non-maternally toxic doses. ETU was also developmentally toxic to the rabbit, but at higher dose levels than seen with the rat. A published cat study demonstrated less severe developmental toxicity at doses similar to the rat, but these dose levels were also maternally toxic.

Although sensitivity of the young was identified in developmental toxicity studies, the potential for reproductive and developmental neurological effects has yet to be characterized. Considering the database deficiencies with respect to toxicity in the young, and the serious developmental effects that occur at non-maternally toxic doses, the pest control products act factor of 10-fold will be retained for those exposure scenarios that refer to the NOAEL for malformations in the risk assessment. The use of the NOAEL for thyroid toxicity in the one-year dog study as a point of departure for long term exposure scenarios provides an adequate margin to levels which caused developmental toxicity. Therefore, the pest control products act factor was reduced to threefold when the one-year dog study is the reference study for risk assessment.

3.2 Occupational and Non-Occupational Risk Assessment

Occupational and non-occupational 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.

Where evidence of carcinogenicity is identified for the active ingredient, a cancer potency factor (q_1^*) is generated and used to estimate cancer risk. The product of the expected exposure and the cancer potency factor (q_1^*) estimates the lifetime cancer risk as a probability. A lifetime cancer risk of 1×10^{-5} in worker populations and 1×10^{-6} in the general population is generally considered acceptable.

Further information on how the potential cancer risks from pesticides are assessed can be found in the Science Policy Notice SPN2000-01, *A Decision Framework for Risk Assessment and Risk Management in the Pest Management Regulatory Agency*.

3.2.1 Toxicology Endpoint Selection for Occupational and Bystander Risk Assessment

3.2.1.1 Mancozeb Acute Dermal (Pick Your Own Scenario)

For acute dermal risk assessment (females ages 13–49), a modified reproductive toxicity study in rats was selected. A NOAEL of 18 mg/kg bw/day was established, with inhibition of implantation occurring at a LOAEL of 24 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. An additional threefold factor for database uncertainty (lack of ETU DNT and mancozeb immunotoxicity studies) was applied. As discussed previously, the Pest control products act factor has been reduced to threefold. The target MOE is 1000.

To estimate acute dermal risk (1 day) for the general population, a LOAEL of 500 mg/kg bw from an acute neurotoxicity study was used. On day 1 there was decreased total session motor activity in all male and female treatment groups. A NOAEL was not established. Standard factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. An additional threefold was applied for use of a LOAEL and an additional threefold uncertainty factor for database uncertainty (lack of ETU DNT and mancozeb immunotoxicity studies). As discussed previously, the Pest control products act factor was reduced to onefold. The target MOE is 1000.

3.2.1.2 Mancozeb Short- and Intermediate-term Dermal (Occupational)

For short-term and intermediate-term dermal risk assessment, a modified reproductive toxicity study in rats was selected. A NOAEL of 18 mg/kg bw/day was established, with inhibition of implantation occurring at a LOAEL of 24 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied to all exposure scenarios.

For occupational exposure scenarios, an additional threefold factor to account for a serious endpoint (embryo-fetal loss) observed in the presence of maternal toxicity and a threefold factor for database uncertainty (lack of ETU DNT and mancozeb immunotoxicity studies) were applied. The target MOE is 1000, which protects worker populations that could include pregnant or lactating women.

3.2.1.3 Mancozeb Short- and Intermediate-term Inhalation (Occupational and Bystander)

For short-term and intermediate-term inhalation risk assessment, a published inhalation developmental toxicity study in rats was selected. A NOAEL of 5.27 mg/kg bw/day was established for both maternal and developmental toxicity, based on decreased body-weight gain, increased resorptions and hindlimb weakness and slower righting reflex in the dams. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied to all scenarios.

For occupational exposure scenarios, an additional threefold factor to account for a serious endpoint (embryo-fetal loss) in the presence of maternal toxicity and a threefold factor for database uncertainty (lack of ETU DNT and mancozeb immunotoxicity studies) were applied. The target MOE is 1000, which protects worker populations that could include pregnant or lactating women.

For bystander exposure scenarios (females ages 13–49), an additional threefold factor for database uncertainty (lack of ETU DNT and mancozeb immunotoxicity studies) was applied. As discussed previously, the pest control product act has been reduced to threefold. The target MOE is 1000.

Concerns for effects on body weight in the study are considered relevant to the general population. An additional threefold factor for database uncertainty (lack of ETU DNT and mancozeb immunotoxicity studies) was applied. As discussed previously, when assessing the risk to the general population, the pest control products act factor has been reduced to onefold. As such, the target MOE is 300.

3.2.1.4 Mancozeb Long-term Dermal and Inhalation (Occupational)

For long-term dermal and inhalation risk assessment, a one-year dog toxicity study was selected. A NOAEL of 2.3 mg/kg bw/day was set based on thyroid hormone effects as well as effects on liver weight, body-weight gain and food consumption. This is supported by the NOAEL of 1.75 mg/kg bw/day in a second one-year dog study. Standard factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. An additional threefold factor for database uncertainty (lack of ETU DNT and mancozeb immunotoxicity studies) was applied. The target MOE is 300, which protects worker populations that could include pregnant or lactating women.

3.2.1.5 ETU Acute, Short and Intermediate-term Dermal and Inhalation

To estimate acute, short- and intermediate-term dermal and inhalation risk, numerous rat developmental toxicity studies were considered. At doses of 10 mg/kg bw/day and greater, increased head and skeletal malformations were observed at non-maternally toxic doses. A NOAEL of 5 mg/kg bw/day was established. Worker populations could include pregnant or lactating women and therefore this endpoint was considered appropriate for occupational risk assessment. The target MOE for these scenarios was 1000, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability.

Since the malformations noted are serious, occur at non-maternally toxic doses, and to address residual concerns related to database uncertainties, an additional 10-fold factor was applied to protect the pregnant worker, an identified sensitive subpopulation.

3.2.1.6 ETU Long Term Dermal and Inhalation

For long term dermal and inhalation risk assessment, a one-year oral dog study was selected. At 1.79 mg/kg bw/day, decreased body weight and increased thyroid weight, hypertrophy and colloid retention were observed. A NOAEL of 0.18 mg/kg bw/day was established. The target MOE is 300. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. An additional threefold factor was applied for database deficiencies. The NOAEL established in the one-year dog study is several fold lower than the NOAEL for serious developmental effects observed in the rat and thus, provides inherent protection for worker populations that could include pregnant or lactating women.

3.2.1.7 ETU Acute and Short-term Aggregate

Females 13–49 Years of Age

For acute and short-term aggregate exposure for females 13–49 years of age, a developmental rat toxicity study was selected. A NOAEL of 5 mg/kg bw/day was established based on head and skeletal malformations at 10 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed previously, the 10-fold pest control products act factor was retained. The composite assessment factor is 1000.

General Population

To account for short-term aggregate exposure for the general population, a 90-day oral mouse study was used. In absence of appropriate dermal and inhalation studies, it was assumed that the thyroid effects that were consistently observed in oral studies were relevant to other routes of exposure. A NOAEL of 1.7 mg/kg bw/day was established, based on increased thyroid follicular cell hyperplasia and decreased colloid density at 18 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The potential for reproductive and developmental neurotoxicity effects have not been characterized. However, this is tempered by the fact that the NOAEL is lower than the NOAEL identified for developmental effects. Therefore, the pest control products act factor was reduced to threefold. The target MOE is 300.

3.2.1.8 ETU Cancer Potency Factor

A published study by the NTP examined the oncogenic potential of ETU in mice and rats. This study was considered a generational study since it examined the effects of ETU exposure on animals during gestation and for 2 years following parturition. Since there is no current evidence supporting a threshold mode of action for liver tumour induction in female mice, a q_1^* of 0.0601 $(mg/kg\ bw/day)^{-1}$ was calculated and used for the cancer risk assessment of ETU and all EBDCs.

3.2.1.9 Dermal Absorption

Mancozeb

Based on a chemical-specific in vivo dermal absorption study, a dermal absorption factor of 1% was determined for risk assessment purposes for mancozeb.

ETU

Based on a chemical-specific in vivo dermal absorption study, a dermal absorption factor of 45% was determined for risk assessment purposes for ETU.

Manganese

Dermal absorption of manganese is expected to be very low as it does not penetrate the skin readily (ATSDR, 2008). No studies were located regarding any health effects in humans or animals after dermal exposure to inorganic manganese (ATSDR, 2008). Even under sustained, heavy industrial exposure in the mining industry, intimate skin contact with manganese-containing mineral dusts did not result in notable skin absorption (Hostynek et al, 1993).

3.2.2 Occupational Exposure and Risk Assessment

Workers can be exposed to mancozeb through mixing, loading or applying the pesticide, and when entering a treated site to conduct activities such as scouting and/or irrigating treated crops.

ETU is a contaminant of mancozeb formulations, a degradate of mancozeb that can be formed in tank mix solutions, and it can also be formed in the body from the metabolic conversion of mancozeb. Potential exposure was also quantified for ETU. To estimate the amount of ETU that can potentially be formed in a tank mix, values of 0.1% and 0.2% were used based on tank mix stability studies summarized in the USEPA Regristration Eligibility Decision (2005). The amount of ETU formed in vivo was estimated by assuming that 7.5% of absorbed mancozeb would be transformed into ETU (see Section 3.1). To estimate postapplication exposure to ETU, direct measurements of ETU were taken in the dislodgeable foliar residue (DFR) studies. For handlers, total ETU exposure was estimated by summing exposure from its presence in the tank mix and the amount formed from handler metabolism of mancozeb. For postapplication workers, total exposure was estimated by summing exposure from the foliage using the DFR study and the amount formed as a result of the worker metabolising mancozeb.

3.2.2.1 Mixer, Loader and Applicator Exposure and Risk Assessment

There are potential exposures to mixers, loaders, and applicators. The following scenarios were assessed:

- Mixing/loading of liquids, wettable powders, dry flowables (used to approximate wettable granules) and wettable powders packaged in water soluble packaging.
- Aerial application to lentils, potatoes and wheat.

- Airblast application to ash, oak, sycamore, hawthorn, arborvitae, juniper, Douglas fir, holly, ivy, pine, apples, grapes and pears.
- Groundboom application to alfalfa (grown for seed), cantaloupe, melons, squash, watermelons, carrots, celery, cucumbers (field), pumpkin, ginseng, lentils, head lettuce, onions (foliar), potatoes, sugar beets, tomatoes, wheat, arborvitae, ash, juniper, Douglas fir, hawthorn, oak, sycamore, holly, ivy, pine, and honeysuckle.
- Broadcast spreader granular application (used to approximate in-furrow application) to onions.
- Handwand or backpack sprayer application to ash, oak, sycamore, hawthorn, arborvitae, juniper, Douglas fir, holly, ivy, honeysuckle, pine, tobacco (greenhouse) and tomatoes (greenhouse).
- Seed treatment:
  - Commercial mixing/loading and applying wettable powders as a slurry seed treatment to barley, corn, oats and wheat seed (activities may include treating, bagging, sewing, tagging, stacking, clean-up and repair).
  - On-farm planting of commercially treated seed.
  - On-farm mixing/loading and applying wettable powders as a dry application for drill or planter box seed treatment to barley, corn, flax, oats and wheat seed and planting reated seed.
  - On-farm mixing/loading and applying wettable powders as a slurry seed treatment to barley, corn, oats and wheat seed and planting treated seed.
- Potato seed piece treatment:
  - Mixing/loading and applying dusts and wettable powders as potato seed piece treatments and planting treated potato seed.
  - Mixing/loading and applying solutions to seed potatoes for storage.

Due to the number of agricultural applications per year (ranging from 1 to 18), exposure is likely to be short- to intermediate-term (up to several months) in duration. Exceptions would be greenhouse tomatoes, where exposure is expected to be long-term (greater than six months) in duration.

To estimate the amount of ETU that can potentially be formed in a tank mix, three tank mix stability studies were submitted by the technical registrants for mancozeb. These tank mix stability studies were evaluated by the USEPA and several major limitations with the data were noted. In the absence of any additional data, values of 0.1% and 0.2% were used to estimate the amount of ETU that is formed in tank mixes of mancozeb during mixing/loading and application, respectively. A value of 0.1% was also used to estimate ETU exposure when handling dry formulations.

The PMRA estimated handler exposure based on different levels of personal protection:

Baseline PPE:	Long sleeved shirt, long pants and chemical-resistant gloves (unless otherwise specified). For groundboom application, this scenario does not include gloves.
Maximum PPE:	Chemical-resistant coveralls over a long sleeved shirt, long pants and chemical-resistant gloves.
Engineering controls:	Represents the use of an appropriate engineering control such as closed tractor cab or closed loading system (for example, water soluble packaging).
Respirator:	A respirator with NIOSH approved organic-vapour removing cartridge with a prefilter approved for pesticides or a NIOSH approved canister approved for pesticides.

Dermal and inhalation exposures were estimated using data from the *Pesticide Handlers Exposure Database* (PHED), *Version 1.1*. 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 personal protective equipment (PPE). In most cases, PHED did not contain appropriate data sets to estimate exposure to workers wearing chemical-resistant coveralls or a respirator. This was estimated by incorporating a 90% clothing protection factor for chemical-resistant coveralls and a 90% protection factor for a respirator into the unit exposure data.

Mancozeb is registered for seed and potato seed piece treatments, which may occur both on-farm and in commercial facilities. PHED scenarios were not considered to be representative of exposure to workers treating or handling treated seed. Surrogate exposure studies were used instead to estimate exposure. None of these studies were chemical-specific; however, they are the best available data. See Appendix IV, Table 1 for a description of the studies and unit exposure values used in this assessment.

Mixer/loader/applicator exposure estimates are based on the best available data at this time. The assessment may be refined with exposure data more representative of modern application equipment and engineering controls. Biological monitoring data might also further refine the assessment.

3.2.2.1.1 Mancozeb Mixer, Loader and Applicator Non-Cancer Risk Estimates

Route specific MOEs for mixer/loader and applicators for agricultural crops are outlined in Appendix IV, Table 2 and Table 3 for short- to intermediate-term and long-term exposure, respectively.

Calculated MOEs for mixer/loaders and applicators of mancozeb to agricultural crops exceed target MOEs for the majority of uses, provided additional personal protective equipment (respirator) and/or engineering controls (wettable powders in water soluble packaging) are used, as summarized in Section 8.1. Calculated long-term MOEs for greenhouse tomatoes exceed the target MOE with engineering controls (wettable powders in water soluble packaging) and additional PPE (chemical-resistant coveralls and a respirator) except for high pressure handwand application equipment. In order to achieve the target MOE of 300, the amount handled per day would need to be restricted to 15 kg a.i./day (approximately 8 ha).

Route specific MOEs for seed and potato seed piece treatment scenarios are outlined in Appendix IV, Table 4. With additional PPE and/or engineering controls, calculated MOEs for some seed treatment scenarios (planting treated seed, on-farm slurry seed treatment and treatment of seed potatoes for storage) exceeded the target MOE, and risks were found to be acceptable.

Calculated inhalation MOEs are less than the target MOE for commercial seed treatment with slurry application (treater and baggers activities) for all seed types (barley, corn, oats and wheat), even after consideration of maximum feasible PPE and engineering controls and therefore, risks were not found to be acceptable. There was no data to assess dry application in commercial seed treatment facilities and the potential for exposure is expected to be greater than slurry treatment scenarios.

Calculated inhalation MOEs are less than the target MOE for on-farm planter box seed treatment (dry application) of barley, corn, flax, oats and wheat seed and therefore, risks were not found to be acceptable. Given that the calculated inhalation MOEs are orders of magnitude lower than the target MOE, no additional mitigation measures (limiting kg a.i. handled) were considered.

For potato seed piece treatment with dust application, in order to reach the inhalation target MOE, the amount of mancozeb active ingredient handled per day would need to be limited to 7.8 kg (9800 kg of potato seed treated per day at rate of 0.8 kg a.i./100 kg seed) with additional PPE (respirator during loading and treating) and engineering controls (closed cab planters). The limit on kg a.i. handled is not considered to be agronomically feasible for farmers or commercial treatment facilities and therefore, risks were not found to be acceptable.

For all seed treatment scenarios where target MOEs were not achieved, or for which feasible mitigation measures are not possible, or for which there is no data, additional data could be submitted to refine the assessment of these uses.

3.2.2.1.2 ETU Mixer, Loader and Applicator Non-Cancer Risk Estimates

Combined MOEs for mixer/loader and applicators for agricultural crops are outlined in Appendix IV, Table 5 and Table 6 for short- to intermediate-term and long-term exposure, respectively. Combined short- to intermediate-term MOEs for seed and potato seed piece treatment scenarios are outlined in Appendix IV, Table 7.

Calculated ETU MOEs for mixer/loaders and applicators of mancozeb to agricultural crops exceed the target MOE with mitigation measures required for the mancozeb non-cancer risk assessment as outlined above, and therefore, risks were found to be acceptable.

Calculated ETU MOEs for seed and potato seed treatment scenarios, exceed the target MOE with additional mitigation measure and were found to be acceptable for all uses except for on-farm seed treatment (dry application). Calculated ETU MOEs for on-farm seed treatment (dry application) failed to reach the target MOE for all seed types (barley, corn, flax, oats, wheat), and therefore, risks were not found to be acceptable. This scenario also had risks that were not found to be acceptable in the mancozeb non-cancer assessment (see above).

3.2.2.1.3 ETU Mixer, Loader and Applicator Exposure Cancer Risk Estimates

The cancer risk for occupational workers was determined by calculating the lifetime average daily dose (LADD) from the total ETU exposure. The LADD was then multiplied by the q_1* to obtain cancer risk estimates. Occupational cancer risk is calculated assuming 40 years of exposure (i.e. a career in agriculture of 40 years) over a 75-year lifetime. For application to agricultural crops, it was assumed farmers and custom applicators would handle mancozeb for 30 days per year. For seed and potato seed piece treatment, it was assumed that workers in commercial facilities would handle mancozeb for 30 days a year and farmers would handle mancozeb 10 days a year when treating on-farm or planting treated seed. The product of the expected exposure (LADD) and the cancer potency factor (q_1*) estimates the lifetime cancer risk as a probability. A lifetime cancer risk in the range of 1×10^{-5} to 1×10^{-6} in worker populations is generally considered acceptable.

Calculated lifetime cancer risk estimates with mitigation measures are summarized in Appendix IV, Table 8 for agricultural crops and Appendix IV, Table 9 for seed and potato seed piece treatment.

Lifetime cancer risk estimates associated with mixing/loading and application of mancozeb to agricultural crops were found to be acceptable with additional protective equipment and/or engineering controls required as a result of the non-cancer risk assessment, as outlined in Section 3.2.2.1.1.

For seed treatment uses, calculated cancer risk estimates with mitigation measures were found to be acceptable for all scenarios except for on-farm seed treatment (dry application) of oat seed. The calculated cancer risk estimate for on-farm seed treatment of oats with dry application is 2×10^{-5}, and iwas not found to be acceptable. This scenario also had risks that were not found to be acceptable in the mancozeb and ETU non-cancer assessments.

3.2.2.1.4 Manganese Mixer, Loader and Applicator Risk Assessment

Mixer/loaders and applicators handle mancozeb formulations that have not been subjected to environmental degradation in the field. Therefore, the estimate of mancozeb inhalation and dermal exposure would adequately consider the inhalation and dermal exposure of manganese from mancozeb. The toxicological points of departure for dermal exposure were derived from animal studies in which mancozeb including its manganese component was administered. Therefore, it is expected that the points of departure for mancozeb cover off the manganese exposure that would occur concurrently, as is the case for mixer/loaders and applicators.

3.2.2.2 Postapplication Worker Exposure and Risk Assessment

The postapplication occupational risk assessment considered exposures to workers who enter treated sites to conduct agronomic activities involving foliar contact (for example, pruning, thinning, harvesting, or scouting). Based on the mancozeb use pattern, there is potential for short- to intermediate-term (>1 day–6 months) postapplication exposure for the majority of scenarios and long-term exposure (>6 months) for workers engaged in tasks for greenhouse tomatoes.

Potential exposure to postapplication workers was estimated using activity-specific transfer coefficients (TCs) and dislodgeable foliar residue (DFR) values. The DFR refers to the amount of residue that can be dislodged or transferred from a surface, such as leaves of a plant. The TC is a measure of the relationship between exposure and DFRs 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. Postapplication exposure activities include harvesting, thinning, pruning, scouting, and irrigation.

All submitted chemical-specific DFR data were considered for use in the assessment. Each study quantified DFR for mancozeb and ETU. Based on a comparison of foliage types, application regime and study conditions, the most appropriate DFR study and site location were used to estimate dislodgeable foliar residues for Canadian agricultural crops. The study and site selected to estimate residues on registered Canadian crops is summarized in Appendix IV, Table 10. Predicted DFR residues for each crop were calculated using the study peak DFR and predicted percent dissipation per day calculated from the linear equation of plotting the natural logarithm of DFR versus dissipation time (postapplication interval) following the final application. Estimated DFR values were adjusted proportionally for maximum Canadian application rates.

As DFR studies were not available for all crop and application scenarios, the extrapolation of study DFR data to a wide variety of crops, formulation types and application regimes was required for the postapplication risk assessment. Since available studies are not necessarily representative of some Canadian crops, use patterns and climatic conditions, this extrapolation represents an uncertainty in the postapplication risk assessment; however, it is the best available data at this time.

3.2.2.2.1 Mancozeb Postapplication Worker Non-Cancer Exposure and Risk Assessment

For workers entering a treated site, restricted-entry intervals (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 before residues decline to a level where performance of a specific activity results in exposures above the target MOE (>1000 for short- to intermediate-term and long-term dermal exposure scenarios for mancozeb).

Postapplication risk estimates are presented in Appendix IV, Tables 11 and 12 for short- to intermediate-term and long-term exposure, respectively. To achieve the target MOEs for postapplication workers in agricultural scenarios, some of the current REIs would need to increase in length or new REIs would need to be added to the label. The majority of calculated REIs range from 12 hours to 10 days and are considered agronomically feasible. For orchard and vine crops (apples, pears and grapes), the restricted-entry intervals required to reach the target MOE for high exposure activities (such as hand thinning), ranged from 53 to 62 days. These REIs are not considered to be agronomically feasible for growers.

Postapplication exposure was not assessed for in-furrow application to onions at planting as it is not expected that this scenario will result in residues on foliage and postapplication exposure is expected to be low in comparison to foliar treatments. A minimum 12 hour REI is required and is considered sufficient to protect workers entering treated areas for this scenario.

3.2.2.2.2 ETU Postapplication Worker Non-Cancer Exposure and Risk Assessment

A postapplication non-cancer risk assessment was conducted for ETU on the calculated REI day for mancozeb non-cancer risk, as outlined above in Section 3.2.2.2.1. Calculated ETU postapplication risk estimates are presented in Appendix IV, Table 11 and Table 12 for short- to intermediate-term and long-term exposure, respectively.

On the proposed REI day, calculated MOEs for ETU are greater than the target MOE for most crop/activity scenarios. For those crop/activity scenarios that failed to reach the ETU target MOE on the mancozeb REI day, the days required to reach the ETU target MOE were also calculated. The increased REIs required to meet ETU target MOEs may not be considered agronomically feasible for some crops/activity scenarios.

Based on the long-term exposure risk assessment, an REI of 27 days is required in order to achieve target MOEs for greenhouse tomato postapplication activities. For greenhouse crops, the maximum agronomically feasible REI is generally considered to be 2 days.

3.2.2.2.3 Postapplication Worker Cancer Exposure and Risk Assessment

Cancer risks for postapplication workers were based on exposure to average residues for a 30 day period starting on the day of the recommended REI required to meet the target MOEs for mancozeb and ETU non-cancer risk, as discussed above in Sections 3.2.2.2.1 and 3.2.2.2.2. Occupational cancer risk is calculated assuming 40 years of exposure (a career in agriculture of 40 years) over a 75-year lifetime. It was assumed that postapplication workers would perform each activity for a period of 30 days. Cancer risks were calculated using a linear low-dose extrapolation approach, in which a LADD was calculated and then multiplied by a q_1^* that had been calculated for ETU based on dose response data in the appropriate toxicology study (q_1^*=0.0601 (mg/kg bw/day)$^{-1}$). The total ETU absorbed daily dose on the established REI day is based on direct exposure to ETU residues on the REI day and metabolic conversion of mancozeb exposure on the REI day.

Calculated lifetime cancer risk estimates are presented in Appendix IV, Table 15. All calculated cancer risk estimates are less than 1×10^{-5}, and therefore, risks were found to be acceptable.

3.2.2.2.4 Manganese Postapplication Worker Exposure and Risk Assessment

The postapplication exposure and risk assessment for mancozeb does not address the assessment for manganese exposure from mancozeb application. REIs were calculated based on the residue decline of the organic component of mancozeb and would not be representative of the manganese component of mancozeb. The dislodgeable residue of manganese from foliage at the time of application and after application is not known.

The fate of the manganese component of mancozeb in foliage is not known, including whether it would degrade to inorganic or organic forms. Since manganese and zinc are in a complex with the organic component, it is assumed that manganese would disassociate from the organic component. The leaf may absorb the manganese or it may be sloughed off and therefore not be available for transfer to the skin. If the manganese is available for exposure and assuming that it is in an inorganic form, dermal absorption is expected to be very low as it does not penetrate the skin readily. Furthermore, no studies were located regarding any health effects in humans or animals after dermal exposure to inorganic manganese (ATSDR, 2008).

Therefore, for postapplication exposures, although REIs were required to address risk concerns for dermal exposure to mancozeb, any dermal exposure to manganese at the REI or after, is expected to be negligible due to very low absorption. Dermal exposure of manganese from use of mancozeb for postapplication workers is considered to be acceptable.

3.2.3 Non-Occupational Exposure and Risk Assessment

Non-occupational (residential) risk assessment estimates risk to the general population, including children/youths, during or after pesticide application.

3.2.3.1 "Pick Your Own" Exposure and Risk Assessment

"Pick Your Own" (PYO) farms are those that allow the public to harvest their own fruit and vegetables. As PYO fruit and vegetable operations become more and more prevalent, the PMRA recognizes the need for a means of assessing exposure to pesticides during hand-harvesting by members of the public. For the purpose of this risk assessment, PYO facilities are considered commercial farming operations that allow public access for harvesting in large-scale fields or orchards treated with commercially labelled mancozeb.

The PYO assessment for mancozeb focuses on apples and was conducted for dermal exposure from hand harvesting fruit. Since members of the public who harvest at PYO facilities may be of any age, the risk assessment was conducted for toddlers, youths and adults. It is assumed that harvesters from the general public may frequent PYO operations a few times per season; however, due to the intermittent nature of this exposure, this exposure scenario was considered to be acute in duration.

Postapplication exposure estimates from harvesting at PYO facilities were quantified for dermal exposure to both residues of mancozeb and residues of ETU. It was assumed that a patron would enter a PYO facility on the first day following the pre-harvest interval.

Total ETU exposure was calculated by summing exposure to ETU from its presence on foliage and the amount formed internally from the metabolic conversion of absorbed mancozeb. Results of the dermal non-cancer risk assessment for mancozeb and ETU are presented in Appendix V, Table 1 and 2.

A deterministic cancer risk assessment was also conducted for dermal exposure from hand harvesting apples. Exposure was amortised over a lifetime to estimate a lifetime average daily dose. When assessing cancer risk, the number of days spent harvesting apples at a PYO operation per year was assumed to be 2 days for toddlers and 5 days for youths and adults. Results of the PYO harvesting exposure cancer risk assessment are presented in Appendix V, Tables 1 and 2. Calculated cancer risk is less than the threshold of 1.0×10^{-6}, and is therefore found to be acceptable.

Estimates of exposure that aggregate the dermal exposure incurred during harvest and the dietary exposure from consuming fresh fruit were not assessed for mancozeb, as dietary risks were not found to be acceptable.

3.2.3.2 Bystander Spray Drift Inhalation Risk Assessment

Bystander exposure may occur when a pesticide drifts from target spray areas and travels to nearby fields or residential areas during or shortly after application. People, including children, playing in the nearby areas or individuals in nearby fields may be exposed to the chemicals as they are drifting.

One published study, conducted by Environment Canada in Prince Edward Island, measured air concentrations adjacent to fields during and after groundboom applications to potatoes and showed detectable levels of mancozeb (Garron et al, 2009). This study suggests there may be potential for inhalation exposure to bystanders in non-target areas adjacent to fields, which is expected to be short- to intermediate-term (up to several months) in duration. The maximum air concentration from this study was used to calculate bystander inhalation exposure estimates. Inhalation exposure and risk estimates for toddlers, youths and adults are presented in Appendix V, Table 3. Calculated MOEs exceed the target MOE for all subpopulations, and therefore, risks were found to be acceptable.

Air concentration measurements for ETU were not available. However, since ETU is a degradate of mancozeb, air concentrations are expected to be low in comparison to mancozeb. In addition, given that the NOAELs for the inhalation route for mancozeb and ETU are similar (5.27 mg/kg bw day versus 5 mg/kg bw/day, target MOE of 1000), and non-cancer short- to intermediate-term MOEs for mancozeb risk estimates are approximately an order of magnitude higher than the target MOE, the current assessment is considered to be sufficiently protective of any additional potential exposure to ETU. Bystander inhalation exposure to ETU was found to be acceptable, and a non-cancer ETU assessment was not conducted.

A cancer risk assessment was conducted considering only ETU exposure from the metabolic conversion of mancozeb. A value of 7.5% was used to estimate the amount of absorbed mancozeb that is metabolized to ETU, as described in Section 3.1. Exposure was amortised over a lifetime to estimate a lifetime average daily dose. Calculated cancer risk is less than the threshold of 1.0×10^{-6}, and therefore, was found to be acceptable.

The mancozeb assessment would also address potential exposure and risk from manganese from mancozeb application, since the maximum concentration of mancozeb at Day 0 was used for the assessment and the toxicological points of departure for inhalation exposure were derived from animal studies in which mancozeb including its manganese component was administered. Therefore, it is expected that the points of departure for mancozeb cover off the manganese exposure that would occur concurrently, as is the case for mixer/loaders and applicators.

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 mancozeb from potentially treated imports 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 (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.

The PMRA considers limiting use of a pesticide when risk exceeds 100% of the reference dose. 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. For cancer risk, the PMRA is concerned when the exposure estimates exceed the cancer risk of 1×10^{-6} (one in a million).

Residue estimates used in the dietary risk assessment (DRA) may be conservatively based on the maximum residue limits (MRL) 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 National Chemical Residue Monitoring Program and the United States Department of Agriculture Pesticide Data Program. However, residue data suitable for the purpose of the mancozeb dietary risk evaluation were not available from these programs. In the case of mancozeb, market basket survey data were used to derive estimates of residues that may remain on food when it is purchased.

The dietary risk assessment considered exposure from all food and water sources that could potentially contain mancozeb and/or ETU. Residue estimates were based on market basket survey data, as well as some field trial data. Specific processing factors of both mancozeb and ETU and conversion factors of mancozeb to ETU, percent of crop treated (CT) in Canada and the United States combined to food supply information were also used in the assessment, where applicable.

There is uncertainty in the use of these data. The field trial studies available were generally not conducted in the Canadian regions and/or according to Canadian good agricultural practice. The magnitude of residues derived from American field trial data and the American market basket survey were not always representative of the Canadian use pattern. In addition, the market basket survey is dated and may not represent residues from the current use pattern. Studies to measure the magnitude of the processing factors and conversion (to ETU) factors were highly variable with many uncertainties. Percent crop treated data for countries other than Canada and the United States was not available.

In situations where the need to mitigate dietary exposure has been identified, the following options are considered. Dietary exposure from Canadian agricultural uses can be mitigated through changes in the use pattern. Revisions of the use pattern may include such actions as reducing the application rate or the number of seasonal applications, establishing longer pre-harvest intervals (PHIs), and/or removing uses from the label. In order to quantify the impact of such measures, new residue chemistry studies which reflect the revised use pattern are required. Imported commodities which have been treated also contribute to the dietary exposure, and are routinely considered in the risk assessment. The mitigation of dietary exposure that may arise from treated imports is generally achieved through the amendment or establishment of MRLs.

Acute, chronic and cancer dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.14), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994–1996 and 1998.

For more information on dietary risk estimates or residue chemistry information used in the dietary assessment, see Appendix VI, VII and VIII.

3.3.1 Determination of Acute Reference Dose

Mancozeb

Acute Reference Dose (ARfD), Females 13–49 Years of Age

To estimate acute dietary risk, for females 13–49 years of age, a NOAEL of 18 mg/kg bw/day from a modified mouse reproductive study was used. In this study, animals dosed gestation days 1–3 had inhibition of implantation at 24 mg/kg bw/day. The dams, at this dose level, exhibited a decrease in the diestrus phase and an increase in the estrus phase of their cycle. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in Section 3.1.1, the pest control products act factor has been reduced to threefold. An additional threefold factor was also applied for database uncertainty (lack of ETU DNT and mancozeb immunotoxicity studies). The composite assessment factor is 1000.

$$\text{ARfD} = \frac{18 \text{ mg/kg bw/day}}{1000} = 0.018 \text{ mg/kg bw/day}$$

Acute Reference Dose (ARfD), General Population (including pick-your-own scenario)

To estimate acute dietary risk for the general population, a LOAEL of 500 mg/kg bw from an acute neurotoxicity study was used. On day 1 there was decreased total session motor activity in all male and female treatment groups. A NOAEL was not established. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. An additional threefold was applied for use of a LOAEL and an additional threefold uncertainty factor for database uncertainty (lack of ETU DNT and mancozeb immunotoxicity studies). As discussed in Section 3.1.1, the pest control products act factor was reduced to onefold. The composite assessment factor is 1000.

ETU

Acute Reference Dose for Ethylene Thiourea, Females 13-49 Years of Age

To estimate acute dietary risk (1 day), numerous rat developmental toxicity studies were considered. At doses of 10 mg/kg bw/day and greater, increased head, (central nervous system) CNS and skeletal malformations were observed at non-maternally toxic doses. A NOAEL of 5 mg/kg bw/day was established. Standard uncertainty factors, 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in Section 3.1.1, the 10-fold pest control products act factor has been retained. The composite assessment factor is 1000.

$$\text{ARfD} = \frac{500 \text{ mg/kg bw/day}}{1000} = 0.005 \text{ mg/kg bw/day}$$

ARfD, General Population (including children)

An ARfD for the general population was not established as there were no acute endpoints of concern indentified.

3.3.2 Acute Dietary Exposure and Risk Assessment

Mancozeb

Acute dietary risk is calculated considering the highest ingestion of mancozeb that would be likely on any one day, and using food consumption and food residue values. A statistical analysis allows all possible combinations of consumption and residue levels to be combined to estimate a distribution of the amount of mancozeb residue that might be consumed in a day. A value representing the high end (99.9^{th} 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. When the expected intake of residues is less than the ARfD, then acute dietary risk is found to be acceptable.

The probabilistic assessment results show that the acute dietary exposure to mancozeb (at the 99.9^{th} percentile) is 37% of the ARfD for females aged 13 to 49 years, and therefore, was found to be acceptable.

Acute dietary exposure to mancozeb is less than 2% of the ARfD for the remaining subpopulations.

ETU

The probabilistic assessment results show that the acute dietary exposure to ETU (at the 99.9^{th} percentile) is 25% of the ARfD for females aged 13 to 49 years, and therefore, was found to be acceptable.

3.3.3 Determination of Acceptable Daily Intake for Mancozeb

Mancozeb

To estimate dietary risk from repeat exposure, a one-year dog toxicity study was selected for risk assessment. A NOAEL of 2.3 mg/kg bw/day was set based on thyroid hormone effects as well as effects on liver weight, body-weight gain and food consumption. This is supported by the NOAEL of 1.75 mg/kg bw/day in a second 1 year dog study. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. An additional threefold factor for database uncertainty (lack of ETU DNT and mancozeb immunotoxicity studies) was applied. As the endpoint selected provided adequate margins to the reproductive and developmental endpoints of concern discussed in Section 3.1.1, the pest control products act factor was reduced to onefold. The composite assessment factor is 300.

$$ADI = \frac{NOAEL}{CAF} = \frac{2.3 \text{ mg/kg bw/day}}{300} = 0.008 \text{ mg/kg bw/day}$$

ETU

To estimate dietary risk from repeat exposure, a one-year dog study was selected. At the LOAEL of 1.79 mg/kg bw/day, decreased body weight and increased thyroid weight, hypertrophy and colloid retention were observed. A NOAEL of 0.18 mg/kg bw/day was established. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in Section 3.1.1, the pest control products act factor of 10-fold was reduced to threefold. The composite assessment factor of 300 provides adequate protection for sensitive subpopulations.

$$ADI = \frac{0.18 \text{ mg/kg bw/day}}{300} = 0.0006 \text{ mg/kg bw/day}$$

This ADI provides a margin of greater than 8000 to the NOAEL for developmental malformations noted in the rat.

Manganese

The ADI for manganese is 0.14 mg/kg bw/day for dietary intake and 0.047 mg/kg bw/day for non-dietary oral exposures (Based on USEPA Integrated Risk Information System (1996) chronic reference dose of 0.14 mg/kg bw/day with a modifying factor of 1 for dietary manganese and a modifying factor of 3 for ingestion in water or soil, ATSDR, 2008).

3.3.4 Chronic Non-Cancer Dietary Exposure and Risk Assessment

The chronic dietary risk was calculated by using the average consumption of different foods and the average residue values on those foods. This expected intake of residues was then compared to the ADI. When the expected intake of residues is less than the ADI, then chronic dietary risk is found to be acceptable.

A refined chronic dietary exposure assessment was performed for the general population and all population subgroups of regulatory concern by using average residues from field trials and the U.S. market basket survey data; average percent crop treated in Canada and in the United States when available; 100% crop treated for all other registered uses; and specific processing factors.

Mancozeb

The assessment results show that the chronic dietary exposure to mancozeb is 2.5% of the ADI for the general population, and ranges from 1.7% to 10% for population subgroups. The most exposed population subgroup is children 1 to 2 years of age with an exposure of 10% of the ADI.

ETU

The assessment results show that the chronic dietary exposure to ETU is 12% of the ADI for the general population, and ranges from 8% to 43% for population subgroups. The most exposed population subgroup is children 1 to 2 years of age with an exposure at 43% of the ADI. The main contributors were dairy products and pome fruits.

Manganese

The dietary exposure assessment for mancozeb does not address potential exposure to manganese from mancozeb. This is because concentrations of mancozeb in food commodities were based on measurements of organic degradates of mancozeb such as carbon disulphide, which were back-calculated to estimate the concentration of mancozeb. These analyses provide an adequate estimate of the residue decline that may occur over time of the organic component of mancozeb in food commodities, but are not a good estimate of the inorganic manganese component. The disassociation and fate of the manganese in the environment from mancozeb application is entirely separate from the organic component of mancozeb.

In general, the greatest source of exposure of manganese for Canadians is through diet, which would encompass all sources of manganese including its natural occurrence, emissions from industrial processes and its pesticidal use (Health Canada, 1987). The Canadian Food Inspection Agency and Health Canada have conducted numerous surveys of manganese in the Canadian food supply (CFIA, 2010 a, b, c, d; HC, 2009). Residues in the Canadian Food Inspection Agency surveillance program ranged from 0.01 to 311 ppm with cereals being the greatest source of dietary manganese. In the 2000 to 2007 Canadian Total Diet Study, which is a market basket survey in which manganese residues are measured in foods purchased in supermarkets and are prepared and processed as they would be in the average household kitchen, the concentration of manganese in various composite food commodities ranged from <0.001 to 140 ppm. In general, relatively higher concentrations were found in organ meats, seeds and nuts, herbs and spices, cereals and breads, blueberries and canned pineapple. Estimated dietary intakes based on this data, using average body weights from the Canadian Community Health Survey Cycle 2.2, indicates that dietary intakes are much lower than 10 mg/day. Dietary intakes of manganese in the literature have been reported to range from 2 to 9 mg/day (Santamaria and Sulsky, 2010). The USEPA ADI for dietary exposure is not based on adverse effects per se, but rather the upper range of dietary intake of 10 mg/day.

Therefore, although the mancozeb dietary risk assessment did not address potential manganese exposure from use of mancozeb, dietary intake surveys which would consider exposure from all sources of manganese indicate that intakes for adult Canadians are generally close to or lower than the reference values established by the USEPA and Health Canada.

3.3.5 Cancer Potency Factor

ETU

As discussed in Section 3.1.1, a unit risk q_1^* of 0.0601 (mg/kg bw/day)$^{-1}$, obtained from a NTP study of ETU, is deemed appropriate for assessing the dietary cancer risk for mancozeb. The amount of ETU formed in vivo was estimated by assuming that 7.5% (see Section 3.1) of absorbed mancozeb would be transformed into ETU.

3.3.6 Carcinogenic Dietary Exposure and Risk Assessment

The lifetime cancer dietary risk for ETU was calculated by using the average consumption of different foods and the average residue values on those foods. This expected intake of residues was then multiplied by the q_1^* to determine the cancer risk. A lifetime cancer risk that is below 1×10^{-6} usually does not indicate an unacceptable risk for the general population when exposure occurs through pesticide residues in or on food, and to person otherwise unintentionally exposed.

Similar to the chronic dietary exposure assessment, the cancer assessment was based on the residue data from the American market basket survey and field trials, specific processing and conversion factors, percentage of treated crops as well as percentage of imported commodities. The lifetime cancer risk for the general population from exposure to ETU through food alone is 4×10^{-6} which was not found to be acceptable. The major contributors to the cancer risk are milk (16.7% of the total exposure), cereal grains (14.4% of the total exposure), tomatoes (11.6% of the total exposure), potatoes (9.8% of the total exposure) and pome fruits (9.2% of the total exposure).

3.4 Exposure from Drinking Water

3.4.1 Concentrations in Drinking Water

Mancozeb is similar in its environmental fate to closely related compounds such as maneb and metiram. They are of low persistence and are strongly bound to most soils. These properties, and their low water solubilities, indicate that they probably do not pose a significant risk to groundwater. They are unstable in the presence of atmospheric moisture and oxygen and are rapidly degraded in biological systems to ETU and other metabolites. These products are of moderate persistence and more mobile, and therefore may pose a slight risk to groundwater. ETU is not applied directly in the environment. It exists in the soil as the common transformation product of applied parent EBDC fungicides, which include mancozeb, metiram, and nabam. As mancozeb is of low persistence in water supplies, the only residue of concern in drinking water is the primary metabolite, ETU.

Estimated environmental concentrations (EECs) ETU in potential drinking water sources (surface water – reservoir and dugout) were estimated based on the total EBDC use pattern, using computer simulation models. For residues in reservoir, refined exposure concentrations predicted by PRZM/EXAMS were estimated to be 16 µg a.i./L and 2.9 µg a.i./L for the daily and yearly concentrations, respectively. These values were used in the dietary assessment of ETU.

3.4.2 Drinking Water Exposure and Risk Assessment

ETU

As indicated in Section 3.4.1, ETU is the only metabolite of mancozeb expected to be found in the drinking water supplies. In the cancer and chronic assessment, residues in drinking water were based on the reservoir yearly EEC (2.9 µg a.i./L), whereas in the acute exposure the residues were based on the daily EEC (16 µg a.i./L). The calculated chronic exposure of ETU from drinking water alone reached an interval of 7–33% of the ADI for all subpopulations, and therefore, risks were found to be acceptable. The acute estimate for drinking water accounted for 16% of the ARfD for females aged 13 to 49 years and is not of concern. However, the cancer risk estimation from drinking water alone was 4×10^{-6} and therefore, was not found to be acceptable.

Manganese

The drinking water assessment for mancozeb, which focussed on the fate of the organic component of mancozeb, would not apply to the manganese component of mancozeb. The degree to which mancozeb application would contribute to drinking water manganese concentrations is not known.

Manganese occurs naturally in water supplies and in addition, industrial emissions of manganese would contribute to water concentrations. Manganese compounds are used as disinfectant and anti-algal agents in water and waste treatment facilities. Therefore, besides application of mancozeb to agricultural commodities which may enter drinking water sources, there are other major sources of manganese in drinking water.

Although it is not known how much manganese would occur in drinking water supplies from use of mancozeb, the presence of high levels of manganese in drinking water would be limited since it causes undesirable tastes in beverages and stains plumbing and laundry fixtures (HC, 1987). Health Canada (1987) has established an aesthetic objective for drinking water of ≤ 0.05 mg/L based on palatability and staining of laundry and plumbing fixtures. This guideline is not considered to represent a threat to health, and drinking water with much higher concentrations has been safely consumed (HC, 1987). The World Health Organization has established a health-based drinking water guideline for manganese of < 0.04 mg/L (WHO, 2006), whereas, the USEPA reference dose was based on the upper range of intake and not health based effects. Median background concentrations of manganese in surface and groundwater are lower than guideline concentrations, with exceedences occurring at high percentiles (Santamaria and Sulsky, 2010). Background concentrations would occur as a result of both the natural occurrence of manganese as well as from its industrial and agricultural uses. Concentrations in Canadian tap water, mineral water and natural spring water as measured in the Canadian Total Diet Study are very low (HC, 2009). In the Canadian Total Diet Study conducted from 2000 to 2007 in various cities across Canada, the concentration of manganese in tap water, natural spring water and mineral water ranged from < 0.67 to 1718 ng/g (6.7 × 10-7 to 0.0017 mg/L) (Health Canada, 2009).

Therefore, it is not expected that manganese resulting from mancozeb use would result in concentrations in drinking water that would cause adverse effects. Furthermore, as noted previously, at high concentrations of manganese, the drinking water would most likely not be consumed.

3.5 Aggregate Risk Assessment (ETU)

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

The aggregate risk assessment considered exposure to mancozeb and ETU from food and drinking water only. Although mancozeb is not registered for residential and non-occupational uses, potential exposure may occur while harvesting at PYO facilities or to bystanders from spray drift. These exposures were not included in the aggregate risk assessment since cancer risk were not found to be acceptable from dietary exposures of ETU (food and water) only (8×10^{-6}, see below).

Mancozeb

Residues of mancozeb are not expected to occur in drinking water. Therefore food-only exposure was considered for mancozeb (refer to Section 3.3.4).

ETU

The acute aggregate risk for females aged 13 to 49 years was 49% of the ARfD and thus, was found to be acceptable. The chronic aggregate risk for the general population was 22% of the ADI, ranging from 18% to 58% for the population subgroups and therefore, was also found to be acceptable.

The lifetime aggregate (food and drinking water) cancer risk for the general population from exposure to ETU is 8×10^{-6} and therefore, the risk was not found to be acceptable. The major contributors to the cancer risk are drinking water (54.8% of the total exposure), milk (9.0% of the total exposure), cereal grains (7.7% of the total exposure), tomatoes (6.2% of the total exposure) and potatoes (5.3% of the total exposure).

Although not a food use, the forests and woodlot uses were considered in the aggregate assessment, since potential residues may occur in drinking water following outdoor applications of mancozeb.

Manganese

The daily intake of manganese from the diet and from tap water was determined in the Canadian Total Diet Study (see Sections 3.3.4 and 3.4.2). Manganese was measured in the Canadian food supply which would encompass all sources of manganese including its natural occurrence, emissions from industrial processes and its pesticidal use from mancozeb.

In this way, it represents the aggegrate exposure to manganese. The Total Diet Study indicates that manganese exposure for Canadians are generally close to or lower than the reference values established by USEPA and Health Canada.

3.6 Cumulative Exposure and Risk Assessment

Exposure to ETU in food and drinking water may also occur from the use of mancozeb or any other EBDC fungicides. Presently, metiram is the only other EBDC fungicide with registered food uses in Canada while nabam is registered in Canada for industrial uses only.

Exposure to ETU in the environment or in occupational settings may occur from non-pesticidal sources of ETU. These sources are regulated separately (*Canadian Environmental Protection Act, 1999*) from the exposure derived from the pesticidal use.

As the aggregate cancer risk from food and water to ETU derived from mancozeb was not found to be acceptable, a combined/cumulative risk assessment was not conducted at this time. It is acknowledged that the drinking water exposure estimates do represent the total exposure from ETU from all pesticidal sources (mancozeb and metiram). However, as the aggregate risk for metiram and mancozeb are estimated independently, this approach does not over-estimate the risk. Furthermore, the use pattern on which the water modelling was performed is identical for metiram and mancozeb.

To mitigate potential aggregate risk from use of multiple EBDC pesticides, the following label statement is proposed to be added to the labels of mancozeb and metiram during the phase-out of metiram:

> "The total quantity of all EBDC products used on a crop must not exceed the specified maximum seasonal quantity of active ingredient allowed per hectare for either mancozeb or metiram."

3.7 Incident Reports (Human Health)

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Incidents are classified into six major categories including effects on humans, effects on domestic animals and packaging failure. Incidents are further classified by severity, in the case of humans for instance, from minor effects such as skin rash, headache, etc., to major effects such as reproductive or developmental effects, life-threatening conditions or death.

The PMRA will examine incident reports and, where there are reasonable grounds to suggest that the health and environmental risks of the pesticide are no longer acceptable, appropriate measures will be taken, ranging from minor label changes to discontinuation of the product.

Incident reports for mancozeb in the United States from 1992 to 2001 and published case reports, involved skin rashes or contact dermatitis, nausea and dizziness. As of 1 June 2011 the PMRA had received three reports for mancozeb; two human and one animal. With respect to the two human reports, one was moderate eye irritation and one was minor gastrointestinal upset. The one animal report was moderate nervous system effects.

Since ETU is not a registered active ingredient, incident reports identifying ETU specific adverse events are not expected.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Mancozeb enters the terrestrial environment when it is used as a fungicide on a variety of food crops, outdoor ornamentals, forest and woodlots and as a seed treatment. The parent form of the active ingredient exists as a polymeric chain and is expected to be non-persistent in natural environments due to rapid hydrolysis. Hydrolytic decomposition appears to be a complex process as it involves breakdown of the polymers into fresh EBDC complex consisting of variable/low molecular weight polymeric chains (polymer fragments), monomeric species, intermediate species, and EBDC ligand in association with other metal ions that might be present in the environment. The intermediate species include EBIS and hydantoin. The transformation products are dominated by ETU and CO_2. Aging of the complex results in enrichment with the transformation product ETU and ETU-transformation products EU. The product of hydrolytic decomposition of mancozeb is a multi-chemical species complex referred to as “mancozeb complex”.

In the terrestrial environment, mancozeb complex is expected to biotransform rapidly (DT_{50}=1.8–8.3 days). A significant portion of the residues from biotransformation, partition onto the soil/sediment particles as bound species. Because the bound residues were not sufficiently characterized in laboratory aerobic soil studies, it is not known whether the bound species contain precursors for ETU. The data that is available, however, indicates that bound residues are unlikely to be released from soil at a rate that would result in significant levels of ETU being produced. Based on this evidence, biotransformation DT_{50} for mancozeb complex were calculated on the assumption that total extractable radioactivity represented immediate bioavailability.

Mancozeb is not shown to photolytically degrade on dry soil, however, rapid decomposition would be expected in moist soil due to hydrolysis.Volatilization from water and/or dry/moist soil surfaces is not expected to be an important route of dissipation. Given the low solubility and rapid transformation of parent mancozeb to mancozeb complex through hydrolysis, it is likely that parent mancozeb would not be available for leaching. When taking into consideration the criteria of Cohen et al (1984) and the groundwater ubiquity score (GUS) it was determined that mancozeb complex is likely a non-leacher. The available field dissipation studies indicate limited downward movement of mancozeb parent as detected in the soil column. Mancozeb (parent and complex), therefore, is not expected to pose a risk to groundwater.

ETU is not applied to the environment in the same manner as pesticide products, instead it is formed via the hydrolysis, phototransformation and biotransformation of mancozeb and other transient transformation products of mancozeb. ETU is shown to be stable to hydrolysis and phototransformation in sterile aqueous solutions and soil media. However, there is evidence indicating that sensitizers in natural waters result in rapid indirect photolysis of ETU via a catalyst process (a half-life in aqueous solutions of 2.3 d was found for sensitized water). ETU is expected to partition in the air as indicated by its high vapour pressure, however, it will not remain in air as it has a half-life ranging from < 2 hours to 9 days as it reacts with hydroxyl radicals in the atmosphere. Once present in the soil environment ETU will undergo rapid aerobic biotransformation however, a slight decrease in the rate of biotransformation is expected with a reduction of available soil moisture. ETU is slightly to moderately persistent in soil. ETU generally does not bind strongly with soils and has high to very high mobility and has a potential to move to surface water and to leach to groundwater, however, it was not detected below 15 cm in two field studies. ETU residues have not been detected in groundwater in Canada, but have been detected in the United States Residues of ETU have been detected in surface water in Canada (Appendix X).

Mancozeb complex may enter the aquatic environment through spray drift from ground, airblast and aerial applications and/or runoff. Photolysis in water is not considered to be an important route of transformation. For the transformation product ETU, sensitizers in natural waters and likely in soil porewater will result in rapid indirect photolysis of ETU via a catalytic process. Under aerobic aquatic conditions, the mancozeb complex is expected to be slightly persistent; as with the soil biotransformation studies, the DT_{50}s determined for mancozeb complex considered the extractable radioactive residues only (DT_{50} range from 19.9 to 62.4 d). Anaerobic conditions appear to be conducive for slowing down mancozeb decomposition in these systems; based on the persistence of parent mancozeb (DT_{50}=80 days), mancozeb complex would be expected to be moderately persistent. ETU is slightly persistent in the aquatic environment under aerobic conditions and moderately persistent to persistent under anaerobic aquatic conditions.

The log octanol water partition coefficient for mancozeb and ETU (1.3 and -0.69, respectively) indicates that bioaccumulation is unlikely. Terrestrial and aquatic environmental fate data for parent mancozeb, mancozeb complex is summarized in Table 1 (Appendix IX); ETU data is summarized in Table 2 (Appendix IX).

4.2 Effects on Non-target Species

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. 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 (i.e., 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 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 risk quotient is then compared to the level of concern (LOC=1). 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 (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 Effects on Terrestrial Organisms

4.2.1.1 Mancozeb

A risk assessment of mancozeb to terrestrial organisms was based upon an evaluation of toxicity data for the following:

- one earthworm species, (acute and chronic exposure)
- one bee and one beneficial arthropod species (acute exposure)
- three bird species (acute, reproduction exposure)
- two mammal species (acute, dietary and reproduction exposure)

A summary of terrestrial toxicity data for mancozeb is presented in Table 3 (Appendix IX). 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 mancozeb. The terrestrial assessment took into account the range of agricultural applications rates that are registered for mancozeb, taking into consideration that there may be multiple applications of mancozeb in a use season.

Terrestrial Invertebrates

The screening level risk assessment indicated that the level of concern for earthworms and bees is not exceeded for any of the mancozeb application rates; Table 4 (Appendix IX) summarizes the screening level risk to earthworms and bees from mancozeb. The risk quotients exceed the LOC for beneficial arthropods within the treatment area and within refugia as a result of drift; the risk to predatory arthropods is presented in Table 5 (Appendix IX).

Terrestrial Plants

Terrestrial plant toxicity data are not available for mancozeb as a sole active ingredient but are available based on an end-use product containing 60% mancozeb co-formulated with 9% dimethomorph. 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; none of the species exposed displayed > 25% inhibition for the parameters tested indicating that mancozeb is relatively non-toxic to terrestrial plants. There are currently no incident reports involving mancozeb in Canada.

Terrestrial vertebrates – Exposure to mancozeb from foliar applications

Standard exposure scenarios on vegetation and other food sources based on correlations in Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994) were used to determine the concentration of pesticide in the diet of small wild birds and mammals. Exposure is dependent on the body weight of the organism and the amount and type of food consumed. In the screening level assessment a set of generic body weights was used for birds and mammals (20, 100 and 1000 g, and 15, 35, 1000 g, respectively) to represent a range of small wild bird and small mammal species. It is noted that diets of animals can be highly variable from season to season as well as day to day. Furthermore, animals are often opportunists and if they encounter an abundant and/or desirable food source, they may consume large quantities of that food. For these reasons, the screening level assessment used relevant food categories for each size group consisting of 100% of a particular dietary item. These items included the most conservative residue values for plants, grains/seeds, insects, and fruits. As no small birds or mammals in North America are known to eat a diet primarily of leafy plant material or grass, estimated daily exposures (EDEs) for small birds (20 and 100 g) and mammals (15 g) based on a 100% diet of plants were not calculated.

The screening level EDEs were calculated for each bird and mammal size based on the maximum residue values in food items at the highest cumulative application rate for apples (4800 g a.i./ha × 6 at 7 d intervals); the cumulative application rate was estimated using a foliar half-life of 20 days; this value is representative of the 90^{th} percentile of a dataset of dislodgeable residue on foliage. In addition to assessing the potential risk of birds and mammals consuming food items that have been directly sprayed with mancozeb (on-field), off-field exposure was also considered. In this assessment, the potential risk associated with the consumption of food items contaminated from spray drift off the treated field was assessed taking into consideration the spray drift spray quality of ASAE fine for airblast applications (74%) given that the scenario being assessed in the screening level is application to apples via airblast.

The screening level risk to birds and mammals is presented in Table 6 and 7 (Appendix IX), respectively; only the bird and mammal sizes and food guilds with risk are shown in the tables. For birds feeding on and off-field, the level of concern is exceeded for acute and reproductive risk birds for most feeding guilds and body sizes. For mammals feeding on field, the level of concern is exceeded for dietary and reproductive effects in 15 g mammals for all feeding guilds; for 15 g mammals feeding off-field, the level of concern is exceeded for dietary effects in insectivores and for reproductive effects in all feeding guilds. For larger mammals (35 and 1000 g) feeding on-field, the level of concern is exceeded for all effects for most feeding guilds; the level of concern for mammals feeding off-field is exceeded for dietary and reproductive effects for most feeding guilds.

Given the conservative assumption taken in the on-field and off-field screening level, a refined assessment was conducted to further characterize the risk to birds and mammals. The refined risk assessment used 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 and highest cumulative mancozeb application rates (lettuce: 1612 g a.i./ha × 3 at 14 d intervals, and apple 4800 g a.i./ha × 6 at 7 d intervals, respectively) and the lowest single application rate for lettuce. The cumulative application rates for commercial products were based on a 10 d foliar half-life; this value is representative of the 50^{th} percentile of a dataset of mancozeb dislodgeable residues on foliage. Since most of the higher foliar half-life values in the dataset were determined from dry regions that are not representative of Canadian ecozones (for example, California), the use of the 50^{th} percentile to calculate the cumulative application rates is considered to remain sufficiently conservative for the risk assessment. The risk associated with the consumption of food items contaminated from spray drift off the treated field was assessed taking into consideration the spray drift deposition of spray quality of ASAE medium for ground application (6%) and ASAE fine for airblast application (74%) at 1 m downwind from the site of application.

A mammalian dietary NOEL of 14.98 mg a.i./kg bw/day based on a 90 day dietary study with rats was used for the screening level assessment. This value is based on multiple effects including decreased body weight, body-weight gain and multiple endocrine effects at the next dose level (LOEL=57.34 mg a.i./kg bw/day, the highest exposure test concentration). The effects of environmental relevance at the LOEC are considered small (8 to 14% decreased body weight, 12 to 13% decreased body-weight gain) and the potential impact to mammalian survival at the LOEC under field conditions at the population level is questionable. The dietary risk to mammals was further characterized by determining risk quotients based on the dietary NOEL (14.98 mg a.i./kg bw/day) and LOEL (57.34 mg a.i./kg bw/day).

A NOEL of 2.5 mg a.i./kg/day, based on no effects to offspring in a 2-generation reproduction study with rats, was used for the screening level assessment. This study showed that effects at the next dose level were minimal (LOEL=15 mg a.i./kg bw/day based on reduced body weight at post natal day 21). In addition, in another 2-generation reproduction study that used the same species and test protocol no effects were observed in offspring at the highest test concentration (NOEL=69 mg a.i./kg bw/day). The NOEL value used in the screening level assessment, therefore, is considered to be highly conservative. Significant effects relevant to mammalian reproductive success were observed at a dose of 110 mg a.i./kg bw/day, based on delayed eye opening, decreased body weight (day 21, F_1; day 14 to 21, F_2) and reduced viability of pups at days 14 to 21. The reproductive risk to mammals was further characterized by determining risk quotients based on the NOEL (2.5 mg a.i./kg/day) and the 110 mg a.i./kg bw/day dose level.

The risk to birds and mammals feeding on-field and off-field based on mean residue values on terrestrial food sources is characterized in Table 8 and 9 (Appendix IX), respectively. In addition, for risk quotients exceeding the LOC, two additional parameters were calculated to assess the relevance of the determined risk: 1) the percent daily diet required to reach the LOC (calculated as 1/RQ × 100), and 2) the number of days that residues remain on food items above the LOC; (calculations were based on the 10 d foliar half-life, representative of the 50th percentile of a dataset of mancozeb dislodgeable residues on foliage).

For birds, the LOC for acute effects is exceeded both on and off-field at the highest cumulative application rate in small and medium sized insectivores (20 and 100 g) and large birds (1000 g) feeding on short grass or leafy foliage. Acute effects are not expected for birds at the lowest single or cumulative application rate (LOC<1). The LOC for reproductive effects is exceeded in all bird feeding guilds feeding on and off-field at the highest cumulative application rate with the exception of large insectivores and granivores feeding off-field. At the lowest cumulative application rate, the LOC for reproductive effects is exceeded in all 20 g birds, 100 and 1000 g insectivore, 100 g frugivores and 1000 g herbivores feeding on-field. At the lowest single application rate, the LOC for reproductive effects is exceeded in birds feeding on-field for the same bird size and feeding guilds as for the cumulative application rate with the exception of 20 g granivores and 1000 g herbivores feeding on long grass.

For mammals, the LOC for acute effects is exceeded only in 35 g mammals feeding on leafy foliage on –field at the highest cumulative application rate. The LOC for dietary and reproductive effects is exceeded for all mammal size and feeding guilds on field, and off-field with the exception of 1000 g insectivores and granivores for dietary effects. In most cases, a dietary and reproductive risk to mammals is identified at both the low and high dietary and reproductive endpoint range.

At the lowest cumulative application rate, the LOC for dietary effects in mammals is exceeded for all insectivores and in 35 and 1000 g herbivores feeding on-field. The LOC for reproductive effects is exceeded for all mammal size and feeding guilds, on-field. The LOC for reproductive effects is also exceeded in mammals feeding off-field for all 35 g herbivores and 1000 g herbivores feeding on short grass and leafy foliage. A dietary risk is identified at both the low and high dietary endpoint range for 35 g herbivores feeding on short grass, forage crops and in 35 g and 1000 g herbivores feeding on leafy foliage, on-field.

At the lowest single application rate, the LOC for dietary effects is exceeded in 15 and 35g insectivores, and in 35 and 1000 g herbivores feeding on-field; the risk to 35 g herbivores feeding on leafy foliage is shown for the low and high dietary endpoint range. The LOC for reproductive effects is exceeded in all mammals feeding on-field. Mancozeb is not expected to pose a risk to mammals feeding off-field at the lowest single application rate.

In some cases, although an exposure risk is identified, the risk is unlikely to manifest in birds or mammals feeding either on or off-field because: 1) birds and mammals would need to consume an unrealistically large proportion of a single food item (for example, 96% diet of large insects for 1000 g mammals feeding on fields treated at the lowest single application rate), and 2) residue levels remaining on food items above the LOC are expected to be short lived (for example, 1 day of less). For the majority of cases, however, the proportion of a single food item required to reach the LOC is relatively low (for example, 9 to 34% for dietary effects in 35 g mammals feeding on small insects in apple orchards treated at the highest cumulative application rate) and birds and mammals may be exposed to residue levels remaining on food items above the LOC for relatively long time periods (for example, 47 to 70 days).

Although an acute risk is identified for birds and mammals, the PMRA expects this risk to be low for the following reasons: 1) For birds, the acute oral toxicity studies provided LD_{50}s ranging from 1500 mg a.i./kg bw/day for the English sparrow and > 6400 mg a.i./kg bw/day for mallard duck and quail, based on multiple oral dose studies (10-days dosing by gavage). These studies, which were initially intended to be dietary feeding studies, were converted to multiple oral dose studies because the birds showed an aversion to eating the mancozeb treated feed. There is the potential that birds may avoid treated food items in the field, however, it is difficult to know based on these acute high dose treated laboratory feed studies. Had these studies been representative of standard single oral dose toxicity tests, the toxicity of mancozeb to birds would be expected to be less than that observed from multiple oral dose tests. 2) For mammals, mancozeb is shown to have low acute toxicity through oral exposures (LD_{50} > 5000 mg a.i./kg bw in rats). 3) There are no incident reports showing mancozeb has been responsible for bird or mammal kills or poisonings as a result of registered use.

Overall, the refined risk assessment shows that reproductive effects from mancozeb pose the greatest risk to birds and mammals. Although there are no incident reports involving birds and mammals from the use of mancozeb, none would be expected from adverse chronic exposure; chronic problems affecting wildlife from the use of mancozeb would be largely unnoticed in the field. The refined risk assessment focused on apples and lettuce with apples representing the highest cumulative application rate (4.8 kg a.i./ha × 6 application for a total of 28.8 kg a.i./ha per season) and lettuce representing the lowest (1.6 kg a.i./ha × 3 applications for a total of 4.8 kg a.i./ha per season).

Foliar applications of mancozeb on all crops pose risks that were not found to be acceptable to birds and small wild mammals, particularly for insectivores foraging both within orchards/vineyards and off-field.

Terrestrial Vertebrates – Exposure to mancozeb from 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 pesticide. Mancozeb is registered as a seed treatment for barley, corn, flax, oats and wheat seed. A risk assessment was conducted for birds and mammals to address the intake 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 the same generic bird and mammal body weights and toxicity endpoints selected for use in the foliar application risk assessment. As was done for the foliar application risk assessment, the low and high dietary and reproductive endpoint range for mammals was considered. These endpoints were converted to the number of seeds needed to be consumed per day to reach the toxicity endpoint for each of the small, medium and large size classes of birds and mammals; shown in Table 11 (Appendix IX). The number of seeds consumed per day calculated for each bird and mammals body weight categories based on type of seed are presented in Table 12 (Appendix IX). To assess the risk to birds from consumption of treated seeds a risk quotient is calculated as:

> Number of seeds normally consumed per day (Table 12) ÷ Number of seeds to the endpoint (Table 11).

The calculated risk quotients are listed in Table 13 (Appendix IX). The calculation of these risk quotients assume that 100% of the seeds consumed by birds and mammals are treated seeds. Risks were found for all birds and mammals with the exception of large birds (1000 g) and mammals (all size categories) for acute risks. Although a risk was indicated for small birds eating corn, small birds are not expected to eat the treated corn due to the size of the corn kernel, therefore, the risk will be minimal. The risks found are only applicable for the few days after planting of the treated seed before transformation of the compound occurs and before the seed germinates.

The risk values presented in Table 13 (Appendix IX) for the screening level assessment assumes that all planted seed is available. Further characterization was conducted for birds and mammals taking into consideration that not all seeds planted will be exposed and available to birds or mammals. De Snoo and Luttik (2004) reported available seeds of 0.5% for precision drilling, 3.3% for standard drilling in spring, and 9.2% for standard drilling in autumn. The maximum seed density after planting for barley, corn, flax, oats and wheat is 346.5, 6.8, 581.2, 412.5 and 256.2 seeds/m^2; using the number of available seeds for standard drilling in spring (3.3%), the maximum seed density is reduced to 11.4, 0.2, 19.2, 13.6 and 8.5 seeds/m^2, respectively. This characterization does not change the RQ determined, but provides an indication of the area required for a bird and mammal to find enough seeds to reach the toxicity endpoint. However, as can be noted in Table 14 (Appendix IX), the area required to achieve most of these high risk quotients are very small. To mitigate against these risks the following label statement is required on the label for seed treatments:

> "Treated seed is 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."

4.2.1.2 ETU

A risk assessment of ETU to terrestrial organisms was based on an evaluation of toxicity data to terrestrial mammals (acute, dietary and reproduction exposure). Mammalian toxicity data for ETU is summarized in Table 3 (Appendix IX). The PMRA chose to conduct a worse-case risk assessment for ETU using the use pattern of mancozeb because it has the broadest use pattern of the EDBC fungicides and the highest application rate (apples at 4800 g mancozeb/ha × 6 applications and 7-day intervals) thus providing an all-inclusive view of risks posed by ETU.

The PMRA does not currently have data on which to evaluate the acute or chronic risks of ETU to birds. Therefore, the risks to birds from ETU exposure are uncertain.

No ETU toxicity data were available for terrestrial invertebrates. The PMRA believes that any acute contact toxicity from ETU would have been expressed in the guideline testing of the parent EBDCs. Since no risk was identified to terrestrial invertebrates from parent EBDCs (earthworms and honeybees), toxicity tests with ETU for terrestrial invertebrates are not required.

No information on the toxicity of ETU to terrestrial plants is available. The PMRA feels that toxicity to plants from ETU would have been expressed in studies conducted with the parent EBDCs. Terrestrial plant toxicity tests for ETU, therefore, are not required.

Terrestrial vertebrates – Exposure to ETU from foliar applications of mancozeb

The mammalian risk assessment for ETU considered the same set of generic body weights for mammals (15, 35 and 1000 g) and food categories as described in the risk assessment for mammals exposed to mancozeb from foliar applications. EDEs for ETU were calculated for each mammal size based on mean residue values and lower limits of ratio wet/dry moisture contents of food items at the highest cumulative airblast and groundboom application for mancozeb (airblast – apples: 4800 g a.i./ha × 6 at 7d intervals, and groundboom – onions: 2600 g a.i./ha × 10 at 7d intervals. Application rates equivalent to ETU were estimated using a conversion rate of mancozeb to ETU of 6.8%; this conversion rate was obtained from a dislogeable foliar residue study on tomatoes. Cumulative application rates for ETU were based on an 11.7 day foliar half-life for ETU; this value is representative of the 80th percentile of a dataset of ETU dislodgeable residue on foliage. The risk associated with the consumption of food items contaminated from spray drift off the treated field was assessed taking into consideration the spray drift deposition of spray quality of ASAE medium for ground application to lettuce (6%) and ASAE fine for airblast application to apples (74%) at 1 m downwind from the site of application. The screening level risk assessment is not shown here because the risk quotients greatly exceeded the LOC in most cases. Therefore, the refined risk assessment provides a more realistic scenario of exposure and risk to terrestrial mammals, foregoing a longer discussion on a screening level risk assessment that is already known to be too conservative for ETU.

The risk to mammals feeding on-field and off-field based on mean residue values of ETU on terrestrial food sources is characterized in Table 9 for airblast application of mancozeb on apples and Table 10 for groundboom application to onions, (Appendix IX); only mammal sizes and food guilds with risk are shown in the tables. In addition, for risk quotients exceeding the LOC, two additional parameters were calculated to assess the relevance of the determined risk: 1) the percent daily diet required to reach the LOC (calculated as 1/RQ × 100), and 2) the number of days that residues remain on food items above the LOC; (calculations were based on an 11.7 d foliar half-life - representative of the 80th percentile of a dataset of ETU dislodgeable residue on foliage).

The risk assessment for ETU exposure as a result of air blast application of mancozeb to apples showed that the level of concern was not exceeded for acute risk to small, medium and large mammals either on the field or off-field due to drift. However, the level of concern for chronic dietary risk was exceeded for most feeding guilds in each size class of mammals both on-field and off-field especially for frugivores and herbivores (RQ=1.2–29.3 and 1.5–21.7 for on-field and off-field risk, respectively, Table 10, Appendix IX). On-field reproductive risk quotients for small mammals are primarily below the level of concern but the risk quotients for medium and large sized mammals indicate that these mammals could be at risk, especially in the herbivorous feeding guilds (RQ=1.2–10 and 1.0–7.4 for on-field and off-field, respectively). This pattern was repeated both on-field and off-field.

The risk assessment for the presence of ETU resulting from ground boom application of mancozeb to onions showed that all acute risk quotients for small, medium and large mammals are below the level of concern (Table 10, Appendix IX). Most risk quotients from dietary on-field exposure scenarios remain above the level of concern for the frugivore and herbivore feeding guilds in each size class (RQ=1.14–17.1). However, the dietary risk is negligible off-field when taking into consideration the drift from ground boom application (6%) to adjacent habitat. The risk of reproductive toxicity is negligible for small sized mammals (RQ<1) on the field. For medium sized and large mammals, the risk of reproductive toxicity is mainly to herbivores (RQs up to 5.8) on the field. Risk quotients for off-field dietary exposure using reproductive toxicity endpoints are all below the level of concern for all feeding groups in small, medium and large mammals.

It was determined that the concentrations of ETU on dietary items of mammals as a result of either airblast (on and off the field scenarios) or ground boom application (on field exposures) will exceed the dietary and developmental toxicity thresholds for a considerable length of time (0 to 93 days for airblast applications and 0 to 111 days for ground boom applications) and indicates a strong potential for chronic effects (Table 10, Appendix IX). In addition, for some food guilds the proportion of a single food item required to reach the LOC is relatively low (for example, 24% for dietary effects in 15 g mammals feeding on small insects in apple orchards treated at the highest cumulative mancozeb application rate.

Concentrations of ETU from ground boom application, on dietary food items located in areas off-field rarely go above the thresholds. However, it is important to note that terrestrial mammals may be at potential risk of effects because the effects observed in the dietary and developmental studies do not necessarily require chronic exposure, but could also manifest themselves as a result of short term exposure during sensitive developmental stages (dietary studies with mammals showed effects after 2 to 3 weeks of feeding and effects were observed in developmental studies after 30 days of feeding on food treated with ETU).

4.2.2 Effects on Aquatic Organisms

4.2.2.1 Mancozeb

A risk assessment of mancozeb to aquatic organisms was based upon an evaluation of toxicity data for the following:

- one freshwater invertebrate species (acute and chronic exposure)
- three freshwater fish species (acute and chronic exposure)
- one algae species (acute)
- three amphibian species (acute and chronic exposure)
- one aquatic mesocosm study
- two estuarine/marine invertebrate species (acute and chronic exposure)
- one estuarine/marine fish species (acute)
- one estuarine marine algae species (acute)

A summary of aquatic toxicity data for mancozeb is presented in Table 3 (Appendix IX).

No data have been submitted by the registrant regarding the toxicity of mancozeb to non-target aquatic vascular plants, nor were any relevant studies found in the open literature. Freshwater aquatic plant growth studies at the Tier I or Tier II level are required for three species of algae: green algae, blue-green algae and a freshwater diatom. Although algal toxicity data based on exposure to formulated product containing mancozeb and the additional active dimethomorph is available for all three species, toxicity data based on exposure to mancozeb alone is available only for green algae (*Selenastrum capricornutum*). An outdoor mesocosm study submitted by the registrant, however, shows that responses of the phytoplankton communities to Penncozeb 80 WP (81.7% mancozeb) are mainly caused by indirect effects arising from alterations to the grazing zooplankton community; a negative dose–response relationship was not observed for the overall phytoplankton community. In addition, no incidents have been reported that indicate that mancozeb use causes adverse effects to aquatic vascular plants or algae. The risks associated with Mancozeb were, therefore, considered acceptable for aquatic vascular plants or algae was found to be acceptable.

Screening Level Assessment

The chemistry of mancozeb in the environment is complicated because the parent compound exists as a polymeric chain that hydrolyses very quickly to form a complex. The mancozeb complex consists of polymeric fragments, single monomers, intermediate species and becomes enriched with transformation products (i.e., ETU) as it ages. The half-life of parent mancozeb in the aquatic environment is < 1 day, whereas estimated DT_{50}s for the mancozeb complex, based on total extractable radioactivity, are much longer (~20–62 days). Environmental exposure, therefore, is predominantly to mancozeb complex rather than parent mancozeb.

For the initial conservative screening level assessment, EECs for mancozeb complex in aquatic systems were calculated based on the lowest single application for lettuce (1612 g a.i./ha) directly applied to water bodies with a depth of 15 cm (seasonal water body for amphibian endpoints) and 80 cm (permanent water body for remaining endpoints), as well as the highest cumulative application rate for apples (4800 g a.i./ha × 6 at 7 day intervals) at the same water depths. The aquatic EEC for the highest cumulative application rate was estimated by adjusting the sum of the applications for dissipation between applications using an aquatic whole system DT50 of 62.4 d, which is the most conservative value for mancozeb complex determined from the aerobic aquatic biotransformation studies.

For several of the aquatic toxicity studies, endpoints were based on mean measured concentrations of parent mancozeb rather than mancozeb complex. Although these studies employed static renewal or flow through conditions, analytical verification frequently showed parent mancozeb to be unstable. Given that parent mancozeb is expected to be short-lived in the aquatic environment, converting quickly into mancozeb complex, the toxicity observed in the aquatic studies may likely be attributed to exposure to mancozeb complex rather than the parent. The use of endpoints based on mean measured concentrations of mancozeb parent, therefore, is considered to be overly conservative for the risk assessment in terms of mancozeb complex. The aquatic endpoints chosen for the risk assessment are based on the nominal exposure concentrations rather than mean measured. This assumes that 100% mancozeb parent is converted to mancozeb complex and that the complex does not degrade over the course of the toxicity studies. The risk assessment was conducted by comparing the EEC of the complex in the environment with the toxicity endpoints based on exposure to the complex.

Toxicity endpoints chosen from the most sensitive species tested were used as surrogates for the wide range of species that can be potentially exposed following treatment with mancozeb. The endpoints were derived by dividing the EC_{50} or LC_{50} from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates, and by a factor of 10 for fish and amphibians. In order to assess the risk to amphibians for acute and chronic exposure to mancozeb, the endpoint value for the most sensitive fish species was used as surrogate data.

The screening level risk assessment for mancozeb to aquatic organisms is summarized in Table 15, Appendix IX. The risk quotients indicate that mancozeb may potentially pose an acute and chronic risk to all freshwater aquatic organisms (RQ=6.3–1994), with the exception of freshwater invertebrates and estuarine/marine fish for acute effects at the lowest application rate.

Spray drift risk assessment

The risk to aquatic organisms was further characterized by taking into consideration the concentrations of mancozeb complex that could be present in aquatic habitat directly adjacent to the site of application through drift of spray. The maximum spray deposit into an aquatic habitat located 1 metre downwind from the application site using ground boom and aerial equipment and a medium droplet size spray quality will not exceed 6 and 23% of the application rate, respectively. The maximum amount of spray that is expected to drift 1 metre downwind from the application site during spraying using airblast equipment is 74% and 59% for early and late application, respectively. Given the variation in percent drift off site for each of the application methods, the assessment of potential risk from drift was assessed for the lowest maximum single application rate and highest cumulative application rate specific to each of the three application methods. Using the percentages for off-site drift to non-target aquatic habitats, the off-site EECs were calculated for each of the application methods. Cumulative EECs for application rates were estimated by adjusting the sum of the applications for dissipation between applications using the 80th percentile of aerobic aquatic biotransformation half-lives of 49.3 days.

The risk assessment for non-target aquatic organisms exposed to mancozeb from spray drift is summarized in Appendix IX, Table 16, 17 and 18 for airblast, ground boom and aerial applications, respectively. The risk quotients indicate that the LOC is exceeded for all organisms and all application methods on an acute basis (RQ=1.1–449), with the exception of freshwater invertebrates for all ground and aerial applications and marine, and estuarine fish for all ground applications and the lowest maximum single aerial application. On a chronic basis, the risk quotients indicate that the LOC is exceeded for invertebrates, freshwater fish and amphibians for all application methods (RQ=2.1–1123). In order to reduce the potential risk to aquatic species, buffer zones are required.

Runoff risk assessment

Aquatic organisms can also be exposed to mancozeb complex from foliar applications as a result of runoff into a body of water. The linked models PRZM (Pesticide Root Zone Model) and EXAMS (Exposure Analysis Modeling System) were used to predict estimated environmental concentrations (EECs) resulting from runoff of mancozeb complex following application. Two sets of PRZM/EXAMS runs were conducted. The use on apples was simulated using four regional apple scenarios with corresponding weather data across Canada. In addition, the use on potatoes was simulated using six regional scenarios and corresponding weather data across Canada. The mancozeb complex EECs of all selected runs for the use pattern on apples and potatoes in different regions of Canada are reported in Table 1 below for an 80 cm deep water body and in Table 2 below for a 15 cm deep water body. The values reported by PRZM/EXAMS are 90^{th} percentile concentrations of the concentrations determined at a number of time-frames including the yearly peak, 96-hr, 21-d, 60-d, 90-d and yearly average.

Table 1 Ecoscenario water modelling EECs (µg a.i./L) for the mancozeb complex in a water body of 80 cm deep, excluding spray drift.

Region	EEC (µg a.i./L)					
	Peak	96-hour	21-day	60-day	90-day	Yearly
Apple use pattern: 6 × 4.8 kg a.i./ha at 7-day intervals						
British Columbia	6.2	6.1	5.3	4.1	3.6	2.1
Ontario	63	61	54	42	38	24
Quebec	47	45	41	35	31	19
Nova Scotia	92	90	82	77	70	43
Potato use pattern: 10 × 1.8 kg a.i./ha at 7-day intervals						
British Columbia	12	12	12	10	9.2	4.8
Manitoba	261	251	225	198	189	120
Ontario	138	131	113	98	93	57
Quebec	104	99	87	74	71	52
New Brunswick	82	80	78	75	73	43
Prince Edward Island	222	215	197	181	172	124

Table 2 Ecoscenario water modeling EECs (µg a.i./L) for mancozeb complex in a water body of 15 cm deep, excluding spray drift.

Region	EEC (µg a.i./L)					
	Peak	96-hour	21-day	60-day	90-day	Yearly
Apple use pattern: 6 × 4.8 kg a.i./ha at 7-day intervals						
British Columbia	37	31	21	16	15	11
Ontario	301	271	198	147	141	113
Quebec	250	208	170	134	124	97
Nova Scotia	493	415	310	264	245	187
Potato use pattern: 10 × 1.8 kg a.i./ha at 7-day intervals						
British Columbia	67	55	41	30	29	22
Manitoba	1289	1126	808	698	665	501
Ontario	677	575	422	364	340	253
Quebec	539	466	359	303	288	253
New Brunswick	457	378	260	243	234	183
Prince Edward Island	1025	905	749	696	674	555

The acute and chronic RQ values for aquatic organisms are reported in Appendix IX, Table 20. The EECs used for calculation of the RQs were the highest values at the appropriate depth and appropriate time-frame. The RQs derived for acute and chronic exposure exceed the LOC in aquatic organisms at all mancozeb application rates (RQ=1.1–101) except for acute effects for freshwater invertebrates.

The limited amount of surface water monitoring data available to the PMRA did not allow for an estimation of the residues of parent EBDCs (or ETU) in Canadian waters. As such an aquatic risk assessment based on surface water monitoring data was not conducted.

4.2.2.2 ETU

A risk assessment of ETU to aquatic organisms was based upon an evaluation of toxicity data for the following:

- one freshwater invertebrate species (acute and chronic exposure)
- two freshwater fish species (acute exposure)
- one freshwater algae and one freshwater plant species (acute exposure)
- one amphibian study (chronic exposure)
- two estuarine/marine invertebrate species (acute exposure)
- one estuarine/marine fish species (acute exposure)

Aquatic toxicity data for ETU is summarized in Appendix IX, Table 3. As was done for the terrestrial risk assessment, the PMRA chose to conduct a worse-case risk assessment for ETU using the use pattern of mancozeb because it has the broadest use pattern of the EDBC fungicides and the highest application rate (apples at 4800 g mancozeb/ha × 6 applications and 7 day intervals)

There were no chronic toxicity studies available with freshwater fish, marine/estuarine invertebrates and fish, and acute toxicity studies with marine/estuarine algae and no pertinent information could be found in the open literature that could address these data gaps. However, given that acute and chronic risks from the use of mancozeb (above) were identified for aquatic biota, it is felt that mitigation measures put in place for mancozeb will sufficiently mitigate risks associated with ETU and therefore these studies are not required.

Screening Level Assessment

The screening level risk assessment for the transformation product ETU to aquatic organisms is summarized in Appendix IX, Table 20. The assessment assumed a 100% conversion of mancozeb to ETU using the highest cumulative application rate for mancozeb (which is the highest of all the EBDCs) for use on apples (4800 g a.i./ha × 6 at 7 day intervals) and corrected for molecular weight. This is a highly conservative scenario, which is unlikely to occur under real use. The risk quotients indicate that the presence of ETU in aquatic systems will result in negligible risk to most aquatic organisms with the exception of chronic effects in freshwater invertebrates and amphibians (RQ=1.1 and 11.6, respectively).

Because the transformation of the EBDCs to ETU is unlikely to be 100% of the application rate, the risk to aquatic organisms was further characterized by taking into consideration the maximum production of ETU observed in the aquatic fate studies of all EBDCs (i.e., 36.9%–anaerobic aquatic biotransformation study with the EBDC nabam). This assessment assumed a 36.9% conversion of mancozeb to ETU, again using the highest cumulative application rate for mancozeb, corrected for molecular weight. The risk quotients indicate that the level of concern for chronic effects in amphibians remains exceeded (RQ=4.3; Appendix IX, Table 21). This exceedence, however, is based on an endpoint for histological changes observed in the thyroid of treated amphibians (1 mg a.i./L). This is a highly conservative endpoint because it is unknown whether the observed histological changes to the thyroid will result in decreased survival in amphibians. An endpoint of 10 mg ETU/L for developmental effects in the forelegs of frogs is also available; this endpoint is considered to be more severe and could result in the decreased survival of amphibians. The level of concern, based on developmental effects in amphibian forelegs is not exceeded (RQ=0.4). Amphibians, therefore, are not expected to be at risk due to the production of ETU at the highest application rates of mancozeb.

4.2.3 Endocrine Disruption Potential

The avian reproduction studies reviewed for mancozeb indicated reproductive effects such as reduced egg production, early and late embryo viability, hatchability, offspring weight at hatch and 14-days of age, and the number of 14-day old survivors. Mammalian toxicity studies for mancozeb and ETU show hormonal, developmental and reproductive effects which indicate potential endocrine disruption; (a detailed summary of effects is provided in Section 3.1).

There is also evidence of possible endocrine mediated mode of action in aquatic organisms from exposure to mancozeb and ETU. Chronic aquatic exposure studies with mancozeb show immobility, and effects on the length and time until first brood in daphnia and reduced survival and lack of growth effects in fathead minnow. Adverse effects in amphibians, resulting from exposure to ETU seperately or in combination with a surrogate of a transformation product (methylisothiocyanate) of ETU, included notochordal malformations, and thyroid and pituitary effects.

Overall, the effects observed in birds, mammals, freshwater fish and invertebrates are indicative of hormonal disruption and would tend to support the concern that mancozeb (as parent and/or complex form) and ETU may be potential endrocrine disrupting compounds.

Mancozeb is listed as an endocrine disruptor in the Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis, USEPA, 1997. In September 2005, the USEPA published its approach for selecting the initial list of chemicals for which testing will be required under the Endocrine Disruptor Screening Program (EDSP). The initial pesticides selected for screening in the EDSP were chosen based on 1) high production volumes and usage (agricultural and residential), and 2) potential for human exposure via food, water, residential use and occupational exposure pathways. Although selection for the list focused on human exposure, it is expected that the list will also capture many pesticides that have potential for widespread environmental exposures.

In June 2007, the USEPA published the draft list of the first group of chemicals proposed for screening in the USEPA's EDSP. Based on the initial selection criteria used, this list should neither be construed as a list of known or likely endocrine disruptors nor characterized as such. The draft list of chemicals for Tier 1 screening in the EDSP does not include mancozeb; however, mancozeb may be added or included in future lists. The results of screening tests and/or testing to better characterize effects of mancozeb related to endocrine disruption will be reviewed by the PMRA, should they become available.

4.2.4 Incident Reports

Environmental incident reports are obtained from two main sources, the Canadian pesticide incident reporting system (including both mandatory reporting from the registrant and voluntary reporting from the public and other government departments) and the USEPA Ecological Incident Information System. If information on environmental incidents is available from other governments (for example, OECD countries) this information is also be taken into consideration. Specific information regarding the mandatory reporting system regulations that came into force 26 April 2007 under the *Pest Control Products Act*.

According to the USEPA's Ecological Incident Information System database, there are ten incidents reported for mancozeb of which four are reported to be the result of registered labelled use, three as the result of a spill, accidental or intentional misuse, and three are reported as undetermined. Of the four incidents that resulted from registered use, two incidents involved crop damage to potatoes and apples, and one incident was the result of spray drift onto a fruit and vegetable garden while neighbouring birch trees were being sprayed. The remaining incident involved a bird kill on an island off the coast of France where 35 birds were found dead and another 31 intoxicated after reportedly drinking dew in a cabbage field the same morning as the application of Lannate 20L (methomyl) and Dithane M-45 (mancozeb).

There were no incident reports concerning ETU. Since ETU is a transformation product that is formed from the EBDCs, incident reports would be most likely for one of the parent EBDCs.

5.0 Value

Appendix II lists the uses of mancozeb that the registrants continue to support during the re-evaluation.

Mancozeb is registered in Canada for use on a broad range of food and non-food sites including as a seed treatment for the control of a wide range of economically important fungal diseases. Having a multi-site mode of action, mancozeb is an important tool for pest management and resistance management by allowing co-formulation, tank-mixing and rotation with many fungicidal active ingredients on pathogens where resistance is known, or that are at high risk for it to develop. Mancozeb contributes to maintaining the continued effectiveness of many other fungicides with a single site mode of action. Resistance management and fungicide rotation are particularly important for sites that have only a few registered alternative fungicides and those that are at high risk to develop resistance.

For the majority of mancozeb uses, there are multiple alternative active ingredients registered to manage most of the economically important diseases on large acerage crops. This includes the multi-site mode of action fungicides chlorothalonil, captan, and folpet, as well as several other single-site mode of action fungicides. However, for some uses, it is recognized that there are few or no alternatives registered to manage certain diseases, or to allow alternation of chemistries for resistance management purposes.

6.0 Pest Control Product Policy Considerations

6.1 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, i.e., 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, mancozeb, and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[1] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Mancozeb does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Table 6.1 for comparison with Track 1 criteria.

- Mancozeb does not form any transformation products that meet all Track 1 criteria.

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

Table 1 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Parent/mancozeb complex Are criteria met?	Transformation Product ETU Are criteria met?
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	No: < 1 hour (parent) 1.8 – 8.3 days (mancozeb complex)	No: < 7 days
	Water	Half-life ≥ 182 days	No: 0.7–0.8 hours (parent) 40.5–62.4 days (mancozeb complex)	No: $t_{1/2}$ 1–-4 days in natural waters
	Sediment	Half-life ≥ 365 days	Not available	No: aerobic half-life = < 21 days Yes: anaerobic half-life = 149–499 days
	Air	Half-life ≥ 2 days or evidence of long range transport	Half-life or volatilization is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (1.07×10^{-7} mm Hg) and Henry's law constant (5.9×10^{-9} atm m^3/mole).	Yes: 8-9 days
Bioaccumulation[4]	Log K_{OW} ≥ 5		No: 1.33	No: -0.69
	BCF ≥ 5000		not available	not available
	BAF ≥ 5000		not available	not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			**No, does not meet all TSMP Track 1 criteria.**	**No, does not meet all TSMP Track 1 criteria**

1 All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e., all other TSMP criteria are met).

2 The policy considers a substance "predominantly anthropogenic" if, based on expert judgment, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

3 If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

4 The log L_{ow} and/or BCF and/or BAF are preferred over log K_{ow}.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical 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 Gazette.*[2] 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

2 *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.*

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.*

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

- There are no formulants or contaminants of concern associated with ETU because it is not manufactured as a technical or used an end-use product.

7.0 Summary

7.1 Human Health and Safety

The published and unpublished toxicity data for mancozeb was adequate to define the majority of toxic effects that may result from exposure, although additional studies are required to assess developmental neurotoxicity potential. The primary targets of toxicity were on the thyroid, fetal development and retinopathy. In reproductive and developmental systems there was an increase in post-implantation loss/resorptions. Retinal degeneration was apparent in both animal and epidemiology studies, after long-term exposure. Cancer concerns exist for mancozeb based on ETU, a metabolite of mancozeb. ETU has been shown to cause thyroid cancer in both mice and rats and liver cancer in female mice. Mancozeb was considered to have genotoxic potential.

ETU is a metabolite of the EBDC group of fungicides, which includes the related active ingredients mancozeb, maneb, metiram, zineb and nabam. Currently, mancozeb, metiram and nabam are registered for use in Canada. The toxicological database for ETU contains numerous published and unpublished studies that were considered in the toxicology assessment. For the purpose of this re-evaluation, the reproduction studies were considered supplemental and the database was lacking a developmental neurotoxicity study with a comparative (adult vs. young) thyroid assay. The primary targets are the thyroid, liver and developmental toxicity. The carcinogenic risk of ETU was addressed with a q_1^* (non-threshold) approach.

7.1.1 Occupational Risk

Non-cancer and cancer risk associated with mixing, loading, and applying activities for most agricultural label uses were found to be acceptable, provided engineering controls, personal protective equipment, and additional mitigation measures as listed in Section 8.1 are implemented.

Postapplication risks for workers were found to be acceptable for most agricultural label uses when the proposed mitigation measures (REIs) are applied. However, for apples, pears and grapes and greenhouse tomatoes, some or all of the proposed REIs are not agronomically feasible and therefore, risks were not found to be acceptable.

For commercial seed treatment (slurry application) and on-farm seed treatment (dry application), risks were not found to be acceptable even when maximum feasible mitigation measures were considered.

7.1.2 Non-Occupational Risk

Risk estimates associated with spray drift exposure or exposure incurred during harvesting activities as a patron of a PYO facility, were found to be acceptable, for adults, youth and children.

7.1.3 Aggregate Risk from Food and Drinking Water

Mancozeb and ETU

Mancozeb is not expected to occur in drinking water. Therefore, the aggregate risk assessment from food and drinking water was conducted only for ETU. Both the acute and chronic aggregate risk estimates are lower than the acute reference dose and ADI, respectively, and are, therefore, were found to be acceptable.

The aggregate cancer risk estimate for ETU is 8×10^{-6} for ETU and was not found to be acceptable. Non-occupational exposures (for example, PYO facilities and bystander exposure from spray drift) were not included in the aggregate assessment since cancer risk for ETU from aggregate food and water exposure alone was not found to be acceptable.

7.1.4 Cumulative Risk

Exposure to ETU in food and drinking water may also occur from the use of mancozeb or any other EBDC fungicides. Presently, metiram is the only other EBDC fungicide with registered food uses in Canada while nabam is registered in Canada for industrial uses only.

Exposure to ETU in the environment or in occupational settings may occur from non-pesticidal sources of ETU. These sources are regulated separately (*Canadian Environmental Protection Act, 1999*) from the exposure derived from the pesticidal use.

As the aggregate exposure from food and water to ETU derived from mancozeb alone was not found to be acceptable, a combined/cumulative risk assessment was not conducted at this time. It is acknowledged that the drinking water exposure estimates do represent the total exposure from ETU from all pesticidal sources (mancozeb and metiram). However, as the aggregate risk for metiram and mancozeb are estimated independently, this approach does not over-estimate the risk.

Mitigation options for the dietary risk includes proposing a revised use pattern for agricultural uses. The registrant has an option to propose this during the consultation period.

As an additional measure, to mitigate potential aggregate risk from ETU exposure (from all EBDC pesticides and sources), the following label statement is proposed to be added to the labels of mancozeb and metiram to limit applications of these actives so that the total quantity of active does not exceed the specified maximum seasonal quantity for either mancozeb or metiram.

"Total quantity of all EBDC products used on a crop must not exceed the specified maximum seasonal quantity of active ingredient allowed per hectare for either mancozeb or metiram."

7.2 Environmental Risk

Available environmental studies suggest that in the natural environment, parent mancozeb will decompose rapidly by hydrolytic reactions into mancozeb complex, which consists of intermediate species, transformation products and other un-identified materials. The intermediate species include EBIS and hydantoin. Transformation products are dominated by ETU, EU (a transformation product of ETU), and CO_2. ETU forms via hydrolysis, phototransformation and biotransformation processes after the application of parent EBDC pesticides to the environment.

In the terrestrial environment, mancozeb complex is expected to biotransform rapidly (DT_{50}=1.8–8.3 days). Under aerobic aquatic conditions, the mancozeb complex is expected to be slightly to moderately persistent, (DT_{50} range from 19.9 to 62.4 d). Anaerobic conditions appear to be conducive for slowing down mancozeb decomposition; based on the persistence of parent mancozeb (DT_{50}=82 days), mancozeb complex would be expected to be moderately persistent. ETU undergoes rapid aerobic biotransformation both in the soil and aquatic environments. But it could be slightly to moderately persistent in soil and water in aerobic conditions and is moderately persistent to persistent under anaerobic aquatic conditions.

Laboratory studies indicate that a significant portion of the mancozeb residues will bind to the soil/sediment particles. Laboratory study results indicate that the bound residues are fairly stable or increase in the soil/sediment over time and, therefore, are not releasing from the soil/sediment in order to produce ETU. The PMRA chose to not include the bound residues into the determination of the aerobic biotransformation DT_{50}s for mancozeb complex; the biotransformation DT_{50}s were based on total extractable radioactivity. Mancozeb (parent and complex) is not expected to leach into groundwater. The transformation product ETU, however, is only weakly adsorbed to soil and, therefore, its high soil mobility makes it a potential contaminant to groundwater. ETU residues have not been detected in groundwater in Canada, but have been in the American Residues of ETU have been detected in surface water in Canada and the U.S.

In the terrestrial environment, mancozeb is expected to pose an acute risk to beneficial predatory arthropods. The risk to beneficial insects living in habitats adjacent to the application site may be reduced by minimizing spray drift. For foliar applications, chronic risks were identified for birds and mammals that may potentially ingest mancozeb residues on food items. Foliar applications of mancozeb on all crops pose a risk to birds and small wild mammals which was not found to be acceptable, particularly for insectivores foraging both within orchards/vineyards and off-field. Also, acute and chronic risks to birds and chronic risk to mammals feeding on treated seed were not found to be acceptable.

Terrestrial mammals could be at chronic risk from ETU concentrations resulting from mancozeb applied using air blast and to a lesser extent ground boom applications. Concentrations of ETU on the food items will quickly reach a level that is above the chronic toxicity and developmental toxicity thresholds for mammals and remain there for extended periods, indicating that terrestrial mammals could be at risk on a chronic basis. There does not appear to be an acute risk to terrestrial mammals.

In the aquatic environment, mancozeb in run-off and drift may pose risks to freshwater and marine organisms. To mitigate the risk from spray drift in to aquatic habitats spray buffer zones are required. Based on the registered use-pattern the spray buffer zones required to protect freshwater habitats from aerial applications of mancozeb are large particularly for habitats of less than 1 m depth. To further mitigate the environmental risk to aquatic organisms from off-target drift from aerial applications, the PMRA is proposing to limit aerial applications to a maximum of one application per season; this will result in maximum aerial spray buffer zones of 275 m.

Spray buffer zones will not mitigate runoff. To reduce the potential for run off of mancozeb to adjacent aquatic habitats precautionary statements for sites with characteristics that may be conducive to runoff and when heavy rain is forecasted are required. In addition, a vegetative strip between the area and the edge of a water body is recommended to reduce runoff of mancozeb to aquatic areas. Aquatic organisms will be at negligible risk due to the formation of ETU from the use of the EBDC pesticides.

7.3 Value

Mancozeb is registered in Canada for use on a broad range of food and non-food sites for the control of a wide range of economically important fungal diseases. Mancozeb is an important tool for maintaining the continued effectiveness of many other fungicides with a single site mode of action. Mancozeb contributes to broad-spectrum pest management resistance management by allowing co-formulation, tank-mixing and rotation with other fungicidal active ingredients on pathogens where resistance is known or that are at high risk for it to develop. Resistance management and fungicide rotation are particularly important for sites that have only a few registered alternative fungicides and those that are at high risk to develop resistance.

8.0 Proposed Regulatory Decision

The PMRA is proposing cancellation of all mancozeb uses, except greenhouse tobacco, due to risks to human health and the environment that were not found to be acceptable.

- Risks associated with the use on greenhouse tobacco were found to be acceptable and therefore, this use is proposed for continued registration with additional risk mitigation measures.

During the phase-out, additional measures may be required to reduce potential human health and environment risks.

No additional scientific data are required at this time. However, during the consultation period, the registrants may consider submission of further data or propose changes to the use pattern that could be used to address the human health and environmental risks identified. Dietary risks may be refined if the number of crop uses is limited. Therefore, the PMRA strongly recommends that registrants collaborate to identify and prioritize critical agricultural uses. Further, the PMRA recommends that agricultural stakeholders, such as grower associations, communicate their needs to the registrants. The PMRA will rely upon the registrants' prioritized list of critical uses to conduct the refined dietary assessment.

8.1 Proposed Regulatory Actions

8.1.1 Proposed Regulatory Action Related to Human Health

8.1.1.1 Toxicological Information

The EBDC fungicides may cause irritation of the skin, respiratory tract and eyes. For mancozeb, the following warning statements should appear on the labels of the technical and end-use product: "Danger: Skin Sensitizer". "Danger: Eye Irritant"

8.1.1.2 Residue Definition and MRL for Risk Assessment and Enforcement

As chemical specific enforcement methods for the EBDC fungicides, including mancozeb, are not currently available, the current residue definition established under the *Pest Control Products Act* is "manganese and zinc ethylene bis(dithiocarbamate) (polymeric)", which is common for all EBDC pesticides. The PMRA is proposing to revise the residue definition for mancozeb, to residues of "mancozeb expressed as carbon disulphide (CS_2)". These proposed changes are pending the availability of acceptable field trial data at the Canadian good agricultural practice if any food uses remain on Canadian labels, upon completion of the re-evaluation.

The residue definition of ETU for risk assessment and enforcement is "ethylene thiourea".

8.1.1.3 Maximum Residue Limits for Mancozeb in Food

Currently, MRLs for EBDC fungicides are established for a number of commodities. MRLs established in Canada may be found using the Maximum Residue Limit Database on the Maximum Residue Limits for Pesticides webpage. The database allows users to search for established MRLs, regulated under the *Pest Control Products Act*, both for pesticides or for food commodities. When no specific MRL has been established, crop uses are regulated under subsection B.15.002(1) of the *Food and Drug Regulations*, which requires that residues not exceed 0.1 ppm.

In general, when the re-evaluation of a pesticide has been completed and dietary risks are unacceptable, the PMRA may remove or revise MRLs for risk mitigation purposes, as appropriate. Any changes to the MRLs will be consulted through a Proposed Maximum Residue Limit document. As mancozeb belongs to the EBDC group of fungicides, amendments to the MRLs will need to take into consideration the regulatory proposals for all EBDC compounds or other related pesticides such as the dimethyldithiocarbamates (i.e., ferbam, ziram and thiram).

8.1.1.4 Maximum Residue Limits for ETU in Food

There are no specific MRLs established for ETU under the *Pest Control Products Act*. However, residues in food from all sources are regulated separately under sections B.01.046 and B.01.047 of the *Food and Drug Regulations*, where a maximum limit of 0.05 ppm is specified for ETU in fruits, vegetables and cereals. No change to this maximum limit is proposed.

8.1.1.5 Proposed Risk-Reduction Measures to Protect Mixers/Loaders/Applicators and Postapplication Exposure

8.1.1.5.1 Proposed Mitigation Measures for Mixer, Loader and Applicator Exposure and Post Application Exposure – Scenarios with Acceptable Occupational Risk

Although all uses, except greenhouse tobacco, are proposed for cancellation due to dietary and environmental risks that were not found to be acceptable, the following proposed mitigation measures could be applicable in the final re-evaluation decision or in the situation that additional uses are retained following the consultation process, since occupational risks were found to be acceptable for these uses.

Residential outdoor ornamentals:

The technical registrants confirmed that mancozeb is not used on outdoor ornamentals in residential areas. Therefore these uses were not assessed for re-evaluation. To ensure that mancozeb will not be used in residential areas, the following statement should appear on all mancozeb labels:

"This product is not to be used around homes or other residential areas such as parks, school grounds and/or playing fields."

All Other Uses:

Water Soluble Packaging

All products currently listed as wettable powders must be contained in water soluble packaging. The registrant is required to include directions and precautionary statements for water-soluble packaging on these end-use product labels.

Number of Applications:

The postapplication assessment was based on the maximum number of applications that was specified by registrants and minimum interval between applications, as listed below. It is necessary to ensure that the product labels reflect the maximum number of application per year and minimum interval between applications as specified in Table 1.

All labels must be changed to specify: "Limit the number of application to a maximum of (see Table 1) with a minimum of (see Table 1) days between applications."

Table 1 Recommended Applications per Year and Application Intervals

Crop	Applications per Year	
	Number	Interval (days)
Ash, oak, sycamore, hawthorn, Douglas Fir, arborvitae, juniper, holly, ivy, pine	6	7
Honeysuckle	3	10
Greenhouse tobacco	18	7

Use Precautions:

There may be potential for exposure to bystanders from drift following pesticide application to agricultural areas. In the interest of promoting best management practices and to minimize human exposure from spray drift or from spray residues resulting from drift, the following label statement is required:

"Apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings."

Engineering Controls and Personal Protective Equipment:

"Wear long pants, long sleeved shirts, shoes plus socks, and chemical-resistant gloves during mixing/loading, application, clean-up and repair. Chemical-resistant gloves are not required while operating groundboom sprayers. Aerial applicators must wear long pants, and long sleeved shirts."

For the following use scenarios, additional PPE, restrictions and/or engineering controls must also be included on labels:

Mixing/loading

A. Mixing and loading liquids, dry flowables and wettable granule formulations:

- Wear a respirator with either a NIOSH approved organic-vapour removing cartridge with a prefilter approved for pesticides or a NIOSH approved canister approved for pesticides.

Application

B. Applying by groundboom to lentils, potatoes, sugar beets and wheat:

- During groundboom application, applicators must either wear a respirator with NIOSH approved organic-vapour removing cartridge with a prefilter approved for pesticides or a NIOSH approved canister approved for pesticides OR Use a closed cab that provides both a physical barrier and respiratory protection (such as dust/mist filtering and/or vapour/gas purification system). The closed cab must have a chemical-resistant barrier that totally surrounds the occupant and prevents contact with pesticides outside the cab.

C. Applying by handheld equipment:

- When handling more than 0.4 kg of active ingredient per day (approximately 130 L at rate of 2.80 kg a.i. per 1000 L), wear a respirator with NIOSH approved organic-vapour removing cartridge with a prefilter approved for pesticides or a NIOSH approved canister approved for pesticides.

D. Seed Treatment (On-farm use only):

- Apply as slurry or mist application only.

- During loading, treating, augering and handling of treated seed, wear a respirator with either a NIOSH approved organic-vapour removing cartridge with a prefilter approved for pesticides or a NIOSH approved canister approved for pesticides.

E. Planting Treated Seed:

- During planting of treated seed, wear either a respirator with either a NIOSH approved organic-vapour removing cartridge with a prefilter approved for pesticides or a NIOSH approved canister approved for pesticides OR Use a closed cab that provides both a physical barrier and respiratory protection (such as dust/mist filtering and/or vapour/gas purification system). The closed cab must have a chemical-resistant barrier that totally surrounds the occupant and prevents contact with pesticides outside the cab.

- Do not plant treated seed by hand.

F. Treatment of seed potatoes for storage:

- Wear a respirator with either a NIOSH approved organic-vapour removing cartridge with a prefilter approved for pesticides or a NIOSH approved canister approved for pesticides.

Restricted-Entry Intervals:

The restricted-entry intervals listed below must be added to the appropriate labels.

Table 2 Recommended Restricted-Entry Intervals

Crop	Activity	Formulation	**REI** (days)
Use-site category 4: Forests and Woodlots & Use-site category 27: Ornamentals Outdoors			
Ash, Arborvitae, Douglas Fir, Hawthorn, Holly, Honeysuckle, Ivy, Juniper, Oak, Pine, Sycamore	All activities	DF, WG, WP	12 hrs
Use-site category 5: Greenhouse Crops			
Tobacco	All activities	DF, WG, WP, SN	12 hrs
Use-site category 7: Industrial Oil Seed Crops and Fibre Crops			
Alfalfa	All activities	DF, WG	12 hrs
Use-site category 14: Terrestrial Food Crops			
Cantaloupe, Cucumber, Melon, Pumpkin, Squash, Watermelon	Hand harvesting, hand pruning, thinning, leaf pulling	SN	9
		WP, DF, WG	8
	All other activities	SN, WP	2
		DF, WG	1
Carrot	Hand harvesting	DF, WG, SN, WP	4
	All other activities		12 hrs
Celery	Hand harvesting	DF	8
		SN, WP	4
	All other activities	DF	1
		SN, WP	12 hrs
Lentils	Hand harvesting	SN	6
		DF, WG	12 hrs
	All other activities	SN	3
		DF, WG	12 hrs
Ginseng	Hand harvesting	SN, WP	12
		DF, WG	11
	Irrigation, scouting	SN, WP	6
		DF, WG	5
	Hand weeding, thinning	DF, WG, SN, WP	12 hrs
Head lettuce	Hand harvesting	WG, WP	2
	All other activities		12 hrs
All other crops (excluding apples, pears, grapes and greenhouse tomatoes)	All activities	All	12 hrs

DF = Dry flowable; SN = Solution; WG = Wettable Granule; WP = Wettable Powder

8.1.1.5.2 Proposed Additional Measures for Mixer, loader and Applicator Exposure and Postapplication Exposure - Scenarios with Occupational Risks that Were Not Found to Be Acceptable

All uses, except greenhouse tobacco, are proposed for cancellation due to dietary and environmental risks that were not found to be acceptable. In addition, the following uses had occupational risks that were not found to be acceptable, even with consideration of feasible mitigation measures, and are therefore proposed for cancellation due to both dietary and occupational risks. This section includes proposed mitigation that may be required during the phase-out period for these uses, and/or in the situation that additional uses are retained following the consultation process.

Uses with occupational risks that were not found to be acceptable are:

- Greenhouse tomatoes;
- Apples, pears, and grapes;
- All seed treatment uses to all seeds, except on-farm slurry applications (barley, corn, oats, and wheat) and planting of treated seed (corn, barley, flax, oats, and wheat); and
- All potato seed piece treatments (commercial and on-farm), except the treatment of seed potatoes for storage.

Uses with occupational risks that were not found to be acceptable and for which adequate data were available

Postapplication worker risks were not found to be acceptable for greenhouse tomatoes; mitigation measures that would reduce these risks are not considered agronomically feasible. Therefore, the PMRA is proposing that use of mancozeb on greenhouse tomatoes be cancelled. During the phase-out period, or in the situation where these uses are retained following the consultation process, additional mitigation measures may be required.

Uses with occupational risks that were not found to be acceptable and for which adequate data were not available

For apples, pears, grapes and commercial (slurry and dry application) and on-farm (dry application) seed treatment for barley, corn, flax, oat and wheat, and potato pieces, additional mitigation measures may be required during the phase out-period and/or in the situation where these uses are retained following the consultation process..

Number of Applications

The postapplication assessment was based on the maximum number of applications that was specified by registrants and minimum interval between applicatios, as listed below. It is necessary to ensure that the labels reflect the maximum number of application per year and minimum interval between applications as specified in Table 3.

All labels must be changed to specify: “Limit the number of application to a maximum of (see Table 3) with a minimum of (see Table 3) days between applications.”

Table 3 Recommended Applications per Year and Application intervals

Crop	Applications per Year	
	Number	Interval Days
Apples	6	7
Grapes (dry flowable formulations)	6	7
Grapes (wettable granule formulations)	1	not applicable
Grapes (wettable powder formulations)	4	10
Pears	4	7

Engineering Controls and Personal Protective Equipment

A. Applying by airblast to apples (all formulations), pears (all formulations) and grapes (wettable powder formulations only):

- During airblast application, applicators must either wear a respirator with NIOSH approved organic-vapour removing cartridge with a prefilter approved for pesticides or a NIOSH approved canister approved for pesticides OR Use a closed cab that provides both a physical barrier and respiratory protection (such as dust/mist filtering and/or vapour/gas purification system). The closed cab must have a chemical-resistant barrier that totally surrounds the occupant and prevents contact with pesticides outside the cab.

B. Potato seed treatment:

- During loading and treating, wear a respirator with either a NIOSH approved organic-vapour removing cartridge with a prefilter approved for pesticides or a NIOSH approved canister approved for pesticides.
- During planting of treated seed, use a closed cab that provides both a physical barrier and respiratory protection (such as dust/mist filtering and/or vapour/gas purification system).
- Limit the amount of active ingredient handled at any farm or facility to 7.3 kg a.i. per day (a limit of approximately 9000 kg of potato may be treated per day at an application rate of 0.8 g a.i. per 100 kg of potato).

Restricted-Entry Interval:

The restricted-entry intervals listed below must be added to the appropriate labels.

Table 4 Recommended Restricted-Entry Intervals

Crop	Activity	Formulation	REI (days)
Use-site category 5: Greenhouse Food Crops			
Tomatoes	All activities	DF, WG, WP	27
Use-site category 14: Terrestrial Food Crops			
Apple	Hand thinning	SN, WP	59
		DF, WG	56
	Hand harvesting	SN, WP	34
		DF, WG	32
	Hand-line irrigation	SN, WP	24
		DF, WG	22
	All other activities	DF, WG, SN, WP	12 hrs
Grape	Girdling, cane turning	WP	81
		WG	53
		DF	41
	Hand harvesting, training, thinning, hand pruning, tying, leaf pulling	WP	60
		WG	34
		DF	28
	Hand-line irrigation	WP	8
		WG	2
		DF	12 hrs
	All other activities	WP	15
		DF, WG	12 hrs
Pear	Hand thinning	WP	65
	Hand harvesting		40
	Hand-line irrigation		30
	Hand pruning, scouting, pinching		5

DF = Dry flowable; SN = Solution; WG = Wettable Granule; WP = Wettable Powder

8.1.1.6 Proposed Measures for Dietary Exposure

Mitigation options for the dietary risk include a revised use pattern for agricultural uses. The registrant has an option to propose this during the consultation period.

Dietary risks may be acceptable if the number of crop uses is limited. Therefore, the PMRA strongly recommends that registrants collaborate to identify and prioritize critical agricultural uses. Further, the PMRA recommends that agricultural stakeholders, such as grower associations, communicate their needs to the registrants. The PMRA will rely upon the registrants' prioritized list of critical uses to conduct the refined dietary assessment.

An additional measure, to mitigate potential aggregate risk from ETU exposure (from all EBDC pesticides and sources), the following label statement is proposed to be added to the labels of mancozeb and metiram to limit applications of these actives so that the total quantity of active does not exceed the specified maximum seasonal quantity for either mancozeb or metiram.

> "Total quantity of all EBDC products used on a crop must not exceed the specified maximum seasonal quantity of active ingredient allowed per hectare for either mancozeb or metiram."

8.1.2 Proposed Regulatory Action Related to Environment

Environmental risks to birds and small wild mammals were identified for foliar sprays of mancozeb and were not found to be acceptable. Therefore, all foliar applications are proposed to be cancelled, unless data or information is provided to address the risks identified. During the phase-out period of all uses, except greenhouse tobacco, the following additional risk mitigation measures may be required, or in the situation where these uses are retained following the consultation process:

To reduce the effects of mancozeb in the environment, mitigation in the form of precautionary label statements and buffer zones are proposed.

Label Amendments for Commercial Class Products Containing Mancozeb

Add an **ENVIRONMENTAL HAZARDS** section to agricultural labels with the following statements**:**

- TOXIC to aquatic organisms. Observe buffer zones specified under DIRECTIONS FOR USE.
- TOXIC to small wild mammals.
- TOXIC to birds
- TOXIC to certain beneficial insects. Minimize spray drift to reduce harmful effects on beneficial insects in habitats next to the application site such as hedgerows and woodland.

- 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.
- The use of this chemical may result in contamination of groundwater particularly in areas where soils are permeable (for example, sandy soil) and/or the depth to the water table is shallow.

Add to GENERAL DIRECTIONS FOR USE after the MIXING INSTRUCTIONS:

- As this pesticide 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.

Add to DIRECTIONS FOR USE:

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) 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.

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) medium classification. To reduce drift caused by turbulent wingtip vortices, the nozzle distribution along the spray boom length **MUST NOT** exceed 65% of the wing- or rotorspan.

Buffer zones:

Use of the following spray methods or equipment **DO NOT** require a buffer zone: hand-held or backpack sprayer and spot treatment.

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

Buffer Zone Table for dry flowable/wettable powder formulations:

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:			
			Freshwater Habitat of Depths:		Estuarine/Marine Habitats of Depths:	
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m
Field sprayer*	Wheat (all varieties)		5	1	1	1
	Head lettuce		10	2	2	1
	Lentils		10	2	2	1
	Celery, carrots, sugar beets		20	4	4	2
	Potato		25	5	5	2
	Cantaloupe, cucumbers, melons, pumpkins, squash, watermelons, tomato, ginseng		30	5	5	3
	Onions (foliar application)		35	5	5	3
Airblast	Pears, grapes	Early growth stage	60	40	40	30
		Late growth stage	50	30	30	20
	Apples	Early growth stage	65	45	45	35
		Late growth stage	50	35	35	25
Aerial	Wheat (all varieties), potato	Fixed wing	275	15	15	5
		Rotary wing	150	10	15	5
	Lentils	Fixed wing	275	15	15	5
		Rotary wing	125	10	10	4

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.

Buffer Zone Table for Dithane F-45 (PCP 20552):

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:			
			Freshwater Habitat of Depths:		Estuarine/Marine Habitats of Depths:	
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m
Field sprayer*	Wheat (all varieties)		5	1	1	1
	Lentils		15	3	3	1
	Celery, carrots		20	4	4	2
	Potato		25	5	5	2
	Cantaloupe, cucumbers, melons, pumpkins, squash, watermelons, tomato, ginseng		30	5	5	3
	Onions (foliar application)		35	5	5	3
Airblast	Apples	Early growth stage	65	45	45	35
		Late growth stage	50	35	35	25
Aerial	Wheat (all varieties)	Fixed wing	275	20	20	10
		Rotary wing	150	15	15	10
	Lentils	Fixed wing	275	25	30	10
		Rotary wing	175	20	20	10

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.

Buffer Zone Table for Ridomil products (PCP 25379, 25419 and 28893):

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:			
			Freshwater Habitat of Depths:		Estuarine/Marine Habitats of Depths:	
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m
Field sprayer	Potato, head lettuce, onions		10	2	2	1
Airblast	Grapes	Early growth stage	35	15	15	10
		Late growth stage	25	10	10	4
Aerial	Potato	Fixed wing	250	15	15	5
		Rotary wing	125	10	10	4

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.

Add an **ENVIRONMENTAL HAZARDS** section to seed treatment labels with the following statements**:**

- Treated seed is 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.

8.1.3 Proposed Regulatory Action Related to Value

Benomyl is no longer registered for use in combination with mancozeb. The following should be deleted from the Registration No. 10526 label:

> - "GREENHOUSE CUCUMBERS: Gummy stem blight, powdery mildew – Apply 550-850 g of BENLATE® Fungicide WP plus 2.25-3.25 kg of MANZATE® 200 WP Fungicide in 500 to 1000 L water per ha. Begin when disease first appears and repeat in 7-14 days of harvest. Apply Tank mix the same day. Do not leave overnight. Precautions on the BENLATE® Fungicide WP label must be followed."

For pumpkins only the strikeout text portion of the Registration No. 10526 label should be deleted as follows:

> - "PUMPKINS: ~~Powdery mildew~~, anthracnose, alternaria leaf spot, downy mildew, gummy stem blight, scab – Apply ~~550-850 g of BENLATE® Fungicide WP plus~~ 2.25 -3.25 kg of MANZATE® 200 WP Fungicide in 500 to 1000 L water per ha. Begin when disease first appears and repeat at 7-14 days interval as needed. Do not apply more than 3 times per crop. For severe disease pressure on susceptible varieties, use the higher rate on a 7-day schedule. Do not apply within 14 days of harvest. ~~Apply tank mix the same day. Do not leave overnight. Refer to BENLATE® Fungicide WP label for USE INSTRUCTIONS and PRECAUTIONS.~~ "

The registrants will be required to implement among other label changes, the rates, number of applications and maximum cumulative rates and other conditions of use resulting from the re-evaluation decision. For liquid products, the label product rate should be expressed as L/ha and not in kg/ha as for the use of mancozeb on lentils in the Registration No. 20552 label.

8.2 Additional Data that May Help Address the Risks Identified in the Assessments

The following studies may address uncertainties in the available information database. Submission of these studies may support more refined risk assessments which could permit continued registration of additional uses of mancozeb (i.e., other than greenhouse tobacco):

8.2.1 Data related to Toxicology

Mancozeb studies:

DACO 4.5.14	Developmental Neurotoxicity Study (DNT) on ETU. Depending on the outcome of this study, a DNT study and/or a developmental thyroid assay on mancozeb may be required.
DACO 4.8	Immunotoxicity study.

ETU studies:

DACO 4.5.1	Two-generation reproductive toxicity study in rat
DACO 4.5.14	Developmental Neurotoxicity Study, with comparative thyroid assay (adult/young)

8.2.2 Data Related to Occupational Exposure

DACO 5.14:	Other Studies/Data/Reports - Data that quantifies the amount of ETU present and/or formed in mancozeb tank mixes. .

Seed Treatment and Potato Seed Piece Treatment:

DACO 5.2	Use Description/Scenario - Information which fully describes the use of mancozeb for seed treatment in commercial and on-farm settings. Qualitative information which will help characterize exposure including types of equipment used, typical worker tasks, amount handled per day and durations of exposure, should be included here. The sources of information should be cited (for example, label, grower groups, surveys, agricultural experts and associations, and databases).
DACO 5.4/5.5	Mixer/Loader/Application - Passive dosimetry and/or biological monitoring data for workers treating seed (barley, corn, flax, oat and wheat) in commercial facilities (slurry and/or dry application) and on-farm seed treatment (dry application) with mancozeb. For biomonitoring studies, the pharmacokinetics of the compound must be adequately characterized for the data to be used.
DACO 5.12:	Laboratory dust-off data: Data to establish dust-off potential between registered seeds and surrogate seeds used in the assessment or submitted.
DACO 5.14:	Other Studies/Data/Reports - Data that quantifies the amount of ETU present and/or formed in dust from treated seed.

Apples, Pears, and Grapes

DACO 5.2	Use Description/Scenario (Application and Postapplication)

- typical rate and number of applications per season;
- typical area treated per day;
- data to support rates of application lower than the registered rates;

DACO 5.9 Dislodgeable Residue - Dislodgeable foliar residue data representative of several of the registered crops and Canadian climatic regions. Dislodgeable foliar residue studies are available for apples and grapes; however, a Canadian study may be more representative.

8.2.3 Data Related to the Dietary Exposure

Data in relation to mancozeb and ETU:

DACO 7.4.1 Supervised Residue Trial Study for all registered uses at the Canadian good agricultural practice .

DACO 7.4.2 Residue Decline Study for all registered uses.

DACO 7.4.5 Processed food/feed studies for all applicable uses.

8.2.4 Data Related to the Environment.

ETU studies:

There were no data available for ETU exposure to terrestrial invertebrates, birds and vascular plants.

DACO 8.6 Additional data may be submitted to better characterize the potential exposure to ETU through drinking water. Based on the identified human health risk coming from the ETU residues potentially present in the water, confirmatory water monitoring data may help address the determined exposure risk

DACO 9.6.1 Wild Birds Summary

DACO 9.6.2 Acute Studies

DACO 9.6.2.1 Oral (LD50) Bobwhite Quail

or

DACO 9.6.2.2 Oral (LD50) Mallard Duck

DACO 9.6.3.1 Avian Reproduction Bobwhite Quail

or
DACO 9.6.3.2 Avian Reproduction Mallard Duck

8.2.5 Data Related to Value

During the consultation period, the registrants may consider submission of further data or propose changes to the use pattern that could be used to address the human health and environmental risks identified. Dietary risks may be refined if the number of crop uses is limited. Therefore, the PMRA strongly recommends that registrants collaborate to identify and prioritize critical agricultural uses. Further, the PMRA recommends that agricultural stakeholders, such as grower associations, communicate their needs to the registrants. The PMRA will rely upon the registrants' prioritized list of critical uses to conduct the refined dietary assessment.

List of Abbreviations

a.i.	active ingredient
AAFC	Agriculture and Agri-Food Canada
AChE	acetylcholinesterase
ADI	acceptable daily intake
AHETF	agricultural Handlers Exposure Task Force
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
atm	atmosphere
ATP	Adenosine-5'-triphosphate
BAF	Bioaccumulation Factor
BCF	Bioconcentration Factor
BChE	brain acetylcholinesterase
BCMAF	British Columbia Ministry of Agriculture, Food and Fisheries
bw	body weight
CAS	chemical abstracts service
ChE	cholinesterase
CI	confidence interval
cm	centimetre(s)
cm2/h	centimetres squared per hour
CNS	central nervous system
CT	crop treated
d	day(s)
DACO	data code
DEEM®	Dietary Exposure Evaluation Model
DER	Data Evaluation Report
DFR	dislodgeable foliar residue
DNA	deoxyribonucleic acid
DNT	developmental neurotoxicity
DRA	dietary risk assessment
DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
DT_{75}	dissipation time 75% (the time required to observe a 75% decline in concentration)
DT_{90}	dissipation time 90% (the time required to observe a 90% decline in concentration)
DU	dust or powder
dw	dry weight
DWLOC	drinking water level of comparison
EBDC	ethylene bis(dithiocarbamate)
EC_{05}	effective concentration on 5% of the population
EC_{10}	effective concentration on 10% of the population
EC_{20}	effective concentration on 20% of the population
EC_{25}	effective concentration on 25% of the population
EChE	erythrocyte cholinesterase
EDE	estimated daily exposure

EEC	expected environmental concentration
EP	end-use Product
ER_{25}	effective rate on 25% of the population
ER_{50}	effective rate on 50% of the population
ETU	ethylene thiourea
EXAMS	Exposure Analysis Modeling System
F_0	parental generation
F_1	first filial generation
F_2	second filial generation
FC	food consumption
FIR	food ingestion rate
FOB	functional observational battery
FRAC	Fungicide Resistance Action Committee
g	gram(s)
GC-FPD	Gas Chromatography-Flame Photometric Detector
GC-MSD	Gas Chromatography-Mass Selective detector
GC-NPD	Gas Chromatography-Nitrogen Phosphorous Detector
ha	hectare(s)
Hct	hematocrit
HDT	highest dose tested
Hg	mercury
Hgb	hemoglobin
HPLC	high performance liquid chromatography
IPM	Integrated Pest Management
IRED	Interim Reregistration Eligibility Decision (USEPA Document)
IUPAC	International Union of Pure and Applied Chemistry
IV	intravenous
JMPR	Joint WHO/FAO Meeting on Pesticide Residues
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
kg	kilogram(s)
kg bw	kilograms of bodyweight
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol–water partition coefficient
L	litre(s)
LADD	lifetime average daily dose
LC_{50}	lethal concentration to 50% (a concentration causing 50% mortality in the test population)
LD_{50}	lethal dose to 50% (a dose causing 50% mortality in the test population)
LDT	lowest dose tested
LMA	locomotor activity
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOEC	lowest observed effect concentration
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
m	metre(s)

m^3	metre(s) cubed
MA	motor activity
MBS	market basket survey
mg	milligram(s)
mg/kg/day	milligrams per kilogram per day
mg/kg bw/day	milligrams per kilogram of bodyweight per day
mL	millilitre(s)
mm	millimetre(s)
MMAD	mass median aerodynamic diameter
MoA	Mode of Action
MOE	margin of exposure
MRID	USEPA’s Master Record Identifier number
MRL	Maximum residue limit
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
MTD	maximum tolerated dose
N/A	not applicable
NAFTA	North American Free Trade Agreement
nd	no detection
N/R	not required
NIOSH	National Institute for Health and Safety
nm	nanometre(s)
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NS	Nova Scotia
NTE	neuropathy target esterase
NTP	National Toxicology Program
OC	organic carbon content
OM	organic matter content
OMAF	Ontario Ministry of Agriculture and Food
OMAFRA	Ontario Ministry of Agriculture Food and Rural Affairs
OP	organophosphate
OR	Odds Ratio
PChE	plasma cholinesterase
PCP	Pest Control Product
PD	Parkinson’s disease
PDP	Pesticide Data Program (United States data)
pH	-log10 hydrogen ion concentration
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
PRZM	Pesticide Root Zone Model
PSI	pre-slaughter interval

PYO	pick your own
Q_1^*	cancer potency factor
QoI	Quinone outside Inhibitors
r.a.n.	repeat as necessary
RBC	red blood cells
REI	restricted-entry interval
RfD	reference dose
RSD	relative standard deviation
S9	mammalian metabolic activation system
$t_{1/2}$	half-life
T_3	triiodothyronine
T_4	thyroxine
TC	transfer coefficient
TOCP	tri-*ortho*-cresylphosphate
TP	transformation product
TPM	triophanate-methyl
TSH	thyroid stimulating hormone
TSMP	Toxic Substances Management Policy
URMULE	User Requested Minor Use Label Expansion
USEPA	United States Environmental Protection Agency
USDA	United States Department of Agriculture
UV	ultraviolet
µg	micrograms(s)
µm	micrometer(s)
v/v	volume per volume dilution
wk	week
↓	decreased
↑	increased
♂	males
♀	females
1/n	exponent for the Freundlich isotherm

Appendix I Mancozeb Products Registered in Canada as of 30 July 2013.

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee (A.I. code [2] -%)
8556	Commercial	DOW AGROSCIENCES CANADA INC.	Dithane M-45 80% WP Fungicide	Wettable Powder	MCZ-80
10186	Commercial	DOW AGROSCIENCES CANADA INC.	Dithane M-45 8% Dust Potato Seed Piece Fungicide	Dust or Powder	MCZ-8
10526	Commercial	UNITED PHOSPHORUS, INC.	Manzate 200 WP Fungicide	Wettable Powder	MCZ-80
17042	Commercial	NORAC CONCEPTS INC.	Tuberseal Potato Seed Piece Dust	Dust or Powder	MCZ-16
20552	Commercial	DOW AGROSCIENCES CANADA INC.	Dithane F-45 Fungicide	Solution	MCZ-37.0
20553	Commercial	DOW AGROSCIENCES CANADA INC.	Dithane DG Rainshield NT Fungicide	Wettable Granules	MCZ-75.0
21057	Commercial	UNITED PHOSPHORUS, INC.	Manzate DF Fungicide	Dry Flowable	MCZ-75.0
23655	Commercial	DOW AGROSCIENCES CANADA INC.	Dithane WSP 80% WP Fungicide	Wettable Powder	MCZ-80
24734	Commercial	WILBUR-ELLIS COMPANY	Potato ST16	Dust or Powder	MCZ-16
24734.01	Commercial	UNITED AGRI PRODUCTS CANADA INC.	PSPT 16%	Dust or Powder	MCZ-16
25379	Commercial	SYNGENTA CROP PROTECTION CANADA INC.	Ridomil Gold MZ 68WP Fungicide	Wettable Powder	MFN-4 MCZ-64
25396	Commercial	UNITED PHOSPHORUS INC.	Penncozeb 80WP Fungicide	Wettable Powder	MCZ-80
25397	Commercial	UNITED PHOSPHORUS INC.	Penncozeb 75DF Fungicide	Wettable Granules	MCZ-75
25419	Commercial	SYNGENTA CROP PROTECTION CANADA INC.	Ridomil Gold MZ 68WP Water Soluble Bag Fungicide	Wettable Powder	MCZ-64 MFN-4
26157	Commercial	NORAC CONCEPTS INC.	Mancoplus Potato Seed Piece Treatment	Dust or Powder	MCZ-16
26158	Commercial	NORAC CONCEPTS INC.	Solan MZ Potato Seed Piece Treatment	Dust or Powder	MCZ-16
26842	Commercial	GOWAN COMPANY, L.L.C.	Gavel 75DF Fungicide	Dry Flowable	ZOX-8.3 MCZ-66.7
27616	Commercial	DOW AGROSCIENCES CANADA INC.	Dithane M-45 Seed Protectant Concentrate	Wettable Powder	MCZ-80
27965	Commercial	SYNGENTA CROP PROTECTION CANADA INC.	Maxim MZ PSP	Dust or Powder	MCZ-5.7 FLD-0.5
28159	Commercial	BAYER CROPSCIENCE INC.	Genesis MZ Potato Seed Piece Treatment	Dust or Powder	MCZ-6.0 IMI-1.25
28160	Commercial	BAYER CROPSCIENCE INC.	Genesis XT Potato Seed Piece Treatment	Dust or Powder	TPM-3.0 MCZ-6.0 IMI-1.25
28217	Commercial	UNITED PHOSPHORUS, INC.	Manzate Pro-Stick Fungicide	Wettable Granules	MCZ-75
28893	Commercial	SYNGENTA CROP PROTECTION CANADA INC.	Ridomil Gold MZ 68WG	Wettable Granules	MCZ-64.0 MFN-4.00
29221	Commercial	DOW AGROSCIENCES CANADA INC.	Dithane DG 75 Fungicide	Dry Flowable	MCZ-75.0
29377	Commercial	NORAC CONCEPTS INC	Solan MZ Potato ST Fungicide	Dust or Powder	MCZ-16

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee (A.I. code [2] -%)
29378	Commercial	NORAC CONCEPTS INC	Tuberseal MZ Potatoe ST Fungicide	Dust or Powder	MCZ-16
30241	Commercial	UNITED PHOSPHORUS INC.	Penncozeb 75 DF Raincoat Fungicide	Wettable Granules	MCZ-75
19788	Technical	UNITED PHOSPHORUS, INC.	Mancozeb Technical Fungicide	Solid	MCZ-93
20734	Technical	DOW AGROSCIENCES CANADA INC.	Dithane Technical Fungicide	Wettable Powder	MCZ-83.2
25166	Technical	UNITED PHOSPHORUS INC.	Penncozeb Technical Fungicide	Dust or Powder	MCZ-87

[1]Discontinued products or products with a submission for discontinuation are not included.
[2] FLD = fludioxonil, IMI = imidacloprid, MCZ = mancozeb, MFN = metalaxyl-M (mefenoxam), TPM = thiophanate-methyl, ZOX = zoxamide.

Appendix II Commercial Class Uses of Mancozeb Registered in Canada as of 30 July 2013[1,2,3]

Site(s)	Pest(s)	Application Methods and Equipment	Formulation Type[4]	Application Rate (kg a.i./ha) unless stated otherwise		Maximum Number of Applications per Year [5,6]	Typical/ Recommended Number of Days Between Applications [5]	Comments [7]
				Maximum Single [5]	Maximum Cumulative [5]			
USC 4: Forest and Woodlots; Use-site category 27: Ornamentals Outdoors								
Ash, oak, sycamore	Anthracnose (*Gloeosporium* spp.)	Ground	DF, WG	2.625 kg/1000 L	[16.8 kg/ha]	Not stated [6]	[10- 14]	There was no maximum seasonal rate proposed by all registrants collectively for these sites. The calculated maximum seasonal rate is based on the maximum label rate multiplied by the maximum proposed number of applications among those proposed by the registrants and assuming a spray volume of 1000 L/ha.
			WP	2.8 kg/1000 L				
Arborvitae, juniper, Douglas fir	Coryneum blight, keithia blight, dieback, rhabdocline needle cast	Ground	DF, WG	2.625 kg/1000 L	[19.6 kg/ha]	Not stated [7]	[10-14]	
			WP	2.8 kg/1000 L				
Hawthorn	Leaf blight (*Diplocarpon* spp.)	Ground	DF, WG	2.625 kg/1000 L	[16.8 kg/ha]	Not stated [6]	10-14 [10]	
			WP	2.8 kg/1000 L				
Holly	Algae leaf and twig blight (*Phytophthora ilicis*)	Ground	DF, WG	1.875 kg/1000 L	[12.0 kg/ha]	Not stated [6]	[7-10]	
			WP	2.0 kg/1000 L				
Honeysuckle (Minor Use)	Honeysuckle blight (*Herpobasidium deformans*)	Ground	DF, WG	1.5 kg/1000 L	4.5 kg/ha	3	[10-14]	The calculated maximum seasonal rate is based on the maximum label rate for this site and the maximum number of applications from the labels and assuming a spray volume of 1000 L/ha.
Junipers (BC only)	Pear trellis rust	Ground	WG	2.625 kg/ha	8.4 kg/ha	3	[7-10]	There was no maximum seasonal rate proposed by all registrants collectively. The calculated maximum seasonal rate is based on the maximum label rate and the maximum number of applications from the labels and assuming a spray volume of 1000 L/ha.
			WP	2.8 kg/ha				
Ivy (*Hedera* spp.)	Leaf spot	Ground	DF, WG	1.875 kg/1000 L	[12.0 kg/ha]	Not stated [6]	7 [7-9]	There was no maximum seasonal rate proposed by all registrants collectively. The calculated maximum seasonal rate is based on the maximum label rate multiplied by the maximum proposed number of applications
			WP	2.0 kg/1000 L				

Site(s)	Pest(s)	Application Methods and Equipment	Formulation Type[4]	Application Rate (kg a.i./ha) unless stated otherwise		Maximum Number of Applications per Year [5,6]	Typical/ Recommended Number of Days Between Applications [5]	Comments [7]
				Maximum Single [5]	Maximum Cumulative [5]			
Pine	Lophodermium needle cast	Ground	DF, WG	1.875 kg/1000 L	(12.0 kg/ha)	not stated [6]	[14 to 21]	among those proposed by the registrants and assuming a spray volume of 1000 L/ha.
			WP	2.0 kg/1000 L				
Use-site category 5: Greenhouse Food Crops								
Tobacco (greenhouse) (Minor Use)	Blue mold	Ground	DF, WG	7.5 kg/ha	(144 kg/ha)	not stated [18]	[3-4]	There was no maximum seasonal rate supported collectively by all registrants. The maximum seasonal rate proposed by one technical registrant is based on 18 application at 8.0 kg a.i./ha (PCP # 25396, 25397). Another registrant is supporting a maximum of 3 applications. The registrants wish to refine this use pattern with the PMRA, based on the preliminary risk assessment. A typical rate of 6 kg a.i./ha and 10 applications per season is also proposed for a seasonal total of 60 kg a.i./ha.
			WP	8.0 kg/ha [typical 6 kg/ha]				
			SN	8.3 kg/ha				
Tomatoes (greenhouse)	Early and late blights, and Septoria leaf spot	Ground	DF, WG, WP	1.8 kg/ha	(9.0 kg/ha)	not stated [5]	7-12 [7]	There was no maximum seasonal rate supported collectively by all registrants. The calculated maximum rate per crop cycle is based on the maximum label rate multiplied by the maximum proposed number of applications from the registrants.

Site(s)	Pest(s)	Application Methods and Equipment	Formulation Type[4]	Application Rate (kg a.i./ha) unless stated otherwise		Maximum Number of Applications per Year [5,6]	Typical/ Recommended Number of Days Between Applications [5]	Comments [7]
				Maximum Single [5]	Maximum Cumulative [5]			
Use-site category 7: Industrial Oilseed Crops and Fibre Crops								
Alfalfa grown for seed (Minor Use)	Leaf spot and stem spot	Ground	DF, WG	1.095 kg/ha	3.285 kg/ha	3	7-10 [7 to 14]	The calculated maximum seasonal rate is based on the maximum label rate for this site and the maximum number of applications from the labels.
Use-site category 10: Seed Treatments Food and Feed								
Barley seed	False, loose and covered smut	Drill box OR slurry treatment with Panogen and Mist-O-Matic machines	WP	26.4 g/25 kg seed	(127.9 g/ha assuming a maximum seeding rate of 121.1 kg seed/ha)	1	Not applicable	The maximum seasonal rate per her ha depends on the seeding rate.
Corn seed	Root rot and seedling blight	Drill box OR slurry treatment with Panogen and Mist-O-Matic machines	WP	44.8 g/25 kg seed	(51.8 g/ha assuming a maximum seeding rate of 28.9 kg seed/ha)	1	Not applicable	
Flax seed	Damping off and seed decay	Drill box	WP	44.8 g/25 kg seed	(80.3 g/ha assuming a maximum seeding rate of 44.8 kg seed/ha)	1	Not applicable	
Oats seed	Loose and covered smut	Drill box OR slurry treatment with Panogen and Mist-O-Matic machines	WP	36.8 g/25 kg seed	(168.2 g/ha assuming a maximum seeding rate of 114.3 kg seed/ha)	1	Not applicable	
Potato seed (cut or whole)	Fusarium seed piece decay	Not specified	DU, WP	80 g/100 kg seed	(1614.4 g/ha assuming a typical seeding rate of 2018 kg seed/ha kg and a single application)	2 [1]	Not applicable	The maximum rate per ha depends on seeding rate. Some labels allow for a second application, on treated whole seed that are cut; as this occurs rarely, the registrant has proposed consideration of a single application on this site. This may be more representative of the use pattern.
Potato seed piece (for on farm use only)	Fusarium dry rot (*Fusarium* spp.)	seed dust metering applicator	DU	45 g per 100 kg of seed pieces	(908.1 g/ha assuming a typical seeding rate of 2018 kg seed/ha)	1	Not applicable	The maximum rate depends on seeding rate.

Site(s)	Pest(s)	Application Methods and Equipment	Formulation Type[4]	Application Rate (kg a.i./ha) unless stated otherwise		Maximum Number of Applications per Year [5,6]	Typical/ Recommended Number of Days Between Applications [5]	Comments [7]
				Maximum Single [5]	Maximum Cumulative [5]			
Seed potatoes in storage (Minor Use)	Fusarium dry rot	Not specified	SN	760 g/1000 kg seed	760 g/1000 kg seed (postharvest treatment)	1	Not applicable	The maximum seasonal rate is not calculable on a surface area basis as this is a postharvest treatment, before storage.
Wheat seed	Stinking smut or bunt	Not specified	WP	20.8 g/25 kg seed	(145.5 g/ha) assuming a maximum seeding rate of 174.9 kg seed/ha)	1	Not applicable	Maximum seasonal rate per ha depends on seeding rate.
Use-site category 13: Terrestrial Feed Crops[8]; and Use-site category 14: Terrestrial Food Crops								
Apples	Cedar apple rust, scab and quince rust	Ground	DF	4.5 kg/ha	[28.8] (see comments)	not stated [6]	not stated [7-10]	The maximum seasonal rate proposed by all registrants collectively is based on 6 applications at the maximum rate of 4.8 kg a.i./ha.
			WG	4.5 kg/ha at 3000 L/ha				
			SN, WP	4.8 kg/ha at 3000 L/ha				
Potatoes (foliar)	Early blight and late blight	Ground and aerial equipment Except DF and SN formulation (Ground only)	DF	1.68 kg/ha	[18.0] (see comments)	not stated [10]	[7-10]	The maximum seasonal rate proposed by all registrants collectively is based on 10 applications at 1.8 kg a.i./ha. Typical number of applications is reported to range from 8 in the Maritimes to 6 in Quebec to 3 in Manitoba to 2 in Alberta.
			SN	1.856 kg/ha				
			WG	1.688 kg/ha				
			WP	1.8 kg/ha				
Wheat (all varieties)	Tan spot, Septoria leaf blotch, and leaf rust	Ground or aerial application equipment	DF	1.688 kg/ha	[2.7] (see comments)	2 [1+1] (see comments)	[NA, depends on crop stage]	The maximum seasonal rate proposed by all registrants collectively is based on one application at one half rate at vegetative stage and one application at the maximum rate of 1.8 kg a.i./ha at heading.
			SN	1.856 kg/ha				
			WG	1.69 kg/ha				
			WP	1.8 kg/ha				
Use-site category 14: Terrestrial Food Crops								
Carrots	Alternaria and Cercospora blights and leaf spot diseases	Ground	DF, WG	1.687 kg/ha	[10.8] (see comments)	not stated [6]	[7-10]	The maximum seasonal rate proposed by all registrants collectively is based on 6 applications at the maximum rate of 1.8 kg a.i./ha.
			SN	1.855 kg/ha				
			WP	1.8 kg/ha				

Site(s)	Pest(s)	Application Methods and Equipment	Formulation Type[4]	Application Rate (kg a.i./ha) unless stated otherwise		Maximum Number of Applications per Year [5,6]	Typical/ Recommended Number of Days Between Applications [5]	Comments [7]
				Maximum Single [5]	Maximum Cumulative [5]			
Cantaloupe	Downy mildew, anthracnose, scab, gummy stem blight and Alternaria leaf spot	Ground	DF	2.437 kg/ha	[20.8] (see comments)	not stated [8]	[7]	The maximum seasonal rate proposed by all registrants collectively is based on 8 applications at 2.6 kg a.i./ha for "fruiting vegetables".
			SN	2.686 kg/ha				
			WG	2.438 kg/ha				
			WP	2.6kg/ha				
Cucumbers	Downy mildew, anthracnose, scab, gummy stem blight and Alternaria leaf spot	Ground	DF, WG	2.438 kg/ha	[20.8] (see comments)	not stated [8]	5-7 [7-12]	The maximum seasonal rate proposed by all registrants collectively is based on 8 applications at 2.6 kg a.i./ha for "fruiting vegetables".
			SN	2.686 kg/ha				
			WP	2.6kg/ha				
Celery	Early and late blight	Ground	DF, WG	2.438 kg/ha	[10.8] (see comments)	not stated [6]	[7-12]	The maximum seasonal rate proposed by all registrants collectively is based on 6 applications at 1.8 kg a.i./ha.
			SN	1.855 kg/ha				
			WP	1.8 kg/ha				
Ginseng	Alternaria leaf blight	Ground	DF, WG	3.3 kg/ha	21.4	6	[14]	
			SN	3.565 kg/ha				
			WP	3.52 kg/ha				
Grapes	Downy mildew	Ground	DF	1.5 kg/ha	[21.6] (see comments)	6	[10-14]	The maximum seasonal rate proposed by all registrants collectively is based on 4 applications at 5.4 kg a.i./ha. This applies to the WP formulation only.
			WG	1.6 kg/ha		1		
			WP	5.4 kg/ha		[4]		
Lentils	Anthracnose and Ascochyta blight	Ground or aerial application equipment	DF, WG	1.688 kg/ha	6.69	3	[10-14]	Registered but not used to any significant extent.
			SN	2.23 kg/ha				
Head lettuce (Minor Use)	Downy mildew (*Bremia lactucae*)	Ground	WG	1.6 kg/ha	4.836	3	14	
			WP	1.612 kg/ha				
Melons	Downy mildew, Anthracnose, scab, gummy stem blight and Alternaria leaf spot	Ground	DF, WG	2.437 kg/ha	[20.8] (see comments)	not stated [8]	[7-14]	The maximum seasonal rate proposed by all registrants collectively is based on 8 applications at 2.6 kg a.i./ha.
			SN	2.686 kg/ha				
			WP	2.6kg/ha				
Onions (including dry bulb) foliar (Minor Use)	Botrytis leaf blight and neck rot, downy mildew and purple blotch	Ground	DF, WG	2.438 kg/ha	[26.0] (see comments)	not stated [10]	7-10 [7-12]	The maximum seasonal rate proposed by all registrants collectively is based on 10 applications at the maximum rate of 2.6 kg a.i./ha.
			SN	2.686 kg/ha				
			WP	2.6 kg/ha				

Site(s)	Pest(s)	Application Methods and Equipment	Formulation Type[4]	Application Rate (kg a.i./ha) unless stated otherwise		Maximum Number of Applications per Year [5,6]	Typical/ Recommended Number of Days Between Applications [5]	Comments [7]
				Maximum Single [5]	Maximum Cumulative [5]			
Onions (dry bulb) in furrow (Minor Use)	Onion smut (*Urocystis cepulae*)	Ground	DF, WG	6.6 kg/ha	6.6	1	Not applicable	
Pears	Pear psylla	Ground	WP	5.4 to 7.2 kg/ha	[21.6] (see comments)	not stated [4]	[7-10]	The maximum seasonal rate proposed by all registrants collectively is based on 4 applications at 5.4 kg a.i./ha.
Pumpkins	Downy mildew, anthracnose, scab, gummy stem blight and Alternaria leaf spot	Ground	DF, WG	2.437 kg/ha	[20.8] see comments)	not stated [8]	[7- 14]	The maximum seasonal rate proposed by all registrants collectively is based on 8 applications at 2.6 kg a.i./ha for “cucurbits and fruiting vegetables”.
			SN	2.686 kg/ha				
			WP	2.6kg/ha				
Sugar beets	Cercospora leaf spot	Ground	DF, WG	1.687 kg/ha	(12.6) (see comments)	[7]	[7- 10]	The maximum seasonal rate proposed by all registrants collectively is based on 7 applications at 1.8 kg a.i./ha. This refers to DF and WG products for which the maximum number of applications is not stated on the label.
			WP	1.8 kg/ha		5		
Squash	Downy mildew, anthracnose, scab, gummy stem blight and Alternaria leaf spot	Ground	DF, WG	2.438 kg/ha	[20.8] (see comments)	not stated [8]	[7-14]	The maximum seasonal rate proposed by all registrants collectively is based on 8 applications at 2.6 kg a.i./ha for “fruiting vegetables”.
			SN	2.686 kg/ha				
			WP	2.6kg/ha				
Tomatoes	Early and late blights, gray leaf spot (*Stemphyllium* sp.) and Anthracnose	Ground	DF, WG	2.438 kg/ha	[18.2] (see comments)	not stated [7]	[7-10]	The maximum seasonal rate proposed by all registrants collectively is based on 7 applications at 2.6 kg a.i./ha.
			SN	2.686 kg/ha				
			WP	2.6 kg/ha				
Watermelons	Downy mildew, anthracnose, scab, gummy stem blight and Alternaria leaf spot	Ground	DF, WG	2.438 kg/ha	[20.8] (see comments)	not stated [8]	[7-14]	The maximum seasonal rate proposed by all registrants collectively is based on 8 applications 2.6 kg a.i./ha for “cucurbits and fruiting vegetables”.
			SN	2.686 kg/ha				
			WP	2.6kg/ha				

Minor Use = Use was registered as a User Requested Minor Use label Expansion (URMULE).
NA = Not Available.
[ ] Values in square brackets provided by the Canadian Technical Registrants.
( ) Values in round brackets calculated by the PMRA.

[1] Uses for discontinued products or products with a submission for discontinuation are not included.
[2] All label uses are supported by the technical registrants.

[3] Where the Mancozeb Canadian Technical Registrants Task Force has recommended a cumulative seasonal rate, only this has been included in this table.
[4] DF = Dry Flowable, DU= Dust or Powder, SN = Solution, WG = Wettable Granules, WP = Wettable Powder.
[5] Unless indicated by square [ ], or round brackets ( ), the application information is from the registered labels.
[6] Provinces may have differing application practices due to varying pest pressures and the presence of specific pests in a province.
[7] This is an interpretation summary of data provided by the registrants.
[8] Note that most individual end-use product labels may preclude feed uses of crops treated with mancozeb (for example, no use of pomace as animal feed), while some labels are silent in this regard.

Appendix III Toxicity Profile and Endpoints for Health Risk Assessment for Mancozeb and ETU

Table 1 Toxicology Profile for Mancozeb from the PMRA and Foreign Reviews

NOTE: Effects noted below are known or assumed to occur in both sexes unless otherwise specified.

Penncozeb is Mancozeb plus oil to increase rain fastness.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Metabolism/Toxicokinetic Studies			
Absorption Distribution Metabolism Elimination Mice, CD-1 PMRA# 1570258	14C-ethylene-U-labelled mancozeb, 2.5 or 150 mg/kg bw, single oral or repeat 14 days. Purity: 98–99%		Absorption: rapid, whole blood peaking at 1 hour for ♂ and 2 hrs for ♀. Extensively metabolized. Rapidly excreted (>90% by 24 h), 97% by day 7. Predominant distributions to thyroid, bone, ovaries, spleen, lungs, kidneys, liver, adrenal, thymus and whole blood. Metabolites (urine): ETU, ethylene thiuram monosulfide, EBIS, ethyl-thiourea-N-thiocarbamide (ETT), N-acetyl-ethlenediamine (N-acetyl-EDA), ethylenediamine (EDA), ethylene urea (EU), creatine and allantoin. 6 unknown metabolites. Feces: ETU, ethylenethiuram monosulfide, EBIS, ETT, EDA, EU and N-acetyl-EDA. Recovery: urine: 26–44%; feces: 48–64%; exhaled: 0–4%; 1.4% remained in the carcass. ETU recovery <1–3% of the dose.
Absorption Distribution Metabolism Elimination Rats, Sprague Dawley (SD) 3/sex PMRA# 1248572, 1215584, 1215586	A. Single oral dose of 1.5 mg/kg bw B. Single oral dose of 100 mg/kg bw C. Pulse oral of 1.5 mg/kg bw, followed by 2 wks dietary D. 1.5 mg/kg bw and bile cannulation E. 100 mg/kg bw and bile cannulation.		Non-linear kinetics between 1.5 and 100 mg/kg bw. Absorption moderately rapid (peak levels at 3 and 6 hours, 1.5 and 100 mg/kg bw, respectively). Elimination was biphasic. Most of the oral dose eliminated by 24h, evenly divided between feces and urine. 2–8% in bile. Plasma elimination t1/2 4.0 and 5.7h for ♂, low and high dose resp., and 4.5 and 6.0h for ♀, low and high dose resp. Principle metabolite found in urine was ETU (30.8–42.7%). ETU in feces and bile was 2.4–4.1% at 1.5 mg/kg bw and 11.2–14.5% at 100 mg/kg bw. Other metabolites were EU, N-acetyl EDA, EBIS, EDA, N-acetyl glycine and glycine. Peak levels in thyroid were about 45 and 10 times higher than whole blood levels. The estimated bioavailability of ETU following the oral dose of 100 mg/kg bw ^{14}C-labelled mancozeb was 3.1–6.4% of the absorbed ^{14}C-mancozeb-derived ^{14}C-label. ETU was rapidly eliminated from the plasma of rats with a calculated t½ for elimination of 3.9–4.7 h. Level of radiolabelled ETU in the liver ranged from 7.9–8.6% at 1.5 mg/kg bw to 0.9–1.1% at 100 mg/kg bw and in the thyroid from non-detectable levels of 1.5 mg/kg bw to 0.4–3.4% of the tissue radio label at 100 mg/kg bw, respectively. Levels of mancozeb in the blood (3.6–11.9%) and in the liver (0.05–1.5%) were detected only at the 100 mg/kg bw level.
Absorption Elimination Monkeys, Rhesus 6 ♂/group	single oral dose of 14C-ETU; ETU + manganous sulfate and zinc sulfate; mancozeb 100 uCi		Supplemental study to determine the uptake into blood and the major route of elimination. ETU and ETU + Mn, Zn sulfate: peak levels of 5% of dose in whole blood at 8h. Rapid decline at 72h (1%). 50% of dose cleared by 24h. Fecal elimination < 1% at 24h. Mancozeb: peak level of 0.5% of dose at 8h, plateaued at 24–72h (1% of

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
PMRA# 1619137		dose). Clearance 3.6% at 24h (much slower). Fecal 12.5–64% at 144h and 0.005–12.7% at 24h. Activity in thyroids ↑ over 48h.	
Acute Toxicity Studies			
Oral Rats, F344, ♂ PMRA# 1570258		LD50 > 5000 mg/kg bw **Low Toxicity**	
Dermal Rabbits, (New Zealand White) NZW, ♂ PMRA# 1248590		LD50 > 5000 mg/kg bw **Low Toxicity**	
Inhalation Rats, SD PMRA# 1570258	4-h inhalation	LC50 > 5.14 mg/L **Low Toxicity**	
Eye Irritation Rabbits PMRA# 1570258	100 mg Purity: >80%	"Substantial irritation at 4, 24, 48, 72 and 96 hours and on days 7, 14, and 22." **Severely Irritating**	
Skin Irritation Rabbits PMRA# 1570258	500 mg applied to intact and abraded skin	Irritation score 0.5 **Slightly Irritating**	
Skin Sensitization Guinea Pigs, Hartley, ♀ PMRA# 1248575, 1248576	Maximization test	**Positive**	
Skin Sensitization Guinea Pigs, Hartley PMRA# 1570258	Buehler	**Negative**	
Subchronic Toxicity Studies			
3 month, dietary Mice, CD-1 15/sex/group PMRA# 1570228	♂: 0, 1.78, 18.13, 166.9 or 1662.5 mg/kg bw/d ♀: 0, 2.34, 21.68, 233.8 or 2160 mg/kg bw/d Purity: 83%	18.13/21.68	**≥ 166.9/233.8 mg/kg bw/d**: ↓ aminopyrine N-demethylase (♂), ↑ thyroid follicular cell hyperplasia and hypertrophy **1662.5/2160 mg/kg bw/d:** ↓ bw, fc, aniline hydroxylase, ↑ abs + rel thyroid wt, rel liver wt, abs liver wt (♂), ↑ rel kidney wt, thyroid vacuolation, interstitial conjestion, ↓ colloid density, ↑ brown pigment in zona reticularis of adrenal cortex (♀)

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
90-day, dietary Rat, SD 14/sex/group Special, in combo with mancozeb and ETU PMRA# 1570229	**Mancozeb**: 0, 30, 60, 125, 250, 1000 ppm ♂: 0, 1.78, 3.49, 7.42, 14.98, 57.34 mg/kg bw/d ♀: 0, 2.20, 4.38, 9.24, 17.82, 76.64 mg/kg bw/d Purity: 84% **ETU**: 250 ppm 14.28/17.81 mg/kg bw/d Purity: 99%	**Mancozeb** ♀: 9.24 ♂: 14.98 No NOAEL for **ETU**, since only one dose was tested.	Mancozeb animals' urine, blood and thyroids were analyzed for EBDC and ETU. Majority of mancozeb metabolized to ETU and was excreted in the urine. Only ETU was found in the thyroid. **Mancozeb:** **≥17.82 mg/kg bw/d**: ♀: ↓ thyroxine levels **57.34/76.64 mg/kg bw/d**: ↓ bw, bwg, T_4, ↑ TSH, changes in liver enzymes, microscopic changes in the liver and thyroid (follicular cell hyperplasia), ↑ abs and rel thyroid wts, ↑ rel liver wts; ↑ centrilobular hepatocyte hypertrophy (♀) **ETU:** **14.28/17.81 mg/kg bw/d**: ↓ bwg, fc; ↑ serum cholesterol, and rel liver and thyroid wt, ↓ T_4, ↑ T_3 and TSH, and thyroid lesions; centrilobular hepatocyte hypertrophy with ↓ hepatic MFO activity
28-day, dermal Rats, SD 10/sex/group PMRA# 1621859	0, 10, 100 or 1000 mg/kg bw/d Purity: 83%	Systemic and dermal ≥1000	**Dermal** Erythema was transient and slight, all doses, 2/sex, 2-4 days. **Systemic** **at 1000 mg/kg bw/d:** ↑ T_3 (♂), no supportive pathology
4 wk or 13 wk, inhalation (nose-only) Rats, SD 38/sex/group PMRA# 1220614	**4 wks**: analytical: 0, 5.7, 22.4 or 80.3 mg/kg bw/d respirable: 0, 2.1, 10.4 or 33.1 mg/kg bw/d **13 wks:** analytical: 0, 4.7, 20.6 or 85 mg/kg bw/d respirable: 0, 2.1, 9.4 or 37.6 mg/kg bw/d)	**9.4**/20.6 (13 wk respirable/analytical)	(Analytical/respirable) 4 wks **80.3/33.1 mg/kg bw/d**: ↓ bw, bwg (♂) 13 wks **85.0/37.6 mg/kg bw/d**: ♂: ↓ bw and bwg, ↓ heart, kidney wt and triglycerides; ♀: ↓ T_4, thyroid hyperplasia, ↑ MCV and ↓ MCHC
90-day Dogs, Beagle 6/sex/group PMRA# 1220603	0, 0.3, 3, 29, 101 mg/kg bw/d Purity: 83.35%, adjusted to 100%	3	**≥ 29 mg/kg bw/d**: dehydration, ↓ fc, bwg, ↑ thymic cortical lymphoid depletion, ↓ thymus size, dark thyroid/parathyroid; ♀: ↓ rbc, hct, hgb, ↑ cholesterol; ♂: prostate hypogenesis **101 mg/kg bw/d**: marked ↓ bw, bwg, fc (anorexic), 2/sex sacrificed in extremis; ↓ T_3, T_4, ALT, ALP, ↑ thyroid wt and thyroid follicular cell hyperplasia, pallor of adrenal zona fasciculata; ♂: ↑ cholesterol, ↓ abs testis wt, hypogenesis of prostate, testes, aspermato/hypospermatogenesis; ♀: ↑ MCV, bilirubin, ↓ calcium, hypogenesis of ovaries.
1-year, dietary Dogs, Beagle 4/sex/group PMRA# 1132298	♂: 0, 1.75, 7.26, 27.26, 53.5 mg/kg bw/d ♀: 0, 1.84, 7.0, 29.24, 59.72 mg/kg bw/d Purity: 84.5%, adjusted to 100%	♂: 1.75 ♀: 7.0	**≥ 7.0/7.26 mg/kg bw/d**: ↓ bwg (♂) **≥ 27.26/29.24 mg/kg bw/d**: ♀: ↓ hgb, packed cell volume, ↑ serum cholesterol **53.5/59.72 mg/kg bw/d**: ↑ abs and rel thyroid wt, thyroid follicular distention and cholesterol; 2 ♂ killed in extremis (had regenerative anemia, necrosis and congestion of kidney)

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
1-year, gelatin capsule Dogs, Beagle 4/sex/group PMRA# 1624089, 1624090	study A: 0, 2.3, 23, 113 mg/kg bw/d study B: single dose, 40 mg/kg bw/d, post study A Purity: 88.6%	2.3	**≥23 mg/kg bw/d**: ↓ fc; ♂: ↓ T_4, ↑ thyroid wt; ♀: ↓ bwg, ↑ liver wt **≥40 mg/kg bw/d**: ↑ MCV,↓ MCHC, T_3 and T_4, swollen spleen, ♀: ↓ bw, bwg, ALT, ↑ ALP, ↑ thyroid wt **113 mg/kg bw/d**: all animals sacrificed in extremis by 26 wks. Animals had severe anemia, ↑ ALT, AST, urea, total bilirubin, cholesterol. *no effect on bwg in males, does not support the above 1-year dog study.
Neurotoxicity			
Acute neurotoxicity, gavage Rats, Fischer 344 10/sex/group PMRA# 1571642	0, 500, 1000 or 2000 mg/kg bw Purity: 83.8%	LOAEL: 500	**≥ 500 mg/kg bw**: all treated animals had decreased total session motor activity on Day 1 **2000 mg/kg bw**: degeneration of individual nerve fibre with myelin ovoid formation in proximal sciatic nerve (1 ♂) and the tibial nerve (2 ♂)
90-day neurotoxicity, dietary Rats, SD 10/sex/group PMRA# 1621862	♂: 0, 1.3, 8.2, 50 or 339 mg/kg bw/d ♀: 0, 1.7, 10.5, 63 or 412 mg/kg bw/d Purity: 79.3%	8.2	In the high dose, 1/sex died. ♀ in high dose were given food only by 5th week on test because of significant toxicity (MTD exceeded). **≥50/63 mg/kg bw/d:** ↑ neuro-histopathological lesions (demyelination, myelin phagocytosis, Schwann cell effects, muscle atrophy of hindlimbs); ♀: ↓ bw, bwg. **339/412 mg/kg bw/d:** animals had abnormal gait, weakness, limited use of hind limbs; ♂: ↓ bw, feed efficiency
in vitro neuron toxicity Rats, SD mesencephalic neurons PMRA# 1852273	10, 30, 60, 120 µM mancozeb, maneb, and nabam for 24 hours		↓ number (dose-dependent) of thyrosine hydroxylase (TH)-positive cells noted in cells treated with mancozeb and maneb; ↓ (dose-dependent) cellular dopamine (DA) and gamma-aminobutyric acid (GABA) uptake also observed with mancozeb and maneb Experiments with nabam suggest that the combination of the organic portion and the metal component of the EBDC fungicides contribute to toxicity in DA and GABA neurons. Dose-dependent ↓ in ATP. **Study considered supplemental**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
in vitro neuron toxicity Rat, SD - mesencephalic cells in vitro PMRA# 1852274	30 µM mancozeb (and 3, 10, 30, 60 µM with other treatments)		Cells treated with an antioxidant (ascorbate) and antioxidant enzyme (Superoxide dismutase) were protected from mancozeb's toxicity, indicating that oxidative stress contributes to mancozeb's effect. 92% of exogenously applied mancozeb remains outside the cell membrane. H_2O_2 generation experiments indicate that reactive oxygen species (ROS) generation occurs primarily extra-cellularly, but mancozeb also ↑s intracellular ROS. Mancozeb's toxicity through ROS generation may involve redox cycling with cellular oxidases such as xanthine and xanthine oxidase since ROS production was ↑ by 37% when these were co-administered with mancozeb. The organic portion of mancozeb in combination with the associated Mn metal may contribute to ROS generation and subsequent toxicity. This finding is based on minimal toxic effect observed (H_2O_2 formation) with nabam (Na ion instead Mn ion is present) that is ↑ when $MnCl_2$ is co-administered. In addition microglia (a major source of NADPH oxidase) contribute to extracellular peroxide generation induced by mancozeb exposure (but are not required). **Mancozeb is identified as pro-oxidant neurotoxicant.** This may be the mechanism of retinal degeneration in the chronic rat study (see below). **Study considered supplemental**
Chronic Toxicity/Oncogenicity Studies			
78-week Mice, CD-1 60/sex/group PMRA# 1624094	0 or 25 ppm or 0, 100 or 1000 ppm ♂: 0, 4, 14 and 144 mg/kg bw/d ♀: 0, 5, 17 and 187 mg/kg bw/d Purity: 88.6%	14/17	10/sex sacrificed at 52 wks. Originally 7000 ppm group, but at wk 60, excessive tox, group removed and 25 ppm group added with own control. **144/187 mg/kg bw/d:** ↓ bwg, ↑ benign liver tumours (♂: 8, 5, 17). **Study considered supplemental**
78-week Mice, CD-1 94/sex/group 24/sex/group interim sacrifice at 12 months PMRA# 1132299	0, 30, 100 and 1000 ppm Purity: 83%, adjusted to 100%	100 ppm ≈13 mg/kg bw/d	**at 1000 ppm**: "minimal" ↓ in bw, bwg, T_3, T_4 *USEPA did not calculate on a mg/kg basis because of test article instability during wks 52-80. The PMRA concurs.*

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
ETU 2 yr with repro dosing (explained in results), dietary Mice, B6C3F1 n = 60 variable #/sex/group 10/sex/group sacrificed at 9 months PMRA# 1570233, 1805515	**Perinatal**: 0, 33, 110 and 330 ppm **Adult**: 0, 330, 1000 ppm for 2 yrs, one group received 100 ppm for 2 yrs. Further explained in results. Purity: 99% Study combined a perinatal exp (in utero and throughout suckling) with traditional NTP chronic bioassay. Female mice (F_0 generation) were fed a diet of 0, 33, 110 or 330 ppm ETU for 1 wk before breeding. After mating all females were kept on the ETU diet. On postpartum day 7 the litters (F_1) were standardized to 8, weaned on day 28 and separated by sex. Exposure continued and at 8 weeks the pups were divided into 60/sex at concentrations of 0, 330 and 1000 ppm. 10/sex were sacrificed at 9 months and 50/sex were sacrificed after 2 years.	Standard adult conversions from ppm to mg/kg bw/d: 100, 330 and 1000 ppm = 15, 50 and 150 mg/kg bw/d	Dose regime: 10 ♀ exposed to 0, 33, 110 or 330 ppm of ETU in feed for 1 wk prior to breeding (to ♂ on control diet) and throughout pregnancy and lactation. Weaning on day 28 postpartum and maternal exp continued until pups were 8 wks of age. On postpartum day 7, litters culled. At 8 wks, pups (60/sex) received 0, 330 or 1000 ppm for 2 yrs. Groups of 34 ♂ and 29 ♀ fed 33 ppm (perinatal) received 100 ppm for up to 2 yrs. **Thus, the following ppm exposures:** **Perinatal-only: 0–0; 330–0** **Adult-only: 0–0; 0–330; 0–1000** **Perinatal + Adult: 33–100; 110–330; 330–330; 330–1000** 9 months All adult exposed mice had centrilobular hepatocellular cytomegaly, ↑ hepatocellular adenomas. at1000 ppm ♀: eosinophilia foci. ↑ abs and rel liver wts in groups receiving adult concentrations, regardless of perinatal exp. at adult exp of 1000 ppm, ↑ abs thyroid wts, T_3 and TSH (♂). Adult-only and perinatal-adult exposures: ↑ cytoplasmic vacuolization of the follicular epithelium (thyroid). 2-years Except for perinatal-only exp, all doses had ↓ bw. **Perinatal-only Exp**: no effects noted. **Adult-only Exp (330 and 1000 ppm)**: Thyroid: **330 ppm:** diffuse cytoplasmic vacuolization, focal hyperplasia, and neoplasia. **at 1000 ppm**: follicular cell adenomas or carcinomas with multiple or bilateral neoplasms (70%). ♀ more susceptible. Liver: **300 ppm**: diffuse centrilobular hepatocellular cytomegaly, marked ↑ in hepatocellular adenomas/carcinomas (♀)[2/50, 33/50 and 14/50 adenomas; 2/50, 29/50 and 47/50 carcinomas for control, low and high doses respectively] **at 1000 ppm**: ↑ hepatocellular carcinomas (♂). Multiple hepatocelluar neoplasms, with carcinomas metastasizing to the lung. Rare hepatoblastomas also occurred, particularly in ♂. Pituitary: **at 1000 ppm**: ↑ focal hyperplasia or adenoma of pars distalis (♂) and ♀: ↑ adenoma (but not hyperplasia). **Combined Perinatal-Adult Exp:** Thyroid, Liver, Pituitary: **330–330 ppm**: marginal ↑ of non-neoplastic and neoplastic lesions in all 3 organs, but not seen at the 330–1000 ppm dose. ♂: all had a marginal↑ in follicular cell hyperplasia.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
2 year dietary study, with repro dosing/ Rats - Fischer F44 **ETU** variable #/sex/dose, n = 60 10/sex/dose sacrificed at 9 months This study is part of the onco mouse study reported above. PMRA# 1570233	**Perinatal**: 0, 9, 30, 90 ppm **Adult**: 0, 25, 83 and 250 ppm for 2 yrs. Standard conversions would be 1.25, 4.15 and 12.5 mg/kg bw/d Purity: 99% Female rats were fed a diet containing 0, 9, 30 or 90 ppm ETU for 1 wk before breeding. After breeding, dosing continued and on PND 4 litters were standardized to 8 and weaned on day 28. Pup exposure continued for 8 wks and then divided into groups of 50/sex and exposed to adult concentrations of 0, 25, 83, and 250 ppm. *This study, combined with the Schmid study above, fulfills the chronic/onco rat data requirement.	**F_0:F_1 ppm treatments were as follows:** 0:0, 0:83, 0:250, 90:0, 90:83, 9:250, 30:83 and 9:25 ppm 9 months **0–83, 0–250, 90–83 and 90–250 ppm**: ↑ abs and rel liver wt (♂), **0–250 and 90–250 ppm:** ↑ thyroid wt. **0–83, 0–250, 30–83, 90–83 and 90–250 ppm**: ↑ thyroid follicular cell hyperplasia **90–250 ppm:** ↑ thyroid follicular cell adenomas. Except for **90–0 ppm**, all dose groups had ↓ T_4 and ↑ TSH. 2-yr **Perinatal-only Exp:** Thyroid: ↑follicular cell hyperplasia (dosed animals 18–64%, conrol: 0–9%) **Adult-only Exp:** Thyroid: **0:83 ppm:**↑ follicular cell hyperplasia **(58% vs. 2% in control ♂, ♀: 16% vs. 4% in control)** , adenomas **0–250 ppm**: follicular cell carcinomas, ♂ appear more sensitive. Some carcinomas invaded the adjacent parenchyma and/or esophagus and trachea, and two metastasized to the lungs. Thyroid tumour incidence in adult-only exposure was (1/49, 12/46, 37/50 for males and 3/50, 7/44, 30/49 at 0, 83 and 250 ppm, resp) **Combined Perinatal-Adult Exp:** Thyroid: **90–83 and 90–250 ppm**: ↑ follicular cell hyperplasia (♂), this was greater than that observed at 0–83 ppm, indicating some type of perinatal action. There was a similar effect with follicular adenomas/carcinomas. For males, tumour incidence was as follows: 3/46, 14/47, 13/50 and 48/50 for 9:25, 30:83, 90:83 and 90:250 ppm exposures, resp. Other Organs: **90–83 and 90–250 ppm**: ↑ neoplasms of the Zymbal's gland and mononuclear cell leukaemia.	
2-year, dietary Rats - SD 72/sex/group PMRA# 1135743	♂: 0, 0.8, 2.3, 4.8 or 31 mg/kg bw/d ♀: 0, 1.1, 3.1, 6.6 or 40 mg/kg bw/d Purity: 83.8% Corrected for purity	NOAEL 3.1 See Agricultural Health study below and bilateral retinopathy	**≥ 3.1 mg/kg bw/d**: mild bilateral retinopathy (♀: 21, 28, 24, 31 and 49, control to high dose, respectively) onset after 1-year exposure **31/40 mg/kg bw/day**: ↓ bw, bwg; bilateral retinopathy (♂: 4, 2, 1, 3, and 19, control to high dose, respectively), ↓ T_4, ↑ TSH and T_3, abs and rel thyroid wt, thyroid follicular hypertrophy, hyperplasia, nodular hyperplasia, adenomas and carcinomas (more prevalent in ♂) [♂: 0,1,3,2,34] A clear mode and mechanism of action are available for the thyroid tumours and thus, a MOE approach was utilized.
60 week oncogenicity, dermal Mice, Swiss (albino) n = 20 PMRA# 1852268	100mg/kg (95%) 3/week		After the first five days of topical mancozeb treatment the animals experienced loss of fur, sluggish movement and ↓ fc and bw after 30 wks. Complete disappearance of fatty layer below the skin after 50–52 weeks of treatment. Benign tumours were first noted after 217 days (31 weeks with 17/20 surviving animals) and 5/14 of animals by wk 48. Final average was 1.8 tumours per mouse at study termination. **Study considered supplemental**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Oncogenicity, intraperitoneal Mice, Swiss (albino) First given to ♀ gd 14 through to F_1 for 6 weeks PMRA# 1852271	DMBA (10 mg/kg bw) + TPA, DMBA (10 mg/kg bw in corn oil) + acetone, Mancozeb (100 mg/kg bw in DMS)+ TPA, DMSO + TPA, Mancozeb (100 mg/kg bw in DMSO) + acetone		Mancozeb and TPA treated mice showed an ↑ (72%) in tumour incidence with the average of 1.91 tumours per F_1 animal. DMSO and TPA treated animals showed no tumour development. Mancozeb and acetone treated mice showed a 10% tumour incidence with the average of 1.5 tumours per F_1 animal. *Although tumour sites not reported, mancozeb and its metabolites can cross placental barrier and exert DNA damage and initiate cells that, after promotion with a tumour promotor, progress to neoplastic cells.* **Study considered supplemental**
Lifetime chronic toxicity Rats, SD 75 sex/group PMRA# 1852269	0, 10, 100, 500 and 1000 ppm (85%)		Typically, in a chronic study, rats are terminated after 104 weeks of treatment. In this study, animals were treated until spontaneous death. Although there was an ↑ in total malignant tumours, there was no dose-reponse for individual tumours. Also, most tumours were noted at 112 weeks, after the standard termination date. This study design is problematic because it is difficult to separate natural old age tumours from actual treatment-related tumours. **Study considered supplemental**
Human Epidemiology Agricultural Health Study PMRA# 1852275	As part of the ongoing Agricultural Health Study in Iowa and North Carolina, United States, Kamel et al (2000) conducted a case-control study to examine the relationship between pesticide exposure and retinal degeneration. Study participants were 17 958 primarily Caucasian ♂ pesticide applicators (99% farmers) who completed both the enrollment and take-home questionnaires. Of these subjects, 154 applicators reported diagnosis with retinal or macular degeneration at the beginning of the study; the remaining applicators served as controls. After adjusting for age, sex, education, and state of residence, applicators reporting greater than 51 days of captan (OR=4.0, 95%CI: 2.0, 8.1), benomyl (OR=2.6, 95%CI: 1.4, 5.0), chlorothalonil (OR=2.4, 95%CI: 1.1, 5.2), **maneb** (OR=2.3, 95%CI: 1.3, 4.3), or metalaxyl (OR=2.3, 95%CI: 1.1, 4.5) exposure had significantly ↑ risks of retinal degeneration. A significantly ↑ risk of retinal degeneration was also reported for exposure to fungicides in general (OR=1.8, 95%CI: 1.3, 2.6). Sensitivity analyses were conducted excluding applicators with conditions that might have been mistaken for retinal degeneration such as cataracts, diabetes, or detached retina, but the findings were not substantially changed. In addition, stratified analyses were conducted and the observed association between fungicides and retinal degeneration was independent of carbamate and organochlorine exposures. For fungicides in general, ↑ risks were limited to applicators that used hand spray guns (OR=1.8, 95% CI: 1.1, 3.0), backpack sprayers (OR=3.1, 95% CI: 1.8, 5.5), and mist blowers/foggers (4.3, 95% CI: 1.9, 9.8); methods that may result in higher exposures. Limitations of the study included the use of prevalent cases and self-reported exposure and disease information. However, the findings presented by Kamel et al (2000) support a potential relationship between occupational exposure to specific fungicides and retinal degeneration.		

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Human Epidemiology Agricultural Health Study PMRA# 1852276	A second case-control study was conducted to examine the association between fungicide exposure and retinal degeneration among wives of farmer pesticide applicators (Kirrane et al., 2005). The study population included 31,173 women, approximately 300 of which were cases. Risk estimates were not statistically significant for specific fungicides, but elevated odds ratios were reported for **maneb/mancozeb** (OR=1.4, 95% CI: 0.6, 3.0) and ziram (OR=1.5, 95%CI: 0.4, 5.0). Potential confounding variables such as severe sunburns, fruit and vegetable intake, and husband's pesticide use were evaluated but did not substantially change model estimates. Subgroup analyses were conducted excluding women with eye disorders possibly confused with retinal degeneration but the relationship between fungicide use and retinal degeneration remained. Additional subgroup analysis according to cardiovascular disease and diabetic status revealed elevated odds ratios for fungicide exposure and retinal degeneration in all subgroups; however, the relationship between fungicide exposure and retinal degeneration was stronger among diabetics than non-diabetics. Limitations of the study included the use of prevalent cases and self-reported exposure and disease information. In general, however, the reported findings support a relationship between fungicide exposure and retinal degeneration. Specific compounds of interest include maneb/mancozeb and ziram.		
Human, Hispanic N = 139 000 PMRA# 1852270	Nested case-control study from United Farm Workers of America Union (California), studying lymphohematopoietic cancers in 131 workers. Workers exposed to a high level of **mancozeb** had a statistically significant ↑ in granulocytic leukemia (OR: 3.35; CI: 1.09–10.31; n=20). There was no ↑ in lymphocytic leukemia or NHL. When divided by sex, only ♀ exhibited an overall ↑ in leukemia (OR=4.78; CI: 1.11–20.44; n=16). Sample sizes were very small, and pesticide exposure information was ecologic. Information on potential confounding factors such as smoking, diet, alcohol consumption, and family history was not collected. Odds ratios were not adjusted for multiple pesticide exposures and correlations between different pesticides were not examined. Given these limitations, this study does not provide convincing evidence of a relationship between mancozeb exposure and lymphohematopoietic cancers.		
Human Breast Cancer Cornell University PMRA# 1852267	No evidence that **mancozeb** causes breast cancer.		
ETU (study reported above with other mouse oncogenicity studies), a metabolite of the EBDC fungicides, is currently classified by the USEPA as a B2 carcinogen, with a $q_1^* = 0.0601$ (mg/kg/day)$^{-1}$. The low dose extrapolation for human risk assessment is based on liver tumours in female mice. The PMRA concurs with this assessment and considers ETU to be the residue of concern for all EBDC fungicides.			
Immunotoxicity			
Published studies by Colosio et al, (1996; 2007) indicate that prolonged low level exposure to mancozeb causes slight immunomodulatory effect on cellular immunity. These studies were based on human data from vineyard workers in Italy. PMRA# 1852265, 1852266			
Reproductive and Developmental Toxicity Studies			
2-generation reproductive Rats, SD Penncozeb (75% mancozeb) 25/sex/group PMRA# 1624102	0, 25, 150 or 1100 ppm (0, 2.5, 15, or 110 mg/kg bw/d) Purity: 88.4%	Parental 15 Offspring 2.5 Reproductive >110	Parental **110 mg/kg bw**: ↓ bw, bwg, fc (♀) Offspring **≥ 15 mg/kg bw**: ↓ bw (PND 21, due to diet, not a lactational effect) **110 mg/kg bw**: delayed eye opening (both gens), ↓ bw (day 21, F_1; days 14–21, F_2), ↓ viability days 14–21

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
2-generation reproductive Rats - SD 25/sex/group PMRA# 1173163	♂: 0, 1.7, 7.0 or 69 mg/kg bw/d ♀: 0, 1.8, 7.5, 79.4 mg/kg bw/d Purity: 84%	Parental 7.0/7.5 Offspring 69/79 Reproductive 69/79	Parental **69/79.4 mg/kg bw**: ↓ bw (premating), ↓ bw (gestation and lactation), ↓ fc. ↑ rel liver wt, abs and rel thyroid wt, rel kidney wt, thyroid follicular cell nodular hyperplasia and adenoma; ♂: hypertrophy and/or vacuolation of cells in the pituitary Offspring no effects noted
Modified reproductive, oral Mice, Swiss albino first 8 days, additional groups dosed on day 3, days 1–3 and days 1–5 6/group PMRA# 1852272	0, 18, 24, 30 and 36 mg/kg bw/d 36 mg/kg bw/d on day 3, days 1–3, 1–5	18	5 groups were used to assess mancozeb (graded response) using doses of 0, 18, 24, 30 and 36 mg/kg bw/d on the first 8 days of pregnancy and 5 groups were used to test the temporal effect of 36 mg/kg bw on day 3 of pregnancy and on days 1–3, 1–5 and 1–8 of pregnancy. **≥24 mg/kg bw/d:** ↓ uterine wt, inhibition of implantation; significant ↓ in diestrus phase with concomitant ↑ in the estrus phase **36 mg/kg bw/d:** 75% inhibition of implantation after dosing days 1–3 and 100% dosing days 1–5 and 1–8 Organ wts after 8 days of dosing only showed decreased uterine wt - no effect on thyroid wt.
Special developmental Mancozeb/ETU Rats, albino Gavage gd 6–15 26/group PMRA# 1651466	0, 2, 8, 32, 128 or 512 mg/kg bw/d Purity: 83% ETU: 50 mg/kg bw/d Purity: 99%	**Mancozeb** Maternal 32 Developmental 128 ETU None set.	**Mancozeb** Maternal: **≥128 mg/kg bw/d**: ↓ fc (days 10–15), bw (gd 20) and bwg (throughout) **512 mg/kg bw/d**: 1 death due to treatment, 2 sacrificed due to abortion; lethargy, scruffy coat, and diarrhea Developmental: **512 mg/kg bw**: ↑ dilated brain ventricles (28 in 9 litters vs 0 in control), incomplete skull ossification, hydrocephaly, forelimb flexure, cryptorchidism, abortions, resorptions, ↓ fetal bw **ETU** Maternal: ↓ bwg (based on available data, appears to be uncorrected) Developmental: ↑ mortality, gross developmental defects, CNS defects, skeletal defects, cryptorchidism, ↓ fetal bw, exencephaly, ectopic kidneys, agenesis of kidneys, hydronephrosis, reduced stomach, edematour fat pads, less than 13 ribs, fused lumbar, sacral or caudal vertebrae, oligodactyl, syndactyl, webbed digits, anal atresia
Developmental, gavage Rabbit - NZW gd 7–19 20/group PMRA# 1132303	0, 10, 30, 80 mg/kg bw/d	Maternal 30 Developmental 30	Maternal **80 mg/kg bw/d:** abortions (1 gd 7–19; 5 gd 20–29), mortality, alopecia, ataxia, scant feces, ↓ bw and fc (5 does that aborted) Developmental **80 mg/kg bw/d**: abortions, no data on aborted fetuses provided, no embryo/fetal tox in live fetuses from any dose group

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Developmental, gavage Rabbits - NZW gd 6–18 18/group PMRA# 1624106	0, 5, 30, 55, 100 mg/kg bw/d Penncozeb (75–80% mancozeb) Purity: 88.4%	Maternal 55 Developmental 55	Maternal **100 mg/kg bw/d**: ↓ bw, fc, ↑ abortions Developmental **100 mg/kg bw/d**: ↑ abortions
Developmental, inhalation (whole body) Rats, SD gd 6–15 27/group PMRA# 1852277	0, 1, 17 or 55 mg/m^3 0, 0.31, 5.27 or 17.05 mg/kg bw/d Purity: 80%	Maternal 5.27 Developmental 5.27	Maternal **17.05 mg/kg bw/d**: ↓ bwg; hindlimb weakness and slower righting reflex after full exposure period, but disappeared during postexp recovery period. Developmental **17.05 mg/kg bw/d**: ↑ wavy rib, resorptions [average % per litter: 4.0, 2.5, 3.1, 6.1, control -high respectively], external petechial hemorrhage [5(1.8%), 4(1.8), 5(2.5) and 9(3.6)]. Study Authors: “It is concluded that, under the conditions used for the present study, mancozeb is not teratogenic in rats by inhalation exposure. Embryo-fetal toxicity was seen only at mancozeb concentrations above that tolerated by the dam.” The PMRA concurs with the study authors and have set both the maternal and developmental NOAELs at the mid-dose.
Genotoxicity Studies (from PMRA# 1570258)			
in vitro			
Salmonella reversion assay, TA1535, TA1537, TA98, TA100	2.5-250 ug/plate ± S9 Purity: 88%	Negative	
Mammalian gene mutation assay CHO/hprt	0.5–45 ug/mL Purity: 88%	Negative	
Point mutation induction	0.125–12 ug/mL, no activation	Positive	
Chromosomal aberrations, human lymphocytes	1.40 ug/mL, in propylene glycol no activation	Positive	
Unscheduled DNA synthesis Rats, Fisher ♂ hepatocytes	0.25–10 ug/ml Purity: 88%	Suggestive Positive	
Unscheduled DNA synthesis Fisher rat - ♂ hepatocytes	0.1–10 ug/mL ± S9 Purity: 82.4%	Negative	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Sister chromatid exchange CHO cells	5–20 ug/mL	Positive without activation only	
Cell transformation C3H/10T ½ cells	0.05–0.5 ug/mL Purity: 88%	Negative	
Cell transformation C3H/10T ½ cells	0.1 ug/mL, + promotion Purity: 88%	Negative	
DNA damage *E.coli* pol A strains		Positive (stronger response without activation)	
in vivo			
Sex-linked recessive lethal, In Vivo *D. Melanogaster*	5–15 mg/100mL of food	Negative	
Bone marrow cytogenetics Mice, ♂	10–1000 mg/kg milk suspension	Negative	
Bone marrow cytogenetics Rats, Wistar	Intraperitoneal injection, 2.5–10 mg/kg in propylene glycol	Positive	
Bone marrow cytogenetics Rats, Wistar	1.7 mg/kg bw/day for 280 days, in feed	Positive	
Bone marrow cytogenetics Rats, Fischer 344 ♂	4.4 g a.i./kg/day for 1 or 5 days, in corn oil Purity: 88%	Negative	
Bone marrow cytogenetics Mice, albino ♂	30–300 mg/kg	Positive	
Lymphocyte cytogenetics Rats, Wistar ♀	3–30 mg/kg, in saline	Positive	
Autosomal recessive lethals	5–15 mg/100 mL of food	Negative	
Micronucleus assay Mice, CD-1	10 000 mg/kg, in methyl-cellulose Purity: 88.2%	Negative	
Mouse host mediated assay	0.5, 2,0, 5.0 g/kg bw in corn oil	Negative	
Incident Reports			
Incident reports in the USA between 1992–2001 and published reports, involve skin rashes or contact dermatitis, nausea and dizziness. PMRA: 3 reports, 1 minor and two moderate. Related to dermal or eye irritation.			

q_1^* for female mouse liver tumours is 0.0601 (mg/kg bw/d) $^{-1}$.

Table 2 Toxicology Profile for ETU

NOTE: Effects noted below are known or assumed to occur in both sexes unless otherwise specified.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Metabolism/Toxicokinetic Studies			
Absorption Distribution Metabolism Excretion Published and unpublished data for mouse, rat, guinea pig, cat and monkey PMRA# 1805552, 1805550, 1805647, 1619137, 1805547	Various dose levels and routes		Absorption: rapid from the digestive tract. Uptake through intact skin is relatively slow. Regardless of absorption pathway, ETU accumulates primarily in the thyroid. Distribution/accumulation in the rat was as follows: thyroid>kidney>liver>brain>heart>spleen>muscle>lung>fat. ETU half-life was 28h in monkey, 9-10 hours in rat and 5 hours in the mouse. Excretion: complete and primarily in the urine (50–80%, depending on species) at 48h. Metabolism: more rapid in the mouse, compared to the rat. However, metabolism is more extensive in the rat. Metabolites include EU and other polar metabolites.
Absorption Distribution Metabolism Excretion Published and unpublished studies in mouse, rat, guinea pig PMRA# 1619136, 1805608, 1805575, 1570232	Various dose levels and routes		During all of gestation, ETU in amniotic fluid, placenta and fetal carcass correlated with maternal blood levels, but levels ↑ in maternal livers. During postpartum, ETU in maternal liver and milk was 10-fold and twofold > than maternal blood. Levels in maternal milk were 13-fold neonatal levels. Pre-treatment did not alter ETU kinetics in postpartum dams/neonates. Radioactivity peaked in mice and rats at 1.3 and 1.4 hours, respectively; maternal and fetal tissues were similar at 3 h posttreatment. The t½ for ETU elimination from maternal blood was 5.5 and 9.4 hours in mice and rats, respectively. Main route of excretion was the urine with 74 and 70% in the mouse and rat, respectively. 40% metabolites in the mouse, compared to 95% in the rat. The mouse appears to have a more rapid metabolism of ETU, while the rat is more extensive. This could be the reason developmental toxicity more severe in rat than mouse. Radioactivity in the fetus peaked at 2 h. ETU distributed homogenously throughout tissues, except thyroid (↑ in activity for first 24h). No sig difference in T4 between treated and control maternal serum, but stat sig ↑ in malformed fetuses (100%) at 100 mg/kg bw.
Acute Toxicity Studies			
Oral Mice, non-pregnant and pregnant (gd 9) PMRA# 1805563, 1805631, 1570258			LD_{50} 2400–4000 mg/kg bw (>3000 mg/kg bw for pregnant mice) **Low Toxicity**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Oral Rats, non-pregnant and pregnant (gd 13) PMRA# 1570258, 1805631, 1805563, 1805536		LD_{50}: 545–1832 mg/kg bw (600 mg/kg bw for pregnant rats) **Moderate Toxicity**	
Oral Hamsters, non-pregnant and pregnant (gd 11) PMRA# 1570258, 1805631		LD_{50} > 2400 mg/kg bw **Low Toxicity**	
Dermal rabbit PMRA# 1571628		LD_{50} > 2000 mg/kg bw **Low Toxicity**	
Inhalation Rats, SD PMRA# 1571628		LC_{50} > 10.4 mg/L	
Dermal irritation Rabbits, NZW PMRA# 1570258		**Not a dermal irritant**	
Eye irritation Rabbits, NZW PMRA# 1570258		No irritation noted, however UV light was not used with fluorescein staining.	
Sensitization Guinea Pigs,Hartley PMRA# 1805564	10 female Maximization	**Potential Sensitizer**	
Sensitization Mice, B6C3F1 ♀ PMRA# 1570258	Maximization	**Not a Sensitizer**	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Subchronic Toxicity Studies			
90-day, dietary Mice, CD-1 15/sex/dose PMRA# 1570233	0, 0.16, 1.7, 18, 168 mg/kg bw/d (♂) 0, 0.22, 2.4, 24, 230 mg/kg bw/d (♀)	1.7	**≥ 18 mg/kg bw/d**: ↑ rel liver wt (♀), ↑ thyroid follicular cell hyperplasia, ↓ colloid density. **168 mg/kg bw/d**: ↑ mixed function oxidase activity, abs and rel thyroid wts, follicular epithelial cytoplasmic vacuolation and interstitial congestion, ↑ centrilobular hypertrophy, nuclear pleomorphism and intranuclear inclusions in the liver. ♂: ↑ abs and rel liver wts
90-day, dietary Rats, SD 60/sex/dose PMRA# 1831764	1, 5, 25, 125, 625 ppm (0.07, 0.35, 1.7, 6.25, 31.25 mg/kg bw/d) Purity: 96.8%	1.7	Liver congestion evident with dose and time. **≥ 6.25 mg/kg bw/d**: hyperaemia of the thyroid, with and without enlargement, ↑ rel (to brain) thyroid wt and ↓ ^{125}I uptake, thyroid binding globulin (TBG), T_3 and T_4. **31.25 mg/kg bw/d**: ↑ mortality, ↓ bwg, excessive salivation, hair loss, rough and bristly hair coat, scaly skin.
90-day, dietary Rats, SD 14/sex/dose Special, in combo with mancozeb PMRA# 1570229	**ETU**: 1 dose - 250 ppm (♂: 14.28 mg/kg bw/d ♀: 17.81 mg/kg bw/d) Purity: 99%	LOAEL: 14.28	**ETU**: **14.28/17.81 mg/kg bw/d**: ↓ bwg, fc; ↑ serum cholesterol, and rel liver and thyroid wt, ↓ T_4, ↑ T_3 and TSH, and thyroid lesions; centrilobular hepatocyte hypertrophy, ↓ hepatic MFO activity
Subchronic, dietary Rats, Osborne-Mendel 20 ♂/dose Treated for 30, 60, 90 or 120 days PMRA# 1805536	0, 50, 100, 500 or 750 ppm (0, 2.5, 5.0, 25 and 37.5 mg/kg bw/d	2.5	**≥ 2.5 mg/kg bw/d**: ↑ rel thyroid wts (≥60 days) **≥ 5 mg/kg bw/d**: ↑ rel thyroid wt (≥30 days), ↓ ^{131}I uptake at 24 h, slight hyperplasia of the thyroid gland. **≥ 25 mg/kg bw/d**: ↓ bw, ^{131}I uptake (4 h) and stat sign after 90 days (up to 13 times lower than control), moderate-marked hyperplasia of thyroid, lack of colloid and heightened epithelial walls, ↑ vascularization, follicular adenomas
13-wk, dietary Dogs 4/sex/dose PMRA# 1570230	0, 10, 150, 2000 ppm (♂: 0, 0.39, 6.02, 66.23 mg/kg bw/d ♀: 0, 0.42, 6.51, 71.62 mg/kg bw/d) Purity: 98%	0.39	≥ **0.39/0.42 mg/kg bw/d**: ↓ AST (♀, wk 13) **≥ 6.02/6.51 mg/kg bw/d**: ↓ hgb, packed cell volume and RBCs, ↑ reticulocytes (♀), ↑ cholesterol and ↓ AST (♂) **66.23/71.62 mg/kg bw/d**: ♂: ↑ mortality (with ↓ bw), 2 that died had slight/minimum focal seminiferous atrophy of the testis, glandular hypotrophy of prostate,↑ serum protein and globulin, and ↓ ALP, RBC, hemoglobin. ♀: ↓ activity, bilobed swelling in pharyngeal area, ↑ cholesterol. Both sexes had ↓ phosphorous, T_3, T_4 and ↑ thyroid, liver and adrenal wts, exophthalmia. Histo showed ↑ hypertrophy of basophilic cells of the pituitary (with micro-vascuolization), moderate involution of thymus, and severe follicular hyperplasia of thyroid (with papillary

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
			projections of follicular epithelium in the luman of the follicles).
1-yr, dietary Dogs 4/sex/dose PMRA# 1619162	0, 5, 50 and 500 ppm (♂: 0, 0.18, 1.99, 20.13 mg/kg bw/d ♀: 0, 0.19, 1.79, 20.15 mg/kg bw/d) Purity: 98%	0.18/0.19	**≥ 1.99/1.79 mg/kg bw/d**: 8% ↓ bw (♂ at 1 yr), ↓ terminal bwg (43% of control, ♂), ↑ thyroid wts. Hypertrophy of thyroid and colloid retention, pigment accumulation in liver (Kupffer's cells). **20.13/20.15 mg/kg bw/d**: ↑ mortality, pale mucous membranes, subdued behaviour, yellow/orange feces, ↓ terminal bw (15%), bwg (-60%), hgb, RBC (2 ♂ and 1 ♀ had anemia with 90% ↓ in hgb), packed cell vol, mean corpuscular hgb, platelet count, albumin/globulin ratio, T_3 and T_4 values (shortly before death). ↑ reticulocytes, mean corpuscular volume, total bilirubin, AST, ALT (♂ only), centrolobular hepatocellular necrosis of the liver (multifocal and moderately severe in ♂), hypertrophy of follicular cells with dilation of follicles in the thyroid, dyspnea and tachycardia.
Chronic Toxicity/Oncogenicity Studies			
2 yr Rats, SD 68/sex/dose NB: only tested for thyroid toxicity PMRA# 1805537, 1805539	0, 5, 25, 125, 250 or 500 ppm (0, 0.25, 1.25, 6.25, 12.5, 25 mg/kg bw/d) animals sacrificed at 2, 6, and 12 months 250 and 500 ppm animals sacrificed at 2 yrs	0.25	**≥ 0.25 mg/kg bw/d**: ↑ thyroid hyperplasia, no effects on thyroid hormones, or wt, unlikely adverse at this dose level. **≥ 1.25 mg/kg bw/d**: ↓ initial bw, ↑ vacuolarity of thyroid. **≥ 6.25 mg/kg bw/d**: ♂ ↑ thyroid wts; ♀ ↓ bw, ↑ rel thyroid wt, thyroids were hypofunctioning at 6 months but hyperfunctioning at 12 months. Development of nodular hyperplasia of thyroid after 1 yr. **≥ 12.5 mg/kg bw/d**: ↑ rel thyroid wt (♂) and ↑ thyroid wt (♀). ↑ thyroid carcinomas in 2 yr animals. **25 mg/kg bw/d**: ↓ survival, and ↑ pneumonia (complicated by obstruction of trachea by enlarged thyroid). ♂ had ↓ bw and ^{131}I uptake; ♀: hypo-functioning thyroid at 24 months Hypo vs hyper thyroid: ETU may initially ↓ thyroid activity, compensation occurs by ↑ release of TSH which stimulates thyroid wt., to overcome blocking effect of ETU. Progression to neoplasia may be a result of excessive pharm stimulation. This is supported, in part, by a lack of thyroid tumours at 1 yr at 5 or 25 ppm, and an ↑ in tumour incidence after 1 yr at 125 ppm, confirmed after 2 yrs (at 250 and 500 ppm). **Study considered supplemental**
2-yr Rats, SD 30/sex/dose Interim sacrifice at 52 wks.	0, 0.5, 2.5, 5 or 125 ppm Purity: 96% USEPA: analytical results of ETU in the feed varied	0.5 ppm	Interim sacrifice: **≥ 2.5 ppm**: diffuse thyroid hyperplasia in ♂ at 52 wks. **≥ 5 ppm**: thyroid follicular cell hyperplasia. **125 ppm**: ↑ thyroid wt, diffuse or nodular enlargement of thyroid, T_3 and TSH, ↓ T_4. ♂: ↑

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
NB: only looked at thyroid toxicity PMRA# 1570235	widely, with large coefficients, and actual compound intake on a mg/kg bw could not be calculated.		protein, albumin, GGT, cholesterol, bilirubin, and ↓ urea. ♀: ↓ glucose,↑ uric acid. Histo: ↑ thyroid follicular hyperplasia, ↑ adenomas (♂) Minimal -slight focal/multifocal cellular hypertrophy of anterior pituitary (♂). Terminal sacrifice: **≥ 2.5 ppm**: excessive diffuse follicular hyperplasia of thyroid, slight-severe nodular hyperplasia, ↑ incidence of benign and malignant follicular neoplasms and anterior pituitary adenomas (♂). **Study considered supplemental**
2 yr with repro dosing (explained in results), dietary Mice, B6C3F1 variable #/sex/dose n = 60 10/sex/dose sacrificed at 9 months PMRA# 1570233, 1805515	**Perinatal**: 0, 33, 110 and 330 ppm **Adult**: 0, 330, 1000 ppm for 2 yrs, one group received 100 ppm for 2 yrs Standard adult conversions 100, 330 and 1000 ppm = 15, 50 and 150 mg/kg bw/d. Purity: 99% Study combined perinatal exp (in utero and throughout suckling) with traditional NTP chronic bioassay. Female mice (F) generation) were fed a diet of 0, 33, 110 or 330 ppm ETU for 1 wk before breeding. After mating all females were kept on the ETU diet. On postpartum day 7 the litters (F_1) were standardized to 8, weaned on day 28 and separated by sex. Exposure continued and at 8 weeks the pups were divided into 60/sex at concentrations of 0, 330 and 1000 ppm. 10/sex were sacrificed at 9 months and 50/sex were sacrificed after 2 years.		**F_0:F_1 ppm treatments were as follows:** 0:0, 0:330, 0:1000, 330:0, 330:330, 330:1000, 33:100, 110:330 9 months All adult exposed mice had centrilobular hepatocellular cytomegaly, ↑ hepatocellular adenomas. **1000 ppm** ♀: eosinophilic foci. ↑ abs and rel liver wts in groups receiving adult concentrations, regardless of perinatal exp.↑ abs thyroid wts, T_3 and TSH (♂). 2-years Except for perinatal-only exp, all doses had ↓ bw. **Perinatal-only Exp**: no effects noted. **Adult-only Exp (330 and 1000 ppm)**: Thyroid: diffuse cytoplasmic vacuolization, focal hyperplasia, and neoplasia. **1000 ppm**: follicular cell adenomas or carcinomas with multiple or bilateral neoplasms (70%). ♀ more susceptible. Liver: diffuse centrilobular hepatocellular cytomegaly, marked ↑ in hepatocellular adenomas/carcinomas (♀). **1000 ppm**: ↑ hepatocellular carcinomas (♂). Multiple hepatocelluar neoplasms, with carcinomas metastasizing to the lung. Rare hepatoblastomas also occurred, particularly in ♂. Pituitary: **at 1000 ppm**: ↑ focal hyperplasia or adenoma of pars distalis (♂) and ♀: ↑ adenoma (but not hyperplasia). **Combined Perinatal-Adult Exp:** Thyroid, Liver, Pituitary: **330** fluorescein **330 ppm**: marginal ↑ of non-neoplastic and neoplastic lesions in all 3 organs compared to adult exposure, but this marginal ↑ not seen at the 330-1000 ppm dose. ♂: all had a marginal↑ in follicular cell hyperplasia compared to adult-only exposure. See Table 1 for tumour tables.
ETU is currently classified by the USEPA as a B2 carcinogen, with a q_1* = 0.0601 $(mg/kg/day)^{-1}$. The low dose extrapolation for human risk assessment is based on liver tumours in female mice. The PMRA concurs with this assessment and considers ETU to be the residue of concern for the cancer assessment of all EBDC fungicides.			
2 yr with repro dosing, dietary	**Perinatal**: 0, 9, 30, 90 ppm		**F_0:F_1 ppm treatments were as follows:** 0:0, 0:83, 0:250, 90:0, 90:83, 9:250, 30:83 and 9:25 ppm

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Rats, Fischer variable #/sex/dose n = 60 10/sex/dose sacrificed at 9 months This study is part of the onco mouse study reported above. PMRA# 1570233, 1805515	**Adult**: 0, 25, 83 and 250 ppm for 2 yrs. Standard conversions would be 1.25, 4.15 and 12.5 mg/kg bw/d Purity: 99% Female rats were fed a diet containing 0, 9, 30 or 90 ppm ETU for 1 wk before breeding. After breeding, dosing continued and on PND 4 litters were standardized to 8 and weaned on day 28. Pup exposure continued for 8 wks and then divided into groups of 50/sex and exposed to adult concentrations of 0, 25, 83, and 250 ppm. *This study, combined with study above (PMRA # 1570235), fulfills the chronic/onco rat data requirement.	9 months **0** fluorescein **83, 0** fluorescein **250, 90** fluorescein **83 and 90** fluorescein **250 ppm**: ↑ abs and rel liver wt (♂), **0–250 and 90–250 ppm:** ↑ thyroid wt. **0–83, 0–250, 30–83, 90–83 and 90–250 ppm**: ↑ thyroid follicular cell hyperplasia **90–250 ppm:** ↑ thyroid follicular cell adenomas. Except for **90–0 ppm**, all dose groups had ↓ T_4 and ↑ TSH. 2-yr **Perinatal-only Exp:** Thyroid: ↑follicular cell hyperplasia (dosed animals 18-64%, conrol: 0-9%) **Adult-only Exp:** Thyroid: **0:83 ppm:**↑ follicular cell hyperplasia **(58% vs. 2% in control ♂, ♀: 16% vs 4% in control)** , adenomas **0–250 ppm**: follicular cell carcinomas, ♂ appear more sensitive. Some carcinomas invaded the adjacent parenchyma and/or esophagus and trachea, and two metastasized to the lungs. Thyroid tumour incidence in adult-only exposure was (1/49, 12/46, 37/50 for males and 3/50, 7/44, 30/49 at 0, 83 and 250 ppm, resp) **Combined Perinatal-Adult Exp:** Thyroid: **90–83 and 90–250 ppm**: ↑ follicular cell hyperplasia (♂), this was greater than that observed at 0–83 ppm, indicating some type of perinatal action. There was a similar effect with follicular adenomas/carcinomas. For males, tumour incidence was as follows: 3/46, 14/47, 13/50 and 48/50 for 9:25, 30:83, 90:83 and 90:250 ppm exposures, resp. Other Organs: **90–83 and 90–250 ppm**: ↑ neoplasms of the Zymbal's gland and mononuclear cell leukaemia.	
Smith (1984). **ETU**: thyroid function in two groups of exposed workers. Brit J of Ind Med 41:362-366. PMRA# 1570247	Clinical examinations and thyroid function tests were carried out over a period of 3 years in the UK on 8 workers involved in the manufacture of ETU (average exposure of 10 years) and 5 workers involved in mixing of ETU with rubber (average exposure of 3 years). All subjects were ♂ and ranged from 26-62 years. In the manufacturing group, a personal sampler noted ETU levels of 330 ug/m^3 (background levels of 10-240 ug/m^3). The mixture group recorded levels of 120–160 ug/m3. Results showed that mixers had significantly lower levels of T4 in their blood compared to controls. No effects were found on TSH or thyroid binding globulin. Although the authors concluded that there was no evidence that thyroid function was severely altered at these dose levels, the T4 results could be accounted for by the exposure scenario of the mixers.		
Reproductive and Developmental Toxicity Studies			
2-generation Rats - SD 25/sex/dose PMRA# 1570238	0, 2.5, 25 and 125 ppm Purity: 98%	Potential NOAELs (ppm): Parental 2.5 Offspring 25 Reproductive 125	Parental **≥ 25 ppm**: follicular cell (thyroid) hypertrophy and hyperplasia; ↑ pituitary hypertrophy (♂). **125 ppm**: F_1 generation had ↓ colloid in the thyroid. The pituitary of the adults had an ↑ in the incidence and severity of anterior cell hypertrophy and the ♂ also had ↑ cellular vacuolization. Offspring **125 ppm**: F_0 pups: ↑ mortality lactation days 1–-4. NOAELs on a mg/kg bw basis could not be determined because of stability problems with the

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
			test material, unknown feed consumption, and missing pups. **Study considered supplemental**
2-phase Reproductive toxicity Rats, Fischer Mice, C57BL/6N Depending on the test, animal numbers ranged from 3–5 per group/litter. PMRA# 1619136	Rats: 0, 8, 25, 83, and 250 ppm (0, 0.8, 2.5, 8.3, 25 mg/kg bw/d) Mice: 0, 33, 100, 333 and 1000 ppm (0, 5, 15, 50, 150 mg/kg bw/d) Purity: 96.7%	Phase I: ♀ dosed before breeding to untreated ♂, then during gestation. Phase II: weanlings dosed for 9 wks. **Rats** All treatment groups: Dams ↓ bwg, thyroid hyperplasia in both sexes **≥8.3 mg/kg bw/d**: ↑ thyroid adenomas (♂), ↓ bwg in weanling ♂. **25 mg/kg bw/d**: ♂: ↓ fc and ↑ pituitary vacuolization. Pups: ↓ survival (pnd 4). **Mice** ↓ fertility or no pregnancy. **≥50 mg/kg bw/d**: ↓ bw in weanlings. **150 mg/kg bw/d**: From initial breeding, thyroid hyperplasia and cellular alteration of hepatocytes (cytomegaly, karyomegaly). ♀: ↓ bw during lactation, pups surviving to day 28 had ↓ bw. NOAELs not set because of low animal numbers. **Study considered supplemental**	
Developmental, gavage Rat, Wistar 10–17/dose PMRA# 1805649, 1805557	0, 5, 10, 20, 40 mg/kg bw/d, Group II also treated with 80 mg/kg bw/d Purity: 100% Published Papers (1973)	Maternal 40 Developmental 5 **Sensitivity** Used for ARfD	Group I dams treated 21-42 days before conception, then until gd 15. Other dams dosed gd 6–15 (Group II) or 7-20 (Group III). Dams **80 mg/kg bw/d**: lethal to 9/11 dams. Fetal **≥ 5 mg/kg bw/d**: ↑ in delayed ossification of the parietal bone (groups I and II). **≥ 10 mg/kg bw/d:** (all groups): ↑ meningoencephalocele, meningorrhagia, meningorrhea, hydrocephalus, obliterated neural canal, abnormal pelvic limb posture with equinovarus, and short or kinked tail. **≥ 40 mg/kg bw/d:** retarded growth
Developmental, gavage Rats, SD n = 6 Acute dose (gd 15) PMRA# 1805524	0, 15, 30, 45 mg/kg bw on gd 15	Pups from each dose group were imaged serially on PND 6, 13, 17 and 27, in order to determine the progression in severity of hydrocephalus. Litter mates were imaged (MRI) on these days and then killed. Hydrocephalus was noted in the images from all animals of the **30 and 45 mg/kg bw** dose levels on PND 6. At this time, the lateral ventricles were dilated less than 1 mm. Hydrocephalus became more severe and by 4 wks of age, all the pups in the high- and about ½ of the mid-dose group had died. Surviving pups of the mid-dose group brains were severely hydrocephalic, with little cortex remaining. In all cases, the MRI corresponded precisely with the brain anatomy observed after termination.	
Gavage Rats, Wistar females PMRA# 1805635	0, 15, 30 mg/kg bw, single dose on gd 13	Histologic study revealed the presence of karyorrhexis in the germinal layer of basal lamina of CNS extending from the thoracid spinal cord to the telencephalon 12h after treatment with **30 mg/kg bw**. At 48h, the spinal cord showed obliteration and duplication of the central canal and disorganization of germinal and mantle layers. In the brain, the ventricular lining was focally denuded, neuroepithelial cells were arranged in the form of rosettes and the nerve cell proliferation was disorganized. In the **15 mg/kg bw** group, cellular necrosis was less severe and consisted of degeneration in a single or a small group of cells widely dispersed in	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
		the germinal layer of neuraxis. The initial degenerative changes were observed in a specific nerve cell type, identified as the undifferentiated migrating neuroblast.	
Developmental, gavage Rats, SD 22/dose gd 6-20 PMRA# 1805574	0, 15, 25, 35 mg/kg bw/d	Maternal 35 Developmental 15 **Sensitivity**	Dams No maternal toxicity noted. Fetal **≥ 25 mg/kg bw/d**: ↑ dilated brain ventricles (33.5%). **35 mg/kg bw/d**: ↑ cranial meningocele and meningorrhea, severe hindlimb talipes, hydroureter and dilated ureter, and ↓ ossification of skull bones. 43.5% of fetuses had short or kinky tails, 93% had ELV, 33.5% had dumbell-shaped or bilobed vertebral centra.
Developmental Mancozeb/ETU Rats, albino 26/dose gd 6-15 PMRA# 1651466	Mancozeb: 0, 2, 8, 32, 128 or 512 mg/kg bw/d Purity: 83% ETU: 50 mg/kg bw/d Purity: 99%	Mancozeb Maternal 32 Developmental 128 ETU None set.	**Mancozeb** Maternal: **≥ 128 mg/kg bw/d**: ↓ fc on days 10-15, bw on gd 20 and bwg throughout **512 mg/kg bw/d**: 1 death due to treatment, 2 sacrificed due to abortion, lethargy, scruffy coat, and diarrhea. Developmental: **512 mg/kg bw/d**: gross dev defects, CNS defects, skeletal defects, cryptorchidism, abortions, ↑ resorptions, ↓ fetal bw. **ETU** Maternal: ↓ bwg (does not appear to be corrected) Developmental: gross dev defects, CNS defects, skeletal defects, cryptorchidism, ↓ fetal bw, exencephaly, ectorpic kidneys, agenesis of kidneys, hydronephrosis, reduced stomach, edematour fat pads, less than 13 ribs, fused lumbar, sacral or caudal vertebrae, oligodactyl, syndactyl, webbed digits, anal atresia. Comment: Although mancozeb and ETU caused many of the same dev effects (except total resorptions), ETU was a more severe dev toxicant for the following reasons: 1) < ETU caused the effects 2) dev defects occurred with ↑ freq 3) more types of dev defects 4) all defects occurred with MINIMAL to NO maternal toxicity.
Developmental, dermal Rats, SD PMRA# 1805579	0, 25, 50 mg/kg bw/d in DMSO gd 10–11. or 50 mg/kg bw/d gd 12-13 Purity: 98%	Potential LOAEL of 50, gd 12–13	gd 10–11: **50 mg/kg bw/d**: short tails (3/83 pups), fused ribs (2/83 pups). gd 12–13: **50 mg/kg bw/d:** fetal deformities in all offspring: encephalocele, part or entire tail missing, missing leg bones, hunchback curvature of the spine, short mandible, fused ribs and sternebrae.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Developmental, dermal Rat, SD albino PMRA# 1619154	100 mg/kg bw/d on gd 12 & 13 50 and 100 mg/kg bw/d on gd 10 & 11		gd 12–13: **100 mg/kg bw/d**: no maternal effects or embryo-mortality. All 73 fetuses demonstrated marked skeletal malformations. gd 10–11: **50 and 100 mg/kg bw/d**: slight ↑ in skeletal malformations.
Special Developmental Rats Single oral dose on gd 15 PMRA# 1805559	0, 15, 30 or 45 mg/kg bw/d	Potential NOAEL of 15	Pups **≥ 30 mg/kg bw/d**: ↑ hydrocephalus, microphtalmia and mortality. Hydrocephalic condition accompanied by atrophy of the cerebral cortex and subcortical white matter. Surviving pups had motor defects and dome-shaped head. A cross-fostering study of survivors found that developmental toxicity was due to in utero exposure and not to exposure in milk.
Developmental, gavage Rabbits, NZW 5–7 dams/dose gd 7–20 PMRA# 1805557	0, 5, 10, 20, 40 or 80 mg/kg bw/d Purity: 100%	Maternal: > 80 Developmental 40 Sensitivity at high doses compared to rat	Not maternal tox Developmental **80 mg/kg bw/d**: ↑ resorption sites, degeneration of proximal convoluted tubules in the kidney and ↓ brain wt. Low animal numbers and lack of detailed reporting. **Study considered supplemental**
Developmental, gel cap Cats - European and Persian 7–14/dose PMRA# 1805550, 1805636	0, 5, 10, 30, 60 mg/kg bw/d days 16-35 or 120 mg/kg bw days 16-34. Purity: Not Specified	Potential maternal 5 Potential developmental 10	Maternal **≥ 10 mg/kg bw/d**: ↑ ataxia, tremors, hindlimb paralysis, mortality **≥ 30 mg/kg bw/d**: no cats survived. Developmental 11/35 fetuses obtained from 6 cats killed in a moribund state (4 from 30 mg/kg bw/d, 1 each from 60 and 120 mg/kg bw/d) were malformed with coloboma, cleft palate, spina bifida, umbilical hernia etc. ETU rapidly metabolizes to S-methyl ETU in cats, but not in rats. May explain why developmental effects in rat are at non-maternally toxic doses, but in the cat developmental effects are at maternally toxic dose.
Special Study using maneb, ETU and EBIS; gastric intubation Mice, CD1 Rats, SD Hamsters, Golden Guinea pigs, Hartley PMRA# 1805604	**Dosing** **Rats:** maneb (0, 120, 240 and 480 mg/kg bw/d, gd 7–16) ETU (0, 5, 10, 20, 30, 40, 80 mg/kg bw/d, gd 7–21) EBIS (0, 7.5, 25, 30 mg/kg bw/d, gd 7–21) **Mice:** maneb (0, 375, 750, 1500 mg/kg bw/d, gd 7–16) ETU (0, 100, 200 mg/kg bw/d, gd 7–16) EBIS (0, 50, 100, 200 mg/kg	Animals for postnatal study were allowed to litter and culled to 4/sex and weaned on day 22 postpartum. **For ETU, no devel effects in mouse, hamster or guinea pig, even at dose levels producing malformations in 100% of the rat pups.** Appears maneb produces paralytic	**Maneb**: maternal *rats*: ↓ bwg, ↑ rel liver wt (dose-related manner). **480 mg/kg bw/d**: ↓ fetal bw, caudal ossification and ↑ hydrocephalus. Maternal *mice*, **≥375 mg/kg bw/d:** ↑ rel liver wt and Compound-induced paralysis. Fetuses had ↓ caudal ossification. **EBIS:** no fetal effects, maternal *rats* had ↓ bwg at **30 mg/kg bw/d**. Amount admin limited by compound-induced paralysis in dams. **ETU**: no apparent effects in *hamsters* or *guinea pigs*. *Rats*: Maternal: **80 mg/kg bw/d**: ↓ bwg and 25% mortality. DEV: **≥ 10 mg/kg bw/d**: ↓ bw

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
	bw/d, gd 7–16) **Hamster:** ETU (0, 25, 50, 100 mg/kg bw/d, gd 5–10) **Guinea Pigs:** ETU (0, 50, 100 mg/kg bw/d, gd 7-25)	effect through metabolic conversion to EBIS, and teratogenic effects through conversion to ETU. Lack of terato of EBIS may be that less compound is needed to produce paralysis than for metabolic conversion to sufficient quantities of ETU. There is a steep dose-response with regard to dev tox of ETU in rat. **ETU Dev NOAEL = 5 mg/kg bw/d** **Thus far, there is nothing to indicate that humans would be less sensitive than the rat to the developmental effects of ETU.**	**≥ 20 mg/kg bw/d**: ↑ hydrocephalus **≥ 40 mg/kg bw/d**: ↓ ossification, ↑ encephalocele, kyphosis and digit defects. **80 mg/kg bw/d**: ↑ mortality, edema, gross defects of the skeletal system and CNS. *Mice*: Maternal: ↑ rel liver wt (**≥100 mg/kg bw/d**). at **200 mg/kg bw/d,** fetuses had ↑ # supernumerary ribs. Postnatal results: **Maneb**: ♂ had a delay in eye opening **EBIS**: delayed eye opening, (♀) ↓ bw **ETU**: there were no apparent differences reported in open field activity between ♂ fetuses surviving the high dose with hydrocephalus and their apparently normal mates.
Special Study, gavage Mice, JCL-ICR Rats, Wistar Hamsters, Golden dosed during organogenesis PMRA# 1805594	Rats: 0, 10, 20, 30, 40, 50 mg/kg bw/d Mice: 0, 200, 400, 800 mg/kg bw/d Hamsters: 0, 90, 270, 810 mg/kg bw/d	No maternal toxicity in any of 3 species Developmental: Rats: 20 (JMPR), < 10 (USEPA and PMRA) Mice: > 800 Hamsters: 90	**Rats**: **≥ 10 mg/kg bw/d**: ↑ dilation of the lateral 4th ventricle (2 %) - this instance is within older historical controls, however a previous reported study indicates severe head malformations at this dose and that result takes precedence in the overall assessment. **≥ 20 mg/kg bw/d**: ↑ dilation of the lateral 4th ventricle (39%) **≥ 30 mg/kg bw/d**: ↓ mean fetal bw, short kinky tail, curved clavicles **≥ 40 mg/kg bw/d**: meningocele (66%), fused/wavy ribs, fused sternebrae, malformed vertebrae and scholiosis. **Mice**: No toxicity noted **Hamsters**: **≥ 270 mg/kg bw/d**: ↓ ♀ fetal bw, ↑ malformed lumbar and sacral vertebrae. **810 mg/kg bw/d**: dilation of the lateral 4th ventricle, ↑ cleft palate, short/kinky tail, oligodactyly.
Liver enzymatic assays , gavage Mice, Swiss albino Rats, Wistar 8 ♂ mice 8 ♂ rats PMRA# 1805566	ETU (98% pure): 0, 100 or 200 mg/kg bw.	**ETU** causes a dose-dependent ↓ of aminopyrine-N-demethylase in rats, but did not modify this activity in mice. ETU did not affect aniline hydroxylase activity in rats, but caused a twofold ↑ in mice. The study authors concluded that qualitatively different responses of hepatic microsomal enzymes may be partially responsible for the differences in acute toxicity and teratogenicity demonstrated in rats and mice.	

<table>
<tr><th>Study/Species/
# of animals per group</th><th>Dose Levels/Purity of Test Material</th><th>NOAEL
(mg/kg bw/day)</th><th>Results/Effects</th></tr>
<tr><td>Further Comparison of rat and mouse teratogenicity

PMRA# 1805569</td><td colspan="3">The ½ life and ↑ metabolism of ETU in the mouse compared with the rat may be partly responsible for the differences in teratogenic response between the 2 species. After 48 hrs, the total amount of ETU excreted is similar between the 2 species, but the radioactive label is still detected in all tissues in the rat, but only in the liver of the mouse. Material excreted in the urine indicated that 95% appeared as ETU in the rat, but only 40% of the material was unchanged ETU in the mouse.
However, the following results confuse the issue:
1) a 10-folddose that produced hydrocephalus in rat fetuses had no effect on mouse development.
2) the rat and guinea pig have similar excretion patterns and ETU is not teratogenic in the guinea pig.
Thus, metabolism and rapid elimination of ETU in the mouse may assist in averting teratogenic effects in this species, but it is not the only factor leading to this ↓ sensitivity. The fact that ETU is only detected in the mouse liver may be related to the carcinogenicity that forms there.</td></tr>
<tr><td>Developmental, gavage
Rats, SD
Rats were hypothyroid and euthyroid

10–12/dose

PMRA# 1805624</td><td>40 mg/kg bw, days 7–15 of gestation.

Purity: 100%</td><td colspan="2">Rats were given thyroxine to determine if ETU terato occurred through alterations of maternal thyroid function.
ETU was determined to be a teratogen, but not directly through alterations of maternal thyroid status. In other words, the thyroid alterations enhanced the developmental toxicity of ETU, but were not the primary factor.
-ETU lowered serum T_4
- ↓T_4 alone was embryotoxic, but not teratogenic
-hypothyroidism altered the spectrum of malformations in response to ETU both quantitatively and qualitatively.</td></tr>
<tr><td colspan="4">Genotoxicity Studies</td></tr>
<tr><td colspan="4">ETU has about 100 genotoxicity studies in the database. Also overviews of the genetic data are available (USEPA, IARC). The USEPA has determined that ETU is weakly genotoxic and IARC states it is not genotoxic.
General overview:
Salmonella reversion assays: 10 positive; 5 negative
ecoli: 1 positive; 2 negative
Mammalian gene mutation assay: 1 positive; 2 negative
Sex-linked recessive lethal: 2 negative; 2 inconclusive
Forward mutation: negative (all)
In vitro chromosomal aberrations: 3 negative; 1 positive
Micronucleus assay: 2 positive; 5 negative
Dominant lethal: 1 positive; 2 negative
Reciprocal assay: 2 positive; 4 negative
In vitro Unscheduled DNA synthesis: 1 positive with activation; 4 negative
Sister Chromatid Exchange in vitro: 5 negative
Sister Chromatid Exchange in vivo: 1 negative
Mitotic gene conversion: 3 positive; 3 negative
Numerous other studies with a equivocal results for differential killing, and negatives for cell transformation and spermhead abnormalities tests.

The PMRA concurs with the USEPA; ETU has weak genotoxic potential.

PMRA# 1805544, 1570258, 1805578</td></tr>
</table>

Table 3 Toxicology Endpoints for Health Risk Assessment for Mancozeb

EXPOSURE SCENARIO	ENDPOINT	STUDY	DOSE (mg/kg bw/day)	CAF or MOE[1]
ARfD Females 13–49	Inhibition of implantation	Modified Reproduction Mouse PMRA# 1852272	NOAEL of 18	1000 3 times database 3 times PCPA
ARfD General Population	Decreased motor activity	Acute Neurotoxicity Rat PMRA# 1571642	LOAEL 500	1000 3 times database 3 times LOAEL 1 times PCPA
ADI	Liver and body-weight gain, food consumption, thyroid hormone effects	1 Year Dog PMRA# 1624089, 1624090	NOAEL 2.3	300 3 times database 1 times PCPA
Acute Dermal2 Females 13-49	**Pick your own**			
	Inhibition of implantation	Modified Reproduction Mouse PMRA# 1852272	NOAEL of 18	1000 3 times database 3 times PCPA
Acute Dermal[2] General population	**Pick your own**			
	Decreased motor activity	Acute Neurotoxicity Rat PMRA# 1571642	LOAEL 500	1000 3 times database 3 times LOAEL 1 times PCPA
Short- and Intermediate-term Dermal[2]	**Occupational**			
	Inhibition of implantation	Modified Reproductive PMRA# 1852272	NOAEL 18	1000 3 times database 3 times serious effect
Short- and Intermediate-term Inhalation	**Bystander (Females 13-49)**			
	Bodyweight, Resorptions, Neurological	Developmental Inhalation PMRA# 1852277	NOAEL 5.27	1000 3 times database 3 times PCPA
	Bystander (General Population)			
	Bodyweight	Developmental Inhalation PMRA# 1852277	NOAEL 5.27	300 3 times database 1 times PCPA
	Occupational			
	Bodyweight, Resorptions, Neurological	Developmental Inhalation PMRA# 1852277	NOAEL 5.27	1000 3 times database 3 times serious effect
Long-term Dermal[2] and Inhalation[3]	**Occupational**			
	Liver and body-weight gain, food consumption, thyroid hormone effects	1 year Dog PMRA# 1624089, 1624090	NOAEL 2.3	300 3 times database 1 times PCPA
Cancer Risk	q_1* of 0.0601 (mg/kg bw/day)$^{-1}$	Based on incidences of liver tumours in a combined chronic/carcinogenicity/reproduction study on ETU		

[1]CAF (Composite assessment factor) refers to the total of uncertainty and pest control products act factors for dietary risk

assessments, MOE refers to target MOE for occupational assessments
[2]Since an oral NOAEL/LOAEL was selected, a dermal absorption factor of 1% is used in a route-to-route extrapolation.
[3]Since an oral NOAEL/LOAEL was selected, an inhalation absorption factor of 100% (default value) is used in route-to-route extrapolation.

Table 4 Toxicology Endpoints for Health Risk Assessment for ETU

EXPOSURE SCENARIO	ENDPOINT	STUDY	DOSE (mg/kg bw/day)	CAF or MOE[1]
Acute Reference Dose Females 13-49	Malformations	Developmental rat PMRA# 1805557	5 mg/kg bw/day NOAEL	1000
Acute Reference Dose Gen Pop	N/A			
Chronic Dietary	Body weight and thyroid	One year dog PMRA# 1619162	0.18 mg/kg bw/day NOAEL	300
Acute, Short-, and Intermediate- term Dermal[2] and Inhalation[3]	**Occupational**			
	Malformations	Developmental rat PMRA# 1805557	5 mg/kg bw/day NOAEL	1000
Long-term Dermal[2] and Inhalation[3]	**Occupational**			
	Bodyweight and thyroid	One year dog PMRA# 1619162	0.18 mg/kg bw/day NOAEL	300
Acute and short-term, Females 13–49	**Aggregate**			
	Malformations	Developmental rat PMRA# 1805557	5 mg/kg bw/day NOAEL	1000
Short-term, General population	**Aggregate**			
	Thyroid effects	90-day mouse PMRA# 1570233	1.7 mg/kg bw/day NOAEL	300
Cancer Risk	q1* of 0.0601 (mg/kg bw/day)-1	Based on incidences of liver tumours in a combined chronic/carcinogenicity/reproduction study		

[1]CAF (Composite assessment factor) refers to the total of uncertainty and pest control products act factors for dietary risk assessments, MOE refers to target MOE for occupational assessments
[2]Since an oral NOAEL was selected, a dermal absorption factor of 45% is used in a route-to-route extrapolation.
[3]Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) is used in route-to-route extrapolation.

Appendix IV Agricultural Mixer/Loader/Applicator and Postapplication Risk Assessment

List of Tables

Table 1 Seed and Potato Seed Piece Treatment Exposure Studies

Study Summary	PPE/Engineering Controls	Tasks	Unit Exposure (µg/kg a.i.) [a]	
			Dermal	Inhalation
Commercial Slurry Application (Barley, Corn, Oats, Wheat)				
Dean, 1993. Exposure of Workers to Triadimenol During Treatment of Grain Seeds with Baytan 312FS. Sponsored by Miles Inc. Unpublished. The study measured exposure of workers during commercial seed treatment of winter wheat with BAYTAN 312 FS, a liquid formulation of triadimenol, at three treatment facilities (large, medium and small) in Ontario, Canada. Workers were monitored for 3–3.5 hours at each facility for a total of 55 half-day replicates. The maximum amount of active ingredient handled per replicate was 21.9 kg. Dermal exposure was estimated using patch dosimeters and hand washes. Inhalation exposure was measured using personal air sampling pumps.	Single layer and gloves.	Treater/Bagger (n=16)	357.42	118.76
		Stacker/Tagger (n=30)	61.68	34.36
		Forklift Operator (n =4)	12.02	1.21
Planting Commercially Treated Seed (Corn)				
Zietz, 2007. Determination of Operator Exposure to Imidacloprid During Loading/Sowing of Gaucho Treated Maize Seeds under Realistic Field Conditions in Germany and Italy. Sponsored by SeedTropex Task Force. Unpublished. The study measured exposure of 16 workers loading and planting corn seed treated with Gaucho in Germany and Italy. Workers were monitored for approximately 6–8 hours, handled an average of 1.20 kg of active ingredient and planted seed to 5.5–40.2 ha of land. Dermal exposure was measured using whole body dosimeters, face/neck wipes and hand wash samples. Inhalation exposure was measured with personal air sampling pumps.	Single layer and gloves. Closed cab planter.	Loading, Planting, Cleanup and Repair (n=15)	1803	82.83

Study Summary	PPE/Engineering Controls	Tasks	Unit Exposure (µg/kg a.i.) [a]	
			Dermal	Inhalation
Planting Commercially Treated Seed (Barley, Flax, Oats, Wheat)				
SeedTropex, 1995. Worker Exposure During Sowing of Seed with Baytan. Sponsored by SeedTropex Task Force. Unpublished. Thirteen workers were monitored while loading treated seed into hoppers and sowing the cereal seed that had been previously treated with a liquid formulation of Baytan. Each worker was monitored throughout a typical workday, including transportation to and from the field, clean-up and repair. Treated seed was supplied in 50 kg bags, 0.5 tonne bags, 1 tonne bags or by bulk trailer. The amount of seed handled per worker averaged 2.7 tonnes. The area seeded averaged 13.5 ha. Dermal exposure was measured with whole body dosimetry, a cap, and cotton gloves. Inhalation exposure was monitored through use of personal air sampling pumps.	Single layer and gloves.	Loading, Planting, Cleanup and Repair (n=13)	1870	248.07
On-farm Slurry Application and Planting (Barley, Corn, Oats, Wheat)				
Purdy, 1999. On-farm Operator Exposure Study with DIVIDEND 36FS Seed Treatment on Wheat. Sponsored by Novartis Crop Protection Canada Inc. Unpublished. Sixteen replicates of on-farm seed treatment procedures were monitored for potential exposure to workers treating seed and handling treated seed for planting (i.e., loading, calibration, planting, repair, cleanup). The study was conducted at 15 different farms in Manitoba using the Canadian liquid formulation of DIVIDEND 36FS. Dermal exposure was monitored with whole body dosimeters, face/neck wipes and hand washes. Inhalation was monitored using personal air sampling pumps.	Single layer and gloves.	Loading, Treating, Planting (n=16)	407.34	223.03
On-farm Planter Box Seed Treatment and Planting (Barley, Corn, Flax, Oats, Wheat)				
Klonne, 2005. Determination of Dermal and Inhalation Exposure of Workers During On-Farm Application of a Dry Hopper Box Pesticide Treatment to Seed, and Planting of Treated Seed. Sponsored by Agricultural Handlers Exposure Task Force. Unpublished. Sixteen workers were monitored for exposure while treating cotton seed with a dry powder formulation of acephate (as Orthene 90S soluble powder) on-farm in open seed hopper boxes and planting the treated seed in a closed cab planter. The monitoring periods lasted approximately 4.5–10 hours. The total kg of a.i. handled across the replicates ranged from 5.2–15.8 kg. The amount of seed planted ranged from 308–671 kg over a total area planted of 25.9–86.2 ha. The dermal exposure was measured using whole body dosimeters, face/neck wipes, and hand washes. Inhalation exposure was measured by means of personal air sampling pumps.	Single layer and gloves. Closed cab planter.	Loading, Treating, Planting (n=16)	10 468	1133

Study Summary	PPE/Engineering Controls	Tasks	Unit Exposure (µg/kg a.i.)[a]	
			Dermal	Inhalation
On-farm Potato Seed Piece Treatment				
Maasfeld, 2001. Determination of Exposure to Pencycuron During Loading and Application of Moncereen® Droogontsmetter (Monceren DS 12.5) in Potato Fields. Sponsored by Bayer. Unpublished. Five farmers were monitored for worker exposure to pencycuron when applying the product formulated as a powder to potato seed pieces and planting treated potatoes seeds. Approximately 15–30 kg of product was handled and the area treated varied from 3.5 ha to 5.5 ha. Work days ranged from 5.75 to 8.5 hours. Dermal exposure was measured with whole body dosimeter and cotton gloves. Inhalation exposure was determined by the use of a personal air sampling pump.	Single layer and gloves. Closed cab planter.	Mixing, Loading (n=5)	2860	34.0
		Application, Planting. (n=5)		43.6
Potato Seed Treatment for Storage				
Mackie, 2006. Admire 240F - Determination of Dermal and Inhalation Exposure of Workers during On-farm Seed Piece Treatment of Potatoes. Sponsored by Bayer. Unpublished. Sixteen worker replicate trials were conducted to generate dermal and inhalation exposure data for workers treating potato seed pieces using Admire 240F, a liquid flowable formulation containing the active ingredient imidacloprid. Mixing, loading and treating activities were monitored at eleven different potato treating cooperator locations in southern Manitoba. Planter exposure was not monitored. Actual monitoring duration ranged from 5.75 hours to just over 10 hours. The amount of imidacloprid handled per monitoring period ranged from 3.63 to 12.72 kg. Total dermal exposure to imidacloprid was measured using whole body dosimeters, hand washes, and face/neck wipes. Inhalation exposure was measured by means of a personal air sampling pumps.	Single layer and gloves.	Treater (n=16)	291	11.5
		Cutter/Sorter (n=14)	NM	18.0
		All Tasks	291	18.0

PPE= personal protective equipment; NM = Not measured; Singe layer = long pants and long sleeved shirt.
[a] Arithmetic mean from surrogate exposure studies.

Table 2 Mancozeb Mixing/Loading and Applying Short- to Intermediate-Term Exposure and Risk Assessment

Use Site Category	Crop	Form. [a]	Method of Application [b]	Rate [c] (kg a.i./ha) or (kg a.i./L)	Area Treated ha/day [d] (ha) or (L)	Daily Exposure (µg/kg bw/day)		MOE	
						Dermal [e]	Inhalation [f]	Dermal [g]	Inhalation [h]
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Open cab groundboom and airblast.									
Use-site category 4 & 27: Forests/Woodlots and Ornamentals Outdoors	Arborvitae, Ash, Juniper, Douglas fir, Hawthorn, Oak, Sycamore	DF, WG	Airblast	2.63	16	4.35	4.09	4135	1288
			Groundboom	2.63	30	2.21	2.23	8132	2366
			LP Handwand	2.63×10^{-3} (kg a.i./L)	150 L	0.06	0.26	289033	20270
			HP Handwand		3750 L	8.08	21.38	2226	247
			Backpack		150 L	0.32	0.36	57045	14843
		WP	Airblast	2.80	16	7.00	39.68	2573	133
			Groundboom	2.80	30	6.77	68.59	2658	77
			LP Handwand	2.80×10^{-3} (kg a.i./L)	150 L	1.18	8.54	15194	617
			HP Handwand		3750 L	9.18	31.08	1962	170
			Backpack		150 L	0.36	0.71	50190	7425
	Holly, Ivy, Pine	DF, WG	Airblast	1.88	16	3.11	2.92	5789	1803
			Groundboom	1.88	30	1.58	1.59	11385	3312
			LP Handwand	1.88×10^{-3} (kg a.i./L)	150 L	0.04	0.19	404646	28378
			HP Handwand		3750 L	5.77	15.27	3117	345
			Backpack		150 L	0.23	0.25	79863	20780
		WP	Airblast	2.00	16	5.00	28.34	3602	186
			Groundboom	2.00	30	4.84	48.99	3721	108
Use-site category 4 & 27: Forests/Woodlots and Ornamentals Outdoors	Holly, Ivy, Pine	WP	LP Handwand	2.00×10^{-3} (kg a.i./L)	150 L	0.85	6.1	21271	864
			HP Handwand		3750 L	6.55	22.2	2747	237
			Backpack		150 L	0.26	0.51	70267	10394
	Honeysuckle	DF, WG	Groundboom	1.50	30	1.26	1.27	14231	4140
			LP Handwand	1.50×10^{-3} (kg a.i./L)	150 L	0.04	0.15	505808	35473
			Backpack		150 L	0.18	0.2	99829	25975
Engineering control: Wettable Powder in Water Soluble Packaging (WSP). Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Respirator for HP Handwand M/L/A. Open cab groundboom and airblast.									
Use-site category 4 & 27: Forests/Woodlots and Ornamentals Outdoors	Arborvitae, Ash, Juniper, Douglas fir, Hawthorn, Oak, Sycamore	DF, WG	HP Handwand	2.63×10^{-3} (kg a.i./L)	3750 L	8.08	2.14	2226	2465
		WP in WSP	Airblast	2.80	16	3.73	3.83	4821	1377
			Groundboom	2.80	30	0.66	1.37	27478	3852
			LP Handwand	2.80×10^{-3} (kg a.i./L)	150 L	0.06	0.27	318009	19432
			HP Handwand		3750 L	8.38	2.27	2148	2327
			Backpack		150 L	0.33	0.37	55088	14144
	Holly, Ivy, Pine	DF, WG	HP Handwand	1.88×10^{-3} (kg a.i./L)	3750 L	5.77	1.53	3117	3451
		WP in WSP	Airblast	2.00	16	2.67	2.73	6750	1928
			Groundboom	2.00	30	0.47	0.98	38469	5393
			LP Handwand	2.00×10^{-3} (kg a.i./L)	150 L	0.04	0.19	445212	27205
			HP Handwand		3750 L	5.98	1.62	3008	3257
			Backpack		150 L	0.23	0.27	77123	19801

Use Site Category	Crop	Form. [a]	Method of Application [b]	Rate [c] (kg a.i./ha) or (kg a.i./L)	Area Treated ha/day [d] (ha) or (L)	Daily Exposure (µg/kg bw/day) Dermal [e]	Daily Exposure (µg/kg bw/day) Inhalation [f]	MOE Dermal [g]	MOE Inhalation [h]
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves.									
Use-site category 5: Greenhouse Food Crops	Tobacco (greenhouse) [1]	DF, WG	LP Handwand	3.00×10^{-3} (kg a.i./L)	150 L	0.07	0.3	252904	17736
			HP Handwand		3750 L	9.24	24.43	1948	216
			Backpack		150 L	0.36	0.41	49914	12988
		WP	LP Handwand	3.20×10^{-3} (kg a.i./L)	150 L	1.35	9.76	13295	540
			HP Handwand		3750 L	10.49	35.52	1717	148
			Backpack		150 L	0.41	0.81	43917	6497
		SN	LP Handwand	3.30×10^{-3} (kg a.i./L)	150 L	0.07	0.32	269826	16488
			HP Handwand		3750 L	9.87	26.69	1823	197
			Backpack		150 L	0.39	0.44	46741	12001
Engineering control: Wettable Powder in WSP. Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves. Respirator for HP Handwand M/L/A.									
Use-site category 5: Greenhouse Food Crops	Tobacco (greenhouse)	DF, WG	HP Handwand	3.00×10^{-3} (kg a.i./L)	3750 L	9.24	2.44	1948	2157
		WP in WSP	LP Handwand	3.20×10^{-3} (kg a.i./L)	150 L	0.06	0.375	278258	17003
			HP Handwand		3750 L	9.58	2.59	1880	2036
		SN	HP Handwand	3.30×10^{-3} (kg a.i./L)	3750 L	9.87	2.67	1823	1974
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Open cab groundboom.									
Use-site category 07: Terrestrial Crops Grown for Seed Only	Alfalfa grown for seed	DF, WG	Groundboom (f)	1.10	100	3.08	3.10	5848	1701
			Groundboom (c)		300	9.23	9.29	1949	567
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Respirator for M/L. Open cab groundboom.									
Use-site category 07: Terrestrial Crops Grown for Seed Only	Alfalfa grown for seed	DF, WG	Groundboom (f)	1.10	100	3.08	1.66	5848	3172
			Groundboom (c)		300	9.23	4.98	1949	1057
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves. Open cab airblast.									
Use-site category 14: Terrestrial Food Crops (Orchard and Vine Crops)	Apple	DF, WG	Airblast	4.50	16	7.46	7.01	2412	751
		WP	Airblast	4.80	16	11.99	68.02	1501	77
		SN	Airblast	4.84	16	6.77	8.18	2657	644
	Grape	DF	Airblast	1.50	16	2.49	2.34	7236	2254
		WG	Airblast	1.60	16	2.65	2.49	6784	2113
		WP	Airblast	5.40	16	13.49	76.53	1334	69
	Pears	WP	Airblast	7.20	16	17.99	102.03	1001	52
Engineering control: Wettable Powders in WSP. Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves. Respirator for applicators. Open cab airblast.									
Use-site category 14: Terrestrial Food Crops (Orchard and Vine Crops)	Apple	DF, WG	Airblast	4.50	16	7.46	1.65	2412	3202
		WP in WSP	Airblast	4.80	16	6.4	0.83	2813	6320
		SN	Airblast	4.84	16	6.77	2.41	2657	2187
	Grape	WP in WSP	Airblast	5.40	16	7.2	0.94	2500	5618
	Pear	WP in WSP	Airblast	7.20	16	9.6	1.25	1875	4213

Use Site Category	Crop	Form. [a]	Method of Application [b]	Rate [c] (kg a.i./ha) or (kg a.i./L)	Area Treated ha/day [d] (ha) or (L)	Daily Exposure (µg/kg bw/day)		MOE	
						Dermal [e]	Inhalation [f]	Dermal [g]	Inhalation [h]
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Open cab groundboom.									
Use-site category 14: Terrestrial Food Crops (Low Acreage Field and Vegetable Crops)	Cantaloupe, Cucumber, Melon, Onion including dry bulb (foliar), Pumpkin, Squash, Tomato, Watermelon	DF, WG	Groundboom	2.44	30	2.06	2.07	8756	2547
		WP	Groundboom	2.60	30	6.29	63.69	2862	83
		SN	Groundboom	2.69	30	0.97	2.95	18588	1788
	Carrot	DF, WG	Groundboom	1.69	30	1.42	1.43	12654	3681
	Carrot, Celery	WP	Groundboom	1.80	30	4.35	44.09	4134	120
		SN	Groundboom	1.86	30	0.67	2.04	26916	2589
	Celery	DF	Groundboom	2.44	30	2.06	2.07	8756	2547
	Ginseng	DF, WG	Groundboom	3.30	30	2.78	2.80	6469	1882
		WP	Groundboom	3.52	30	8.51	86.23	2114	61
		SN	Groundboom	3.57	30	1.29	3.91	14005	1347
	Head Lettuce	WG	Groundboom	1.60	30	1.35	1.36	13342	3882
		WP	Groundboom	1.61	30	3.90	39.49	4617	133
	Onion dry bulb (in-furrow)	DF, WG	Broadcast Spreader	6.60	30	5.08	7.41	3542	711
Engineering control: Wettable Powder in WSP. Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Open cab groundboom.									
Use-site category 14: Terrestrial Food Crops (Low Acreage Field and Vegetable Crops)	Cantaloupe, Cucumber, Melon, Onion including dry bulb (foliar), Pumpkin, Squash, Tomato, Watermelon	WP in WSP	Groundboom	2.60	30	0.61	1.27	29591	4149
Use-site category 14: Terrestrial Food Crops (Low Acreage Field and Vegetable Crops)	Carrot, Celery	WP in WSP	Groundboom	1.80	30	0.42	0.88	42743	5993
	Ginseng	WP in WSP	Groundboom	3.52	30	0.82	1.72	21857	3064
	Head Lettuce	WP in WSP	Groundboom	1.61	30	0.38	0.79	47728	6691
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves. Respirator for M/L.									
Use-site category 14: Terrestrial Food Crops (Low Acreage Field and Vegetable Crops)	Onion dry bulb (in-furrow)	DF, WG	Broadcast Spreader	6.60	30	5.08	4.81	3542	1095
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application).									
Use-site category 14: Terrestrial Food Crops (High Acreage Field and Vegetable Crops) (also Use-site category 13: Terrestrial Feed Crops (Potato and	Lentil	SN	Aerial M/L	2.23	400	6.52	20.39	2762	258
			Aerial A			1.23	0.89	14623	5908
			Groundboom (f)		100	2.68	8.16	6717	646
			Groundboom (c)		300	8.04	24.47	2239	215
	Lentil, Potato, Sugar beet (ground application only), Wheat	DF, WG	Aerial M/L	1.69	400	15.80	9.84	1139	536
			Aerial A			0.93	0.68	19318	7805
			Groundboom (f)		100	4.74	4.77	3794	1104
			Groundboom (c)		300	14.23	14.32	1265	9
	Potato, Sugar beet (ground	WP	Aerial M/L	1.80	400	54.66	578.06	329	536

Use Site Category	Crop	Form. [a]	Method of Application [b]	Rate [c] (kg a.i./ha) or (kg a.i./L)	Area Treated ha/day [d] (ha) or (L)	Daily Exposure (µg/kg bw/day) Dermal [e]	Inhalation [f]	MOE Dermal [g]	Inhalation [h]
Wheat)	application only), Wheat		Aerial A			0.99	0.72	18116	7319
			Groundboom (f)		100	14.51	146.98	1240	36
			Groundboom (c)		300	43.54	440.95	413	12
Use-site category 14: Terrestrial Food Crops (High Acreage Field and Vegetable Crops) (Also Use-site category 13: Terrestrial Feed Crops (Potato and Wheat)	Potato (ground application only), Wheat	SN	Groundboom (f)	1.86	100	2.23	6.79	8070	776
			Groundboom (c)		300	6.69	20.36	2690	259
			Aerial M/L		400	5.42	16.97	3319	311
			Aerial A			1.02	0.74	17569	7099
Engineering control: Wettable Powder in WSP. Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Respirator for M/L (except WSP) and A.									
Use-site category 14: Terrestrial Food Crops (High Acreage Field and Vegetable Crops) (also Use-site category 13: Terrestrial Feed Crops (Potato and Wheat)	Lentil	SN	Aerial M/L	2.23	400	6.52	2.04	2762	2585
			Groundboom (f)		100	2.68	0.82	6717	6462
			Groundboom (c)		300	8.04	2.45	2239	2154
	Lentil, Potato, Sugar beet (ground application only), Wheat	DF, WG	Aerial M/L	1.69	400	15.80	0.98	1139	5356
			Groundboom (f)		100	4.74	0.48	3794	11038
			Groundboom (c)		300	14.23	1.43	1265	3679
	Potato, Sugar beet (ground application only), Wheat	WP in WSP	Aerial M/L	1.80	400	2.22	1.85	8098	2846
			Groundboom (f)		100	1.40	0.71	12823	7426
			Groundboom (c)		300	4.21	2.13	4274	2475
	Potato (ground application only), Wheat	SN	Aerial M/L	1.86	400	5.42	1.7	3319	3106
			Groundboom (f)		100	2.23	0.68	8070	7764
			Groundboom (c)		300	6.69	2.04	2690	2588

Shaded cells indicate MOEs that are less than the target.

[a] Form. refers to formulation type, WP = Wettable powder; WG = Wettable granules; DF = Dry flowable; SN = Solution; WSP = Water soluble packaging.

[b] M/L = Mixer/Loader; A = Applicator; Groundboomc) = custom groundboom application; Groundboom (f) = farmer groundboom application; HP Handwand = high pressure handwand; LP Handwand = low pressure handwand.

[c] Maximum listed label rate in kilograms of active ingredient per hectare (kg a.i./ha) unless specified as kilograms of active ingredient per litre (kg a.i./L). Rates per litre were calculated assuming the following spray volumes: Trees and ornamentals assumed 1000 L/ha and greenhouse tobacco assumed 2500 L/ha.

[d] Based on default assumptions.

[e] Where dermal exposure µg/kg bw/day = (unit exposure (PHED) × area treated × use rate × 1% dermal absorption)/70 kg bw.

[f] Where inhalation exposure µg/kg bw/day = (unit exposure (PHED) × area treated × use rate)/70 kg bw.

[g] Based on the short- to intermediate-term dermal NOAEL of 18 mg/kg bw/day from the oral modified reproductive toxicity study, target MOE of 1000.

[h] Based on the short- to intermediate-term inhalation NOAEL of 5.27 mg/kg bw/day from the inhalation developmental toxicity study, target MOE of 1000.

Table 3 Mancozeb Mixing/Loading and Applying Long-Term Exposure and Risk Assessment

Use Site Category	Crop	Form. [a]	Method of Application [b]	Rate [c] (kg a.i./L)	Area Treated ha/day [d] (ha) or (L)	Daily Exposure (µg/kg bw/day)		Margin of Exposure (MOE)		
						Dermal [e]	Inhalation [f]	Dermal [g]	Inhalation [g]	Combined [h]
Baseline PPE: Long pants, long sleeved shirts, and chemical										
Use-site category 5: Greenhouse Food Crops	Tomato (greenhouse)	DF, WG	LP Handwand	6.00×10^{-3} (kg a.i./L)	150 L	0.14	0.59	16158	3870	3122
			HP Handwand		3750 L	18.48	48.86	124	47	34
			Backpack		150 L	0.72	0.81	3189	2834	1501
		WP	LP Handwand	6.00×10^{-3} (kg a.i./L)	150 L	2.54	18.30	906	126	110
			HP Handwand		3750 L	19.66	66.60	117	35	27
			Backpack		150 L	0.77	1.52	2993	1512	1005
Engineering control: Wettable Powder in Water Soluble Packaging (WSP). Maximum PPE: Chemical-resistant coveralls over long pants, long sleeved shirts, and chemical-resistant gloves. Respirator for all handheld M/L/A.										
Use-site category 5: Greenhouse Food Crops	Tomato (greenhouse)	DF, WG	LP Handwand	6.00×10^{-3} (kg a.i./L)	150 L	0.10	0.06	23197	38704	14504
			HP Handwand		3750 L	6.12	4.89	376	471	209
			Backpack		150 L	0.27	0.08	8499	28341	6538
		WP in WSP	LP Handwand	6.00×10^{-3} (kg a.i./L)	150 L	0.09	0.06	25792	39577	15615
			HP Handwand		3750 L	5.87	4.85	392	474	214
			Backpack		150 L	0.26	0.08	8824	28807	6755
Engineering control: Wettable Powder in WSP. Maximum PPE: Chemical-resistant coveralls over long pants, long sleeved shirts, and chemical-resistant gloves. Respirator for M/L/A. Restriction on amount handled per day (2.25 kg a.i./day, approx. 375 L at 6 kg a.i. per 1000 L).										
Use-site category 5: Greenhouse Food Crops	Tomato (greenhouse)	DF, WG	HP Handwand	6.00×10^{-3} (kg a.i./L)	2500 L	4.08	3.26	564	706	313
		WP in WSP	HP Handwand	6.00×10^{-3} (kg a.i./L)	2500 L	3.92	3.24	587	711	322

Shaded cells indicate MOEs that are less than the target. M/L = Mixer/Loader; A = Applicator.

[a] Form. refers to formulation type, WP = Wettable powder; WG = Wettable granules; DF = Dry flowable; SN = Solution; WSP = Water soluble packaging.

[b] HP Handwand = high pressure handwand; LP Handwand = low pressure handwand.

[c] Maximum listed label rate in kilograms of active ingredient per litre (kg a.i./L). Rate per litre was calculated assuming a spray volume of 300 L/ha.

[d] Based on default assumptions.

[e] Where dermal exposure µg/kg bw/day = (unit exposure (PHED) × area treated × use rate × 1% dermal absorption)/70 kg bw

[f] Where inhalation exposure µg/kg bw/day = (unit exposure (PHED) × area treated × use rate)/70 kg bw

[g] Based on the long-term dermal and inhalation NOAEL of 2.3 mg/kg bw/day from the oral chronic toxicity study, target MOE of 300.

[h] Calculated using the following equation: Combined MOE = LOAEL/[Exposure $_{Dermal}$ + Exposure $_{Inhalation}$]

Table 4 Mancozeb Seed and Potato Seed Piece Treatment Short- to Intermediate-term Exposure and Risk Assessment

Use Scenario	Crop	Activity	Form. [a]	Rate [b] (g a.i./kg Seed)	Seed Treated per Day (kg seed/day)	Daily Exposure (µg/kg bw/day)		Margins of Exposure (MOE)	
						Dermal [c]	Inhalation [d]	Dermal [e]	Inhalation [f]
PPE: Long sleeved shirt, long plants, and chemical-resistant gloves. Open mix/load [g]									
Commercial Seed Treatment (Slurry)	Barley	Treater/Bagger	WP	1.06	65 000	8.72	171.56	2065	31
		Stacker/Tagger			65 000	0.60	33.69	29761	156
		Forklift Operator			65 000	0.12	1.19	152717	4442
	Corn	Treater/Bagger	WP	1.79	60 000	13.65	268.74	1318	20
		Stacker/Tagger			60 000	0.95	52.78	18999	100
		Forklift Operator			60 000	0.18	1.86	97494	2836
	Oat	Treater/Bagger	WP	1.47	65 000	12.15	239.15	1482	22
		Stacker/Tagger			65 000	0.84	46.97	21350	112
		Forklift Operator			65 000	0.16	1.65	109558	3186
	Wheat	Treater/Bagger	WP	0.83	65 000	6.87	135.17	2621	39
		Stacker/Tagger			65 000	0.48	26.55	37774	199
		Forklift Operator			65 000	0.09	0.93	193834	5638
Engineering controls: WP in Water Soluble Packaging (WSP) .[h] PPE: Long sleeved shirt, long plants, and chemical-resistant gloves. Respirator.									
Commercial Seed Treatment (Slurry)	Barley	Treater/Bagger	WP in WSP	1.06	65 000	3.50	11.65	5136	453
		Stacker/Tagger			65 000	0.60	3.37	29761	1564
		Forklift Operator			65 000	0.12	0.12	152717	44417
	Corn	Treater/Bagger	WP in WSP	1.79	60 000	5.49	18.24	3279	289
		Stacker/Tagger			60 000	0.95	5.28	18999	999
		Forklift Operator			60 000	0.18	0.19	97494	28355
Commercial Seed Treatment (Slurry)	Oat	Treater/Bagger	WP in WSP	1.47	65 000	4.89	16.23	3684	325
		Stacker/Tagger			65 000	0.84	4.70	21350	1122
		Forklift Operator			65 000	0.16	0.17	109558	31864
	Wheat	Treater/Bagger	WSP	0.83	65 000	2.76	9.18	6519	574
		Stacker/Tagger			65 000	0.48	2.65	37774	1985
		Forklift Operator			65 000	0.09	0.09	193834	56375
PPE: Long pants, long sleeved shirt, and chemical-resistant gloves. Open cab planter.									
Handling and Planting Treated Seed	Barley	Loader/Planter	WP	1.06	9600	2.71	35.93	6647	147
	Flax	Loader/Planter	WP	1.79	3600	1.72	22.86	10445	231
	Oats	Loader/Planter	WP	1.47	9200	3.62	47.99	4975	110
	Wheat	Loader/Planter	WP	0.83	14 000	3.11	41.28	5785	128
PPE: Long pants, long sleeved shirt, and chemical-resistant gloves. Open cab planter. Respirator for Loading and Planting.									
Handling and Planting Treated Seed	Barley	Loader/Planter	WP	1.06	9600	2.71	3.59	6647	1467
	Flax	Loader/Planter	WP	1.79	3600	1.72	2.29	10445	2305
	Oats	Loader/Planter	WP	1.47	9200	3.62	4.80	4975	1098
	Wheat	Loader/Planter	WP	0.83	14 000	3.11	4.13	5785	1277
Engineering Controls: Closed cab planter. PPE: Long pants, long sleeved shirt, and chemical-resistant gloves.									
Handling and Planting Treated Seed	Corn	Loader/Planter (f)	WP	1.79	1200	0.55	2.54	32498	2071
		Loader/Planter (c)	WP		2400	1.11	5.09	16249	1036

Use Scenario	Crop	Activity	Form. [a]	Rate [b] (g a.i./kg Seed)	Seed Treated per Day (kg seed/day)	Daily Exposure (µg/kg bw/day)		Margins of Exposure (MOE)	
						Dermal [c]	Inhalation [d]	Dermal [e]	Inhalation [f]
Engineering controls: Closed cab planter. PPE: Long sleeved shirt, long plants, and chemical-resistant gloves while loading and treating.									
On-farm Seed Treatment (Planter or Drill Box Treatment, Dry Application)	Barley	Loader/treater/planter	WP	1.06	9600	15.16	164.08	1187	32
	Corn	Loader/treater/planter (c)	WP	1.79	2400	6.43	69.61	2799	76
		Loader/treater/planter (f)	WP		1200	3.22	34.81	5597	151
	Flax	Loader/treater/planter	WP	1.79	3600	9.65	104.42	1866	50
	Oat	Loader/treater/planter	WP	1.47	9200	20.25	219.19	889	24
	Wheat	Loader/treater/planter	WP	0.83	14000	17.42	188.53	1033	28
PPE: Long sleeved shirt, long plants, and chemical-resistant gloves. Open mix/load [g] Open cab planter.									
On-farm Seed Treatment (Slurry)	Barley	Loader/treater/planter	WP	1.06	9600	1.36	40.44	13240	130
	Corn	Loader/treater/planter (c)	WP	1.79	2400	0.58	17.16	31209	307
		Loader/treater/planter (f)			1200	0.29	8.58	62419	614
	Oat	Loader/treater/planter	WP	1.47	9200	1.82	54.02	9911	98
	Wheat	Loader/treater/planter	WP	0.83	14000	1.56	46.46	11523	113
Engineering controls: WP in WSP.[h] PPE: Open mix/load. Long sleeved shirt, long plants, and chemical-resistant gloves. Respirator.									
On-farm Seed Treatment (Slurry)	Barley	Loader/treater/planter	WSP	1.06	9600	0.59	3.23	30513	1632
	Corn	Loader/treater/planter (c)	WSP	1.79	2400	0.25	1.37	71922	3846
		Loader/treater/planter (f)			1200	0.13	0.69	143845	7693
	Oat	Loader/treater/planter	WSP	1.47	9200	0.79	4.31	22841	1222
	Wheat	Loader/treater/planter	WSP	0.83	14000	0.68	3.71	26556	1420
PPE: Long sleeves, long pants and chemical-resistant gloves. Closed cab planter.									
Potato Seed Piece Treatment	Potato	Loader/treater/planter	DU	0.80	40 000	13.07	35.47	1377	149
		Loader/treater/planter	DU		90 000	29.42	79.82	612	66
	Potato	Loader/treater/planter	DU	0.45	40 000	7.35	19.95	2448	264
		Loader/treater/planter	DU		90 000	16.55	44.90	1088	117
PPE: Long sleeves, long pants and chemical-resistant gloves. Respirator for loader/treater. Closed cab planter.									
Potato Seed Piece Treatment	Potato	Loader/treater/planter	DU	0.80	40 000	13.07	21.49	1377	245
		Loader/treater/planter	DU		90 000	29.42	48.34	612	109
	Potato	Loader/treater/planter	DU	0.45	40 000	7.35	12.09	2448	436
		Loader/treater/planter	DU		90 000	16.55	27.19	1088	194
PPE: Long sleeves, long pants and gloves. Respirator for loader/treater. Closed cab planter. Restriction on amount handled per day (7.85 kg a.i./day).									
Potato Seed Piece Treatment	Potato	Loader/treater/planter	DU	0.80	9800	3.20	5.26	5619	1001
	Potato	Loader/treater/planter	DU	0.45	17 440	3.21	5.27	5614	1000
PPE: Long sleeves, long pants and chemical-resistant gloves.									
Seed Potatoes for Storage	Potato	Treater	SN	0.72	64 000	1.92	7.57	9396	696
		Cutter/Sorter	SN		64 000	NM	11.85	NM	445
		All tasks	SN		64 000	1.92	11.85	9396	445
PPE: Long sleeves, long pants and chemical-resistant gloves. Respirator.									
Seed Potatoes for Storage	Potato	Treater	SN	0.72	64 000	1.92	0.76	9396	6961
		Cutter/Sorter	SN		64 000	NM	1.18	NM	4448
		All tasks	SN		64 000	1.92	1.18	9396	4448

Shaded cells indicate MOEs that are less than the target. N/A= not applicable; NM = not measured
[a] Form. refers to formulation type, WP = Wettable powder; DU = Dust; SN = Solution.
[b] Maximum registered application rate of mancozeb in grams of active ingredient per kilogram of seed.
[c] Where dermal exposure µg/kg bw/day = (unit exposure from surrogate exposure study (See Appendix II, Table 1) × seed treated per day (kg) × application rate (kg a.i./kg seed) × dermal absorption (1%)/70 kg bw.
[d] Where inhalation exposure µg/kg bw/day = (unit exposure × seed treated per day(kg) × application rate)/70 kg bw.
[e] Based on the short- to intermediate-term dermal NOAEL of 18 mg/kg bw/day from the oral modified reproductive toxicity study, target MOE of 1000.
[f] Based on the short- to intermediate-term inhalation NOAEL of 5.27 mg/kg bw/day from the inhalation developmental toxicity study, target MOE of 1000.
[g] For closed mix/load scenarios, the wettable powder formulations were assumed to be in water soluble packets, and exposure was assumed to be equivalent to the liquid formulation.
[h] PHED wettable powder mix/load data was added to the unit exposure values for mixers/loaders to estimate exposure with wettable powders for open mix/load scenarios.

Table 5 ETU Mixing/Loading and Applying Short- to Intermediate-Term Exposure and Risk Assessment

Use Site Category	Crop	Form [a]	Method of Application [b]	Rate [c] (kg a.i./ha) or (kg a.i./L)	Area Treated ha/day [d] (ha) or (L)	Daily Exposure (µg/kg bw/day)				Combined MOE [I]
						ETU Tank Mix		Metabolic Conversion from MCZ [g]	Total ETU [h]	
						Dermal [e]	Inhalation [f]			
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Open cab groundboom and airblast.										
Use-site category 4 & 27: Forests/Woodlots and Ornamentals Outdoors	Arborvitae, Ash, Juniper, Douglas fir, Hawthorn, Oak, Sycamore	DF, WG	Airblast	2.63	16	3.48×10^{-1}	7.57×10^{-3}	6.33×10^{-1}	9.88×10^{-1}	5058
			Groundboom	2.63	30	1.16×10^{-1}	3.31×10^{-3}	3.33×10^{-1}	4.53×10^{-1}	11045
			LP Handwand	2.63×10^{-3} (kg a.i./L)	150 L	5.19×10^{-3}	5.14×10^{-4}	2.42×10^{-2}	2.99×10^{-2}	167367
			HP Handwand		3750 L	7.17×10^{-1}	4.26×10^{-2}	2.21	2.97	1684
			Backpack		150 L	2.80×10^{-2}	7.04×10^{-4}	5.03×10^{-2}	7.90×10^{-2}	63305
		WP	Airblast	2.80	16	4.77×10^{-1}	4.34×10^{-2}	3.50	4.02	1244
			Groundboom	2.80	30	3.23×10^{-1}	6.97×10^{-2}	5.65	6.04	827
			LP Handwand	2.80×10^{-3} (kg a.i./L)	150 L	1.07×10^{-1}	1.71×10^{-2}	7.29×10^{-1}	8.53×10^{-1}	5862
			HP Handwand		3750 L	7.90×10^{-1}	5.37×10^{-2}	3.02	3.86	1294
			Backpack		150 L	3.08×10^{-2}	1.08×10^{-3}	8.01×10^{-2}	1.12×10^{-1}	44620
	Holly, Ivy, Pine	DF, WG	Airblast	1.88	16	2.48×10^{-1}	5.41×10^{-3}	4.52×10^{-1}	7.06×10^{-1}	7082
			Groundboom	1.88	30	8.31×10^{-2}	2.36×10^{-3}	2.38×10^{-1}	3.23×10^{-1}	15464
			LP Handwand	1.88×10^{-3} (kg a.i./L)	150 L	3.71×10^{-3}	3.67×10^{-4}	1.73×10^{-2}	2.13×10^{-2}	234314
			HP Handwand		3750 L	5.12×10^{-1}	3.04×10^{-2}	1.58	2.12	2357
			Backpack		150 L	2.00×10^{-2}	5.03×10^{-4}	3.59×10^{-2}	5.64×10^{-2}	88627
		WP	Airblast	2.00	16	3.40×10^{-1}	3.10×10^{-2}	2.50	2.87	1741
			Groundboom	2.00	30	2.30×10^{-1}	4.98×10^{-2}	4.04	4.32	1158
Use-site category 4 & 27: Forests/Woodlots and Ornamentals Outdoors	Holly, Ivy, Pine	WP	LP Handwand	2.00×10^{-3} (kg a.i./L)	150 L	7.62×10^{-2}	1.22×10^{-2}	5.21×10^{-1}	6.09×10^{-1}	8207
			HP Handwand		3750 L	5.64×10^{-1}	3.84×10^{-2}	2.16	2.76	1812
			Backpack		150 L	2.20×10^{-2}	7.73×10^{-4}	5.72×10^{-2}	8.00×10^{-2}	62468
	Honeysuckle	DF, WG	Groundboom	1.50	30	6.65×10^{-2}	1.89×10^{-3}	1.90×10^{-1}	2.59×10^{-1}	19329
			LP Handwand	1.50×10^{-3} (kg a.i./L)	150 L	2.97×10^{-3}	2.94×10^{-4}	1.38×10^{-2}	1.71×10^{-2}	292893
			Backpack		150 L	1.60×10^{-2}	4.02×10^{-4}	2.87×10^{-2}	4.51×10^{-2}	110784
Engineering control: Wettable Powder in Water Soluble Packaging (WSP). Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Respirator for HP Handwand M/L/A. Open cab groundboom and airblast.										
Use-site category 4 & 27: Forests/Woodlots	Arborvitae, Ash, Juniper, Douglas fir, Hawthorn, Oak,	DF, WG	HP Handwand	2.63×10^{-3} (kg a.i./L)	3750 L	7.17×10^{-1}	4.26×10^{-3}	7.67×10^{-1}	1.49	3360
		WP in	Airblast	2.80	16	3.30×10^{-1}	7.54×10^{-3}	5.67×10^{-1}	9.04×10^{-1}	5529

Use Site Category	Crop	Form [a]	Method of Application [b]	Rate [c] (kg a.i./ha) or (kg a.i./L)	Area Treated ha/day [d] (ha) or (L)	Daily Exposure (µg/kg bw/day) ETU Tank Mix: Dermal [e]	Daily Exposure (µg/kg bw/day) ETU Tank Mix: Inhalation [f]	Daily Exposure (µg/kg bw/day) Metabolic Conversion from MCZ [g]	Daily Exposure (µg/kg bw/day) Total ETU [h]	Combined MOE [I]
and Ornamentals Outdoors	Sycamore	WSP	Groundboom	2.80	30	4.73×10^{-2}	2.52×10^{-3}	1.52×10^{-1}	2.02×10^{-1}	24809
			LP Handwand	2.80×10^{-3} (kg a.i./L)	150 L	5.09×10^{-3}	5.42×10^{-4}	2.46×10^{-2}	3.02×10^{-2}	165444
			HP Handwand		3750 L	7.54×10^{-1}	4.53×10^{-3}	7.98×10^{-1}	1.56	3212
			Backpack		150 L	2.94×10^{-2}	7.45×10^{-4}	5.25×10^{-2}	8.26×10^{-2}	60530
	Holly, Ivy, Pine	DF, WG	HP Handwand	1.88×10^{-3} (kg a.i./L)	3750 L	5.12×10^{-1}	3.04×10^{-3}	5.48×10^{-1}	1.06	4704
		WP in WSP	Airblast	2.00	16	2.36×10^{-1}	5.39×10^{-3}	4.05×10^{-1}	6.46×10^{-1}	7740
			Groundboom	2.00	30	3.38×10^{-2}	1.80×10^{-3}	1.08×10^{-1}	1.44×10^{-1}	34733
Use-site category 4 & 27: Forests/Woodlots and Ornamentals Outdoors	Holly, Ivy, Pine	WP in WSP	LP Handwand	2.00×10^{-3} (kg a.i./L)	150 L	3.64×10^{-3}	3.87×10^{-4}	1.76×10^{-2}	2.16×10^{-2}	231621
			HP Handwand		3750 L	5.39×10^{-1}	3.24×10^{-3}	5.70×10^{-1}	1.11	4496
			Backpack		150 L	2.10×10^{-2}	5.32×10^{-4}	3.75×10^{-2}	5.90×10^{-2}	84742
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves.										
Use-site category 5: Greenhouse Food Crops	Tobacco (greenhouse)	DF, WG	LP Handwand	3.00×10^{-3} (kg a.i./L)	150 L	5.93×10^{-3}	5.88×10^{-4}	2.76×10^{-2}	3.41×10^{-2}	146446
			HP Handwand		3750 L	8.20×10^{-1}	4.87×10^{-2}	2.53	3.39	1473
			Backpack		150 L	3.20×10^{-2}	8.05×10^{-4}	5.75×10^{-2}	9.03×10^{-2}	55392
		WP	LP Handwand	3.20×10^{-3} (kg a.i./L)	150 L	1.22×10^{-1}	1.95×10^{-2}	8.33×10^{-1}	9.75×10^{-1}	5130
			HP Handwand		3750 L	9.03×10^{-1}	6.14×10^{-2}	3.45	4.41	1133
			Backpack		150 L	3.52×10^{-2}	1.24×10^{-3}	9.16×10^{-2}	1.28×10^{-1}	39043
		SN	LP Handwand	3.30×10^{-3} (kg a.i./L)	150 L	6.00×10^{-3}	6.39×10^{-4}	2.90×10^{-2}	3.56×10^{-2}	140376
			HP Handwand		3750 L	8.89×10^{-1}	5.34×10^{-2}	2.74	3.68	1357
			Backpack		150 L	3.47×10^{-2}	8.78×10^{-4}	6.18×10^{-2}	9.74×10^{-2}	51359
Engineering control: Wettable Powder in WSP. **Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves. Respirator for HP Handwand M/L/A.**										
Use-site category 5: Greenhouse Food Crops	Tobacco (greenhouse)	DF, WG	HP Handwand	3.00×10^{-3} (kg a.i./L)	3750 L	8.20×10^{-1}	4.87×10^{-3}	8.76×10^{-1}	1.70	2940
		WP in WSP	HP Handwand	3.20×10^{-3} (kg a.i./L)	3750 L	8.62×10^{-1}	5.18×10^{-3}	9.12×10^{-1}	1.78	2810
		SN	HP Handwand	3.30×10^{-3} (kg a.i./L)	3750 L	8.89×10^{-1}	5.34×10^{-3}	9.41×10^{-1}	1.83	2725
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Open cab groundboom.										
Use-site category 07: Terrestrial Crops Grown for Seed Only	Alfalfa grown for seed	DF, WG	Groundboom (f)	1.10	100	1.62×10^{-1}	4.60×10^{-3}	4.63×10^{-1}	6.29×10^{-1}	7944
			Groundboom (c)		300	4.85×10^{-1}	1.38×10^{-2}	1.39	1.89	2648
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Respirator for M/L. Open cab groundboom.										
Use-site category 07: Terrestrial Crops Grown for Seed Only	Alfalfa grown for seed	DF, WG	Groundboom (f)	1.10	100	1.62×10^{-1}	3.16×10^{-3}	3.55×10^{-1}	5.20×10^{-1}	9610
			Groundboom (c)		300	4.85×10^{-1}	9.49×10^{-3}	1.07	1.56	3203
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves. Open cab airblast.										
Use-site category 14: Terrestrial Food	Apple	DF, WG	Airblast	4.50	16	5.96×10^{-1}	1.30×10^{-2}	1.09	1.69	2951
		WP	Airblast	4.80	16	8.17×10^{-1}	7.44×10^{-2}	6.00	6.89	725

Use Site Category	Crop	Form [a]	Method of Application [b]	Rate [c] (kg a.i./ha) or (kg a.i./L)	Area Treated ha/day [d] (ha) or (L)	Daily Exposure (µg/kg bw/day)				Combined MOE [I]
						ETU Tank Mix		Metabolic Conversion from MCZ [g]	Total ETU [h]	
						Dermal [e]	Inhalation [f]			
Crops (Orchard and Vine Crops)		SN	Airblast	4.84	16	5.84×10^{-1}	1.46×10^{-2}	1.12	1.72	2906
	Grape	DF	Airblast	1.50	16	1.99×10^{-1}	4.33×10^{-3}	3.62×10^{-1}	5.65×10^{-1}	8852
		WG	Airblast	1.60	16	2.12×10^{-1}	4.62×10^{-3}	3.86×10^{-1}	6.03×10^{-1}	8299
		WP	Airblast	5.40	16	9.19×10^{-1}	8.37×10^{-2}	6.75	7.75	645
	Pear	WP	Airblast	7.20	16	1.23	1.12×10^{-1}	9.00	10.34	484
Engineering control: Wettable Powders in WSP. Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves. Respirator for applicators. Open cab airblast.										
Use-site category 14: Terrestrial Food Crops (Orchard and Vine Crops)	Apple	DF, WG	Airblast	4.50	16	5.96×10^{-1}	2.24×10^{-3}	6.83×10^{-1}	1.28	3903
		WP in WSP	Airblast	4.80	16	5.65×10^{-1}	1.47×10^{-3}	5.43×10^{-1}	1.11	4507
		SN	Airblast	4.84	16	5.84×10^{-1}	3.05×10^{-3}	6.89×10^{-1}	1.28	3918
Use-site category 14: Terrestrial Food Crops (Orchard and Vine Crops)	Grape	WP in WSP	Airblast	5.40	16	6.36×10^{-1}	1.65×10^{-3}	6.10×10^{-1}	1.25	4006
	Pears	WP in WSP	Airblast	7.20	16	8.48×10^{-1}	2.21×10^{-3}	8.14×10^{-1}	1.66	3005
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Open cab groundboom.										
Use-site category 14: Terrestrial Food Crops (Low Acreage Field and Vegetable Crops)	Cantaloupe, Cucumber, Melon, Onion including dry bulb (foliar), Pumpkin, Squash, Tomato, Watermelon	DF, WG	Groundboom	2.44	30	1.08×10^{-1}	3.07×10^{-3}	3.09×10^{-1}	4.20×10^{-1}	11893
		WP	Groundboom	2.60	30	3.00×10^{-1}	6.48×10^{-2}	5.25	5.61	891
		SN	Groundboom	2.69	30	6.07×10^{-2}	4.05×10^{-3}	2.94×10^{-1}	3.58×10^{-1}	13953
	Carrot	DF, WG	Groundboom	1.69	30	7.47×10^{-2}	2.13×10^{-3}	2.14×10^{-1}	2.91×10^{-1}	17187
	Carrot, Celery	WP	Groundboom	1.80	30	2.07×10^{-1}	4.48×10^{-2}	3.63	3.89	1287
		SN	Groundboom	1.86	30	4.19×10^{-2}	2.80×10^{-3}	2.03×10^{-1}	2.47×10^{-1}	20203
	Celery	DF, WG	Groundboom	2.44	30	1.08×10^{-1}	3.07×10^{-3}	3.09×10^{-1}	4.20×10^{-1}	11893
	Ginseng	DF, WG	Groundboom	3.30	30	1.46×10^{-1}	4.16×10^{-3}	4.19×10^{-1}	5.69×10^{-1}	8786
		WP	Groundboom	3.52	30	4.06×10^{-1}	8.77×10^{-2}	7.11	7.60	658
		SN	Groundboom	3.57	30	8.05×10^{-2}	5.38×10^{-3}	3.90×10^{-1}	4.76×10^{-1}	10512
	Head Lettuce	WG	Groundboom	1.60	30	7.09×10^{-2}	2.02×10^{-3}	2.03×10^{-1}	2.76×10^{-1}	18121
		WP	Groundboom	1.61	30	1.86×10^{-1}	4.02×10^{-2}	3.25	3.48	1437
	Onion dry bulb (in-furrow)	DF, WG	Broadcast Spreader	6.60	30	2.49×10^{-1}	1.19×10^{-2}	9.37×10^{-1}	1.20	4174
Engineering control: Wettable Powder in WSP. Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Open cab groundboom.										
Use-site category 14: Terrestrial Food Crops (Low Acreage Field and Vegetable Crops)	Cantaloupe, Cucumber, Melon, Onion including dry bulb (foliar), Pumpkin, Squash, Tomato, Watermelon	WP in WSP	Groundboom	2.60	30	4.39×10^{-2}	2.34×10^{-3}	1.41×10^{-1}	1.87×10^{-1}	26718
	Carrot, Celery	WP in WSP	Groundboom	1.80	30	3.04×10^{-2}	1.62×10^{-3}	9.75×10^{-2}	1.30×10^{-1}	38592
	Ginseng	WP in WSP	Groundboom	3.52	30	5.94×10^{-2}	3.17×10^{-3}	1.91×10^{-1}	2.53×10^{-1}	19735

Use Site Category	Crop	Form [a]	Method of Application [b]	Rate [c] (kg a.i./ha) or (kg a.i./L)	Area Treated ha/day [d] (ha) or (L)	Daily Exposure (µg/kg bw/day)				Combined MOE [I]
						ETU Tank Mix		Metabolic Conversion from MCZ [g]	Total ETU [h]	
						Dermal [e]	Inhalation [f]			
	Head Lettuce	WP in WSP	Groundboom	1.61	30	2.72×10^{-2}	1.45×10^{-3}	8.74×10^{-2}	1.16×10^{-1}	43093
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves. Respirator for M/L.										
Use-site category 14: Terrestrial Food Crops (Low Acreage Field and Vegetable Crops)	Onion dry bulb (in-furrow)	DF, WG	Broadcast Spreader	6.60	30	2.49×10^{-1}	9.34×10^{-3}	7.42×10^{-1}	1.00	4998
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application).										
Use-site category 14: Terrestrial Food Crops (Low Acreage Field and Vegetable Crops)	Lentil	SN	Aerial M/L	2.23	400	2.93×10^{-1}	2.04×10^{-2}	2.02	2.33	2145
			Aerial A			1.11×10^{-1}	1.78×10^{-3}	1.59×10^{-1}	2.72×10^{-1}	18396
			Groundboom (f)		100	1.68×10^{-1}	1.12×10^{-2}	8.13×10^{-1}	9.92×10^{-1}	5042
			Groundboom (c)		300	5.04×10^{-1}	3.36×10^{-2}	2.44	2.98	1681
Use-site category 14: Terrestrial Food Crops (High Acreage Field and Vegetable Crops) (also Use-site category 13: Terrestrial Feed Crops (Potato and Wheat)	Lentil, Potato, Sugar beet (ground application only), Wheat	DF, WG	Aerial M/L	1.69	400	7.11×10^{-1}	9.84×10^{-3}	1.92	2.64	1892
			Aerial A			8.39×10^{-2}	1.35×10^{-3}	1.21×10^{-1}	2.06×10^{-1}	24303
			Groundboom (f)		100	2.49×10^{-1}	7.09×10^{-3}	7.14×10^{-1}	9.70×10^{-1}	5153
			Groundboom (c)		300	7.48×10^{-1}	2.13×10^{-2}	2.14	2.91	1718
	Potato, Sugar beet (ground application only), Wheat	WP	Aerial M/L	1.80	400	2.46	5.78×10^{-1}	47.45	50.49	99
			Aerial A			8.94×10^{-2}	1.44×10^{-3}	1.29×10^{-1}	2.19×10^{-1}	22791
			Groundboom (f)		100	6.91×10^{-1}	1.49×10^{-1}	12.11	12.95	386
			Groundboom (c)		300	2.07	4.48×10^{-1}	36.34	38.86	129
	Potato (ground application only), Wheat	SN	Aerial M/L	1.86	400	2.44×10^{-1}	1.70×10^{-2}	1.68	1.94	2577
			Aerial A			9.22×10^{-2}	1.48×10^{-3}	1.33×10^{-1}	2.26×10^{-1}	22103
			Groundboom (f)		100	1.40×10^{-1}	9.33×10^{-3}	6.76×10^{-1}	8.25×10^{-1}	6058
			Groundboom (c)		300	4.19×10^{-1}	2.80×10^{-2}	2.03	2.48	2019
Engineering control: Wettable Powder in WSP. **Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Respirator for M/L (except WSP) and A.**										
Use-site category 14: Terrestrial Food Crops (High Acreage Field and Vegetable Crops) (also Use-site category 13: Terrestrial Feed Crops (Potato and Wheat)	Lentil	SN	Aerial M/L	2.23	400	2.93×10^{-1}	2.04×10^{-3}	6.42×10^{-1}	9.37×10^{-1}	5336
			Groundboom (f)		100	1.68×10^{-1}	1.12×10^{-3}	2.62×10^{-1}	4.31×10^{-1}	11597
			Groundboom (c)		300	5.04×10^{-1}	3.36×10^{-3}	7.86×10^{-1}	1.29	3866
	Lentil, Potato, Sugar beet (ground application only), Wheat	DF, WG	Aerial M/L	1.69	400	7.11×10^{-1}	9.84×10^{-4}	1.26	1.97	2538
			Groundboom (f)		100	2.49×10^{-1}	7.09×10^{-4}	3.92×10^{-1}	6.42×10^{-1}	7792
			Groundboom (c)		300	7.48×10^{-1}	2.13×10^{-3}	1.17	1.92	2597
Use-site category 14: Terrestrial Food	Potato, Sugar beet (ground application	WP in WSP	Aerial M/L	1.80	400	1.00×10^{-1}	1.85×10^{-3}	3.06×10^{-1}	4.07×10^{-1}	12272
			Groundboom (f)		100	1.01×10^{-1}	9.57×10^{-4}	1.59×10^{-1}	2.61×10^{-1}	19172

Use Site Category	Crop	Form [a]	Method of Application [b]	Rate [c] (kg a.i./ha) or (kg a.i./L)	Area Treated ha/day [d] (ha) or (L)	Daily Exposure (µg/kg bw/day)				Combined MOE [I]
						ETU Tank Mix		Metabolic Conversion from MCZ [g]	Total ETU [h]	
						Dermal [e]	Inhalation [f]			
Crops (High Acreage Field and Vegetable Crops) (also Use-site category 13: Terrestrial Feed Crops (Potato and Wheat)	only), Wheat		Groundboom (c)		300	3.04×10^{-1}	2.87×10^{-3}	4.76×10^{-1}	7.82×10^{-1}	6391
	Potato (ground application only), Wheat	SN	Aerial M/L	1.86	400	2.44×10^{-1}	1.70×10^{-3}	5.34×10^{-1}	7.80×10^{-1}	6412
			Groundboom (f)		100	1.40×10^{-1}	9.33×10^{-4}	2.18×10^{-1}	3.59×10^{-1}	13934
			Groundboom (c)		300	4.19×10^{-1}	2.80×10^{-3}	6.55×10^{-1}	1.08	4645

Shaded cells indicate MOEs that are less than the target. M/L = Mix/Load; A = Apply.

[a] Form. refers to formulation type, WP = Wettable powder; WG = Wettable Granules; DF = Dry flowable; SN = Solution; WSP = Water soluble packaging.

[b] M/L = Mixer/Loader; groundboom c) = custom groundboom application; groundboom (f) = farmer groundboom application ; hp handwand = high pressure handwand; lp handwand = low pressure handwand

[c] Maximum listed label rate in kilograms of active ingredient per hectare (kg a.i./ha) unless specified as kilograms of active ingredient per litre (kg a.i./L). Rates per litre were calculated assuming the following spray volumes: Trees and ornamentals assumed 1000 L/ha and greenhouse tobacco assumed 2500 L/ha.

[d] Based on default assumptions.

[e] Where dermal exposure µg/kg bw/day = (unit exposure (PHED) × area treated × use rate × tank mix conversion factor (0.1% for M/L and 0.2% for A) × 45% dermal absorption)/70 kg bw.

[f] Where inhalation exposure µg/kg bw/day = (unit exposure (PHED) × area treated × tank mix conversion factor (0.1% for M/L and 0.2% for A) × use rate)/70 kg bw.

[g] Systemic exposure µg/kg bw/day = total exposure to mancozeb (as expressed in Table 2, dermal exposure + inhalation exposure) × metabolic conversion of mancozeb to ETU (7.5%).

[h] Total daily exposure to ETU µg/kg bw/day = Sum of daily exposure to ETU from tank mix (dermal exposure + inhalation exposure) and metabolic conversion to ETU.

[I] Based on the short- to intermediate-term NOAEL of 5 mg/kg bw/day from the oral developmental toxicity study, target MOE of 1000.

Table 6 ETU Mixing/Loading and Applying Long-Term Exposure and Risk Assessment

Use Site Category	Crop	Form [a]	Method of Application [b]	Rate [c] (kg a.i./ha) or (kg a.i./L)	Area Treated ha/day [d] (ha) or (L)	Daily Exposure (µg/kg bw/day)				Combined MOE[i]
						ETU Tank Mix		Metabolic Conversion from MCZ [g]	Total ETU[h]	
						Dermal [e]	Inhalation [f]			
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves.										
Use-site category 5: Greenhouse Food Crops	Tomato	DF, WG	LP Handwand	6.00×10^{-3} (kg a.i./L)	150 L	1.19×10^{-2}	1.18×10^{-3}	5.52×10^{-2}	6.83×10^{-2}	2636
			HP Handwand		3750 L	1.64	9.74×10^{-2}	5.05	6.79	27
			Backpack		150 L	6.40×10^{-2}	1.61×10^{-3}	1.15×10^{-1}	1.81×10^{-1}	997
		WP	LP Handwand	6.00×10^{-3} (kg a.i./L)	150 L	2.28×10^{-1}	3.66×10^{-2}	1.56	1.83	98
			HP Handwand		3750 L	1.69	1.15×10^{-1}	6.47	8.28	22
			Backpack		150 L	6.61×10^{-2}	2.32×10^{-3}	1.72×10^{-1}	2.40×10^{-1}	750

Use Site Category	Crop	Form [a]	Method of Application [b]	Rate [c] (kg a.i./ha) or (kg a.i./L)	Area Treated ha/day [d] (ha) or (L)	Daily Exposure (µg/kg bw/day)				Combined MOE[i]
						ETU Tank Mix		Metabolic Conversion from MCZ [g]	Total ETU[h]	
						Dermal [e]	Inhalation [f]			
Engineering control: Wettable Powder in Water Soluble Packaging (WSP). Maximum PPE: Chemical-resistant coveralls over long pants, long sleeved shirts, and chemical-resistant gloves. Respirator for all handheld M/L/A.										
Use-site category 5: Greenhouse Food Crops	Tomato	DF, WG	LP Handwand	6.00×10^{-3} (kg a.i./L)	150 L	8.47×10^{-3}	1.18×10^{-4}	1.19×10^{-2}	2.05×10^{-2}	8787
			HP Handwand		3750 L	5.40×10^{-1}	9.74×10^{-3}	8.26×10^{-1}	1.38	131
			Backpack		150 L	2.39×10^{-2}	1.61×10^{-4}	2.64×10^{-2}	5.05×10^{-2}	3568
		WP in WSP	LP Handwand	6.00×10^{-3} (kg a.i./L)	150 L	8.03×10^{-3}	1.16×10^{-4}	1.10×10^{-2}	1.92×10^{-2}	9380
			HP Handwand		3750 L	5.29×10^{-1}	9.71×10^{-3}	8.04×10^{-1}	1.34	134
			Backpack		150 L	2.35×10^{-2}	1.60×10^{-4}	2.55×10^{-2}	4.92×10^{-2}	3662
Engineering control: Wettable Powder in WSP. Maximum PPE: Chemical-resistant coveralls over long pants, long sleeved shirts, and chemical-resistant gloves. Respirator for M/L/A. Restriction on amount handled per day (2.25 kg a.i./day, approx. 375 L at 6 kg a.i. per 1000 L).										
Use-site category 5: Greenhouse Food Crops	Tomato	DF, WG	HP Handwand	6.00×10^{-3} (kg a.i./L)	375 L	5.40×10^{-2}	9.74×10^{-4}	8.26×10^{-2}	1.38×10^{-1}	1309
		WP in WSP	HP Handwand	6.00×10^{-3} (kg a.i./L)	375 L	5.29×10^{-2}	9.71×10^{-4}	8.04×10^{-2}	1.34×10^{-1}	1341

Shaded cells indicate MOEs that are less than the target.
[a] Form. refers to formulation type, WP = Wettable powder, WG = Wettable Granules, DF = Dry flowable, SN = Solution
[b] hp handwand = high pressure handwand; lp handwand = low pressure handwand
[c] Maximum listed label rate in kilograms of active ingredient per litre (kg a.i./L). Rate per litre were calculated assuming a spray volumes of 300 L/ha.
[d] Based on default assumptions, see Section 3.7 for details.
[e] Where dermal exposure µg/kg bw/day = (unit exposure (PHED) × area treated × use rate × tank mix conversion factor (0.1% for M/L and 0.2% for A) × 45% dermal absorption)/70 kg bw
[f] Where inhalation exposure µg/kg bw/day = (unit exposure (PHED) × area treated × tank mix conversion factor (0.1% for M/L and 0.2% for A) × use rate)/70 kg bw
[g] Systemic exposure µg/kg bw/day = total exposure to mancozeb (as expressed in Table 3 , dermal exposure + inhalation exposure) × metabolic conversion of mancozeb to ETU (7.5%)
[h] Total daily exposure to ETU µg/kg bw/day = Sum of daily exposure to ETU from tank mix (dermal exposure + inhalation exposure) and metabolic conversion to ETU
[I] Combined MOE, based on the long-term NOAEL of 0.18 mg/kg bw/day from the oral chronic toxicity study, target MOE of 300.

Table 7 ETU Seed and Potato Seed Piece Treatment Short- to Intermediate-term Exposure and Risk Assessment

Use Scenario	Crop	Activity	Form. [a]	Rate [b] (g a.i./kg Seed)	Seed Treated per Day [c] (kg seed/day)	Daily Exposure (µg/kg bw/day)				Combined MOE [h]
						ETU in tank mix		Metabolic Conversion from MCZ [f]	Total ETU [g]	
						Dermal [d]	Inhalation [e]			
PPE: Long sleeved shirt, long plants, and chemical-resistant gloves. Open mix/load [h]										
Commercial Seed Treatment (Slurry)	Barley	Treater/Bagger	WP	1.06	65 000	5.50×10^{-1}	2.88×10^{-1}	13.52	14.36	348
		Stacker/Tagger			65 000	5.44×10^{-2}	6.47×10^{-2}	2.57	2.69	1856
		Forklift Operator			65 000	1.06×10^{-2}	2.37×10^{-3}	9.78×10^{-2}	1.11×10^{-1}	45 123
	Corn	Treater/Bagger	WP	1.79	60 000	8.61×10^{-1}	4.51×10^{-1}	21.18	22.49	222
		Stacker/Tagger			60 000	8.53×10^{-2}	1.06×10^{-1}	4.03	4.22	1185
		Forklift Operator			60 000	1.66×10^{-2}	3.72×10^{-3}	1.53×10^{-1}	1.74×10^{-1}	28 806
	Oat	Treater/Bagger	WP	1.47	65 000	7.67×10^{-1}	4.01×10^{-1}	18.85	20.02	250
		Stacker/Tagger			65 000	7.59×10^{-2}	9.39×10^{-2}	3.59	3.76	1331
		Forklift Operator			65 000	1.48×10^{-2}	3.31×10^{-3}	1.36×10^{-1}	1.54×10^{-1}	32 371
	Wheat	Treater/Bagger	WP	0.83	65 000	4.33×10^{-1}	2.27×10^{-1}	10.65	11.31	442
		Stacker/Tagger			65 000	4.29×10^{-2}	5.31×10^{-2}	2.03	2.12	2356
		Forklift Operator			65 000	8.36×10^{-3}	1.87×10^{-3}	7.71×10^{-2}	8.73×10^{-2}	57 272
Engineering controls: WP in Water Soluble Packaging (WSP). PPE: Long sleeved shirt, long plants, and chemical-resistant gloves. Respirator.										
Commercial Seed Treatment (Slurry)	Barley	Treater/Bagger	WP in WSP	1.06	65 000	3.15×10^{-1}	2.33×10^{-2}	1.14	1.47	3390
		Stacker/Tagger			65 000	5.44×10^{-2}	6.74×10^{-3}	2.98×10^{-1}	3.59×10^{-1}	13 919
		Forklift Operator			65 000	1.06×10^{-2}	2.37×10^{-4}	1.77×10^{-2}	2.86×10^{-2}	174 925
	Corn	Treater/Bagger	WP in WSP	1.79	60 000	4.94×10^{-1}	3.65×10^{-2}	1.78	2.31	2164
		Stacker/Tagger			60 000	8.53×10^{-2}	1.06×10^{-2}	4.67×10^{-1}	5.63×10^{-1}	8886
		Forklift Operator			60 000	1.66×10^{-2}	3.72×10^{-4}	2.78×10^{-2}	4.48×10^{-2}	111 671

Use Scenario	Crop	Activity	Form. [a]	Rate [b] (g a.i./kg Seed)	Seed Treated per Day [c] (kg seed/day)	Daily Exposure (µg/kg bw/day)				Combined MOE [h]
						ETU in tank mix		Metabolic Conversion from MCZ [f]	Total ETU [g]	
						Dermal [d]	Inhalation [e]			
Engineering controls: WP in WSP. [I] PPE: Long sleeved shirt, long plants, and chemical-resistant gloves. Respirator.										
Commercial Seed Treatment (Slurry)	Oat	Treater/Bagger	WP in WSP	1.47	65 000	4.40×10^{-1}	3.25×10^{-2}	1.58	2.06	2432
		Stacker/Tagger			65 000	7.59×10^{-2}	9.39×10^{-3}	4.15×10^{-1}	5.01×10^{-1}	9985
		Forklift Operator			65 000	1.48×10^{-2}	3.31×10^{-4}	2.47×10^{-2}	3.98×10^{-2}	125 490
	Wheat	Treater/Bagger	WP in WSP	0.83	65 000	2.49×10^{-1}	1.84×10^{-2}	8.95×10^{-1}	1.16	4303
		Stacker/Tagger			65 000	4.29×10^{-2}	5.31×10^{-3}	2.35×10^{-1}	2.83×10^{-1}	17 666
		Forklift Operator			65 000	8.36×10^{-3}	1.87×10^{-4}	1.40×10^{-2}	2.25×10^{-2}	222 020
PPE: Long pants, long sleeved shirt, and chemical-resistant gloves. Open cab planter.										
Handling and Planting Treated Seed	Barley	Loader/Planter	WP	1.06	9600	2.44×10^{-1}	7.19×10^{-2}	2.90	3.21	1556
	Flax	Loader/Planter	WP	1.79	3600	1.55×10^{-1}	4.57×10^{-2}	1.84	2.04	2445
	Oats	Loader/Planter	WP	1.47	9200	3.26×10^{-1}	9.60×10^{-2}	3.87	4.29	1165
	Wheat	Loader/Planter	WP	0.83	14 000	2.80×10^{-1}	8.26×10^{-2}	3.33	3.69	1354
PPE: Long pants, long sleeved shirt, and chemical-resistant gloves. Open cab planter. Respirator for Loading and Planting.										
Handling and Planting Treated Seed	Barley	Loader/Planter	WP	1.06	9600	2.44×10^{-1}	7.19×10^{-3}	4.73×10^{-1}	7.23×10^{-1}	6911
	Flax	Loader/Planter	WP	1.79	3600	1.55×10^{-1}	4.57×10^{-3}	3.01×10^{-1}	4.60×10^{-1}	10 860
	Oats	Loader/Planter	WP	1.47	9200	3.26×10^{-1}	9.60×10^{-3}	6.31×10^{-1}	9.66×10^{-1}	5173
	Wheat	Loader/Planter	WP	0.83	14 000	2.80×10^{-1}	8.26×10^{-3}	5.43×10^{-1}	8.31×10^{-1}	6015
Engineering Controls: Closed cab planter. PPE: Long pants, long sleeved shirt, and chemical-resistant gloves.										
Handling and Planting Treated Seed	Corn	Loader/Planter (f)	WP	1.79	1200	9.97×10^{-2}	1.02×10^{-2}	4.65×10^{-1}	5.75×10^{-1}	8701
		Loader/Planter (c)	WP		2400	4.98×10^{-2}	5.09×10^{-3}	2.32×10^{-1}	2.87×10^{-1}	17 402
Engineering controls: Closed cab planter. PPE: Long sleeved shirt, long plants, and chemical-resistant gloves while loading and treating.										
On-farm Seed Treatment (Planter or Drill Box	Barley	Loader/treater/planter	WP	1.06	9600	6.82×10^{-1}	1.64×10^{-1}	13.44	14.29	350
	Corn	Loader/treater/planter (c)	WP	1.79	2400	2.89×10^{-1}	6.96×10^{-2}	5.70	6.06	825

Use Scenario	Crop	Activity	Form.[a]	Rate[b] (g a.i./kg Seed)	Seed Treated per Day[c] (kg seed/day)	Daily Exposure (µg/kg bw/day)				Combined MOE[h]
						ETU in tank mix		Metabolic Conversion from MCZ[f]	Total ETU[g]	
						Dermal[d]	Inhalation[e]			
Treatment, Dry Application)		Loader/treater/planter (f)	WP		1200	1.45×10^{-1}	3.48×10^{-2}	2.85	3.03	1650
	Flax	Loader/treater/planter	WP	1.79	3600	4.34×10^{-1}	1.04×10^{-1}	8.55	9.09	550
	Oat	Loader/treater/planter	WP	1.47	9200	9.11×10^{-1}	2.19×10^{-1}	17.96	19.09	262
	Wheat	Loader/treater/planter	WP	0.83	14 000	7.84×10^{-1}	1.89×10^{-1}	15.45	16.42	305
PPE: Long sleeved shirt, long plants, and chemical-resistant gloves. Open mix/load .[h] Open cab planter.										
On-farm Seed Treatment (Slurry)	Barley	Loader/treater/planter	WP	1.06	9600	8.77×10^{-2}	7.27×10^{-2}	3.13	3.30	1517
	Corn	Loader/treater/planter (c)	WP	1.79	2400	3.72×10^{-2}	3.09×10^{-2}	1.33	1.40	3576
		Loader/treater/planter (f)			1200	1.86×10^{-2}	1.54×10^{-2}	6.65×10^{-1}	6.99×10^{-1}	7153
	Oat	Loader/treater/planter	WP	1.47	9200	1.17×10^{-1}	9.72×10^{-2}	4.19	4.40	1136
	Wheat	Loader/treater/planter	WP	0.83	14 000	1.01×10^{-1}	8.36×10^{-2}	3.60	3.79	1321
Engineering controls: WP in WSP.[I] PPE: Open mix/load. Long sleeved shirt, long plants, and chemical-resistant gloves. Respirator.										
On-farm Seed Treatment (Slurry)	Barley	Loader/treater/planter	WP in WSP	1.06	9600	5.31×10^{-2}	6.46×10^{-3}	2.86×10^{-1}	3.46×10^{-1}	14 450
	Corn	Loader/treater/planter (c)	WP in WSP	1.79	2400	2.25×10^{-2}	2.74×10^{-3}	1.22×10^{-1}	1.47×10^{-1}	34 062
		Loader/treater/planter (f)			1200	1.13×10^{-2}	1.37×10^{-3}	6.08×10^{-2}	7.34×10^{-2}	68 123
	Oat	Loader/treater/planter	WP in WSP	1.47	9200	7.09×10^{-2}	8.63×10^{-3}	3.83×10^{-1}	4.62×10^{-1}	10 817
	Wheat	Loader/treater/planter	WSP	0.83	14 000	6.10×10^{-2}	7.42×10^{-3}	3.29×10^{-1}	3.98×10^{-1}	12 577
PPE: Long sleeves, long pants and chemical-resistant gloves. Closed cab planter.										
On-farm Potato Seed Piece Treatment	Potato	Loader/treater/planter	DU	0.80	40 000	5.88×10^{-1}	3.55×10^{-2}	3.64	4.26	1172
		Loader/treater/planter	DU		90 000	1.32	7.98×10^{-2}	8.19	9.60	521
	Potato	Loader/treater/planter	DU	0.45	40 000	3.31×10^{-1}	2.00×10^{-2}	2.05	2.40	2084
		Loader/treater/planter	DU		90 000	7.45×10^{-1}	4.49×10^{-2}	4.61	5.40	926

Use Scenario	Crop	Activity	Form. [a]	Rate [b] (g a.i./kg Seed)	Seed Treated per Day [c] (kg seed/day)	Daily Exposure (µg/kg bw/day)				Combined MOE [h]
						ETU in tank mix		Metabolic Conversion from MCZ [f]	Total ETU [g]	
						Dermal [d]	Inhalation [e]			
PPE: Long sleeves, long pants and chemical-resistant gloves. Respirator for loader/treater. Closed cab planter.										
On-farm Potato Seed Piece Treatment	Potato	Loader/treater/planter	DU	0.80	40 000	5.88×10^{-1}	2.15×10^{-2}	2.59	3.20	1562
		Loader/treater/planter	DU		90 000	1.32	4.83×10^{-2}	5.83	7.20	694
	Potato	Loader/treater/planter	DU	0.45	40 000	3.31×10^{-1}	1.21×10^{-2}	1.46	1.80	2776
		Loader/treater/planter	DU		90 000	7.45×10^{-1}	2.72×10^{-2}	3.28	4.05	1234
PPE: Long sleeves, long pants and chemical-resistant gloves. Respirator for loader/treater. Closed cab planter. Restriction on amount handled per day (7.85 kg a.i./day).										
On-farm Potato Seed Piece Treatment	Potato	Loader/treater/planter	DU	0.80	9800	1.44×10^{-1}	5.26×10^{-3}	6.35×10^{-1}	7.84×10^{-1}	6374
	Potato	Loader/treater/planter	DU	0.45	17440	1.44×10^{-1}	5.27×10^{-3}	6.36×10^{-1}	7.85×10^{-1}	6367
PPE: Long sleeves, long pants and chemical-resistant gloves.										
Seed Potatoes for Storage	Potato	Treater	SN	0.72	64 000	1.72×10^{-1}	1.51×10^{-2}	7.11×10^{-1}	8.99×10^{-1}	5562
		Cutter/Sorter	SN		64 000	NM	2.37×10^{-2}	8.89×10^{-1}	9.12×10^{-1}	5480
		All tasks	SN		64 000	1.72×10^{-1}	2.37×10^{-2}	1.03	1.23	4070
PPE: Long sleeves, long pants and chemical-resistant gloves. Respirator.										
Seed Potatoes for Storage	Potato	Treater	SN	0.72	64 000	1.72×10^{-1}	1.51×10^{-3}	2.00×10^{-1}	3.74×10^{-1}	13356
		Cutter/Sorter	SN		64 000	NM	2.37×10^{-3}	8.89×10^{-2}	9.12×10^{-2}	54801
		All tasks	SN		64 000	1.72×10^{-1}	2.37×10^{-3}	2.33×10^{-1}	4.07×10^{-1}	12276

Shaded cells indicate MOEs that are less than the target. N/A= not applicable; NM = not measured; c) = custom; (f) = farmer

[a] Form. refers to formulation type, WP = Wettable powder; DU = Dust; SN = Solution.

[b] Maximum listed label rate of mancozeb in grams of active ingredient per kilogram of seed.

[d] Where dermal exposure µg/kg bw/day = (unit exposure from surrogate exposure study (See Appendix II, Table 1) × seed treated per day × use rate × ETU conversion factor (0.1 % dry mix/load and application, 0.2% solution or slurry application and handling treated seed) × 45% dermal absorption)/70 kg bw.

[e] Where inhalation exposure µg/kg bw/day = (unit exposure from surrogate exposure study (See Appendix II, Table 1) × ETU conversion factor (0.1 % dry mix/load and application, 0.2% solution or slurry application and handling treated seed) × use rate)/70 kg bw.

[f] Systemic exposure µg/kg bw/day = total exposure to mancozeb (as expressed in Appendix II, Table 4, dermal exposure + inhalation exposure) × metabolic conversion of mancozeb to ETU (7.5%).

[g] Total daily exposure to ETU µg/kg bw/day = Sum of daily exposure to ETU from tank mix (dermal exposure + inhalation exposure) and metabolic conversion to ETU.

[h] Combined Margin of Exposure (MOE), based on the short- to intermediate-term NOAEL of 5 mg/kg bw/day from the oral developmental toxicity study, target MOE of 1000.

[n] PHED wettable powder mix/load data was added to the unit exposure vales for mixers/loaders to estimate exposure with wettable powders for open mix/load scenarios.

[o] For closed mix/load scenarios, the wettable powder formulations were assumed to be in water soluble packets, and exposure was assumed to be equivalent to the liquid formulation.

Table 8 Cancer Exposure and Risk Assessment for Mixing/Loading and Applying

Use Site Category	Crop	Form [a]	Method of Application [b]	Rate [c] (kg a.i./ha) or (kg a.i./L)	Area Treated ha/day [d] (ha) or (L)	ETU Absorbed Daily Dose [e] (µg/kg bw/day)	Lifetime Average Daily Dose [f] (µg/kg bw/day)	Cancer Risk [g]
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Open cab groundboom and airblast.								
Use-site category 4 & 27: Forests/Woodlots and Ornamentals Outdoors	Arborvitae, Ash, Juniper, Douglas fir, Hawthorn, Oak, Sycamore	DF, WG	Airblast	2.63	16	9.88×10^{-1}	4.33×10^{-2}	3×10^{-6}
			Groundboom	2.63	30	4.53×10^{-1}	1.98×10^{-2}	1×10^{-6}
			LP Handwand	2.63×10^{-3} (kg a.i./L)	150 L	2.99×10^{-2}	1.31×10^{-3}	8×10^{-8}
			HP Handwand		3750 L	2.97	1.30×10^{-1}	8×10^{-6}
			Backpack		150 L	7.90×10^{-2}	3.46×10^{-3}	2×10^{-7}
		WP	Airblast	2.80	16	4.02	1.76×10^{-1}	1×10^{-5}
			Groundboom	2.80	30	6.04	2.65×10^{-1}	2×10^{-5}
			LP Handwand	2.80×10^{-3} (kg a.i./L)	150 L	8.53×10^{-1}	3.74×10^{-2}	2×10^{-6}
			HP Handwand		3750 L	3.86	1.69×10^{-1}	1×10^{-5}
			Backpack		150 L	1.12×10^{-1}	4.91×10^{-3}	3×10^{-7}
	Holly, Ivy, Pine	DF, WG	Airblast	1.88	16	7.06×10^{-1}	3.10×10^{-2}	2×10^{-6}
			Groundboom	1.88	30	3.23×10^{-1}	1.42×10^{-2}	9×10^{-7}
			LP Handwand	1.88×10^{-3} (kg a.i./L)	150 L	2.13×10^{-2}	9.35×10^{-4}	6×10^{-8}
			HP Handwand		3750 L	2.12	9.30×10^{-2}	6×10^{-6}
			Backpack		150 L	5.64×10^{-2}	2.47×10^{-3}	1×10^{-7}
		WP	Airblast	2.00	16	2.87	1.26×10^{-1}	8×10^{-6}
			Groundboom	2.00	30	4.32	1.89×10^{-1}	1×10^{-5}
Use-site category 4 & 27: Forests/Woodlots and Ornamentals Outdoors	Holly, Ivy, Pine	WP	LP Handwand	2.00×10^{-3} (kg a.i./L)	150 L	6.09×10^{-1}	2.67×10^{-2}	2×10^{-6}
			HP Handwand		3750 L	2.76	1.21×10^{-1}	7×10^{-6}
			Backpack		150 L	8.00×10^{-2}	3.51×10^{-3}	2×10^{-7}
	Honeysuckle	DF, WG	Groundboom	1.50	30	2.59×10^{-1}	1.13×10^{-2}	7×10^{-7}
			LP Handwand	1.50×10^{-3}	150 L	1.71×10^{-2}	7.48×10^{-4}	4×10^{-8}

Use Site Category	Crop	Form [a]	Method of Application [b]	Rate [c] (kg a.i./ha) or (kg a.i./L)	Area Treated ha/day [d] (ha) or (L)	ETU Absorbed Daily Dose [e] (µg/kg bw/day)	Lifetime Average Daily Dose [f] (µg/kg bw/day)	Cancer Risk [g]
			Backpack	(kg a.i./L)	150 L	4.51×10^{-2}	1.98×10^{-3}	1×10^{-7}
Engineering control: Wettable Powder in Water Soluble Packaging (WSP). Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Respirator for HP Handwand M/L/A. Open cab groundboom and airblast.								
Use-site category 4 & 27: Forests/Woodlots and Ornamentals Outdoors	Arborvitae, Ash, Juniper, Douglas fir, Hawthorn, Oak, Sycamore	DF, WG	HP Handwand	2.63 × 10-3 (kg a.i./L)	3750 L	1.49	6.52×10^{-2}	4×10^{-6}
		WP in WSP	Airblast	2.80	16	9.04×10^{-1}	3.96×10^{-2}	2×10^{-6}
			Groundboom	2.80	30	2.02×10^{-1}	8.83×10^{-3}	5×10^{-7}
			LP Handwand	2.80×10^{-3} (kg a.i./L)	150 L	3.02×10^{-2}	1.32×10^{-3}	8×10^{-8}
			HP Handwand		3750 L	1.56	6.82×10^{-2}	4×10^{-6}
			Backpack		150 L	8.26×10^{-2}	3.62×10^{-3}	2×10^{-7}
	Holly, Ivy, Pine	DF, WG	HP Handwand	1.88×10^{-3} (kg a.i./L)	3750 L	1.06	4.66×10^{-2}	3×10^{-6}
		WP in WSP	Airblast	2.00	16	6.46×10^{-1}	2.83×10^{-2}	2×10^{-6}
			Groundboom	2.00	30	1.44×10^{-1}	6.31×10^{-3}	4×10^{-7}
			LP Handwand	2.00×10^{-3} (kg a.i./L)	150 L	2.16×10^{-2}	9.46×10^{-4}	6×10^{-8}
			HP Handwand		3750 L	1.11	4.87×10^{-2}	3×10^{-6}
			Backpack		150 L	5.90×10^{-2}	2.59×10^{-3}	2×10^{-7}
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves.								
Use-site category 5: Greenhouse Food Crops	Tobacco (greenhouse)	DF, WG	LP Handwand	3.00×10^{-3} (kg a.i./L)	150 L	3.41×10^{-2}	1.50×10^{-3}	9×10^{-8}
			HP Handwand		3750 L	3.39	1.49×10^{-1}	9×10^{-6}
			Backpack		150 L	9.03×10^{-2}	3.96×10^{-3}	2×10^{-7}
		WP	LP Handwand	3.20×10^{-3} (kg a.i./L)	150 L	9.75×10^{-1}	4.27×10^{-2}	3×10^{-6}
			HP Handwand		3750 L	4.41	1.94×10^{-1}	1×10^{-5}
			Backpack		150 L	1.28×10^{-1}	5.61×10^{-3}	3×10^{-7}
		SN	LP Handwand	3.30×10^{-3} (kg a.i./L)	150 L	3.56×10^{-2}	1.56×10^{-3}	9×10^{-8}
			HP Handwand		3750 L	3.68	1.62×10^{-1}	1×10^{-5}

Use Site Category	Crop	Form [a]	Method of Application [b]	Rate [c] (kg a.i./ha) or (kg a.i./L)	Area Treated ha/day [d] (ha) or (L)	ETU Absorbed Daily Dose [e] (µg/kg bw/day)	Lifetime Average Daily Dose [f] (µg/kg bw/day)	Cancer Risk [g]
			Backpack		150 L	9.74×10^{-2}	4.27×10^{-3}	3×10^{-7}
	Tomato	DF, WG	LP Handwand	6.00×10^{-3} (kg a.i./L)	150 L	6.83×10^{-2}	2.99×10^{-3}	2×10^{-7}
			HP Handwand		3750 L	6.79	2.98×10^{-1}	2×10^{-5}
			Backpack		150 L	1.81×10^{-1}	7.91×10^{-3}	5×10^{-7}
		WP	LP Handwand	6.00×10^{-3} (kg a.i./L)	150 L	1.83	8.01×10^{-2}	5×10^{-6}
			HP Handwand		3750 L	8.28	3.63×10^{-1}	2×10^{-5}
			Backpack		150 L	2.40×10^{-1}	1.05×10^{-2}	6×10^{-7}
Engineering control: Wettable Powder in WSP. Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves. Respirator for HP Handwand M/L/A.								
Use-site category 5: Greenhouse Food Crops	Tobacco (greenhouse)	DF, WG	HP Handwand	3.00×10^{-3} (kg a.i./L)	3750 L	1.70	7.46×10^{-2}	4×10^{-6}
		WP in WSP	HP Handwand	3.20×10^{-3} (kg a.i./L)	3750 L	1.78	7.80×10^{-2}	5×10^{-6}
Use-site category 5: Greenhouse Food Crops	Tobacco (greenhouse)	SN	HP Handwand	3.30×10^{-3} (kg a.i./L)	3750 L	1.83	8.04×10^{-2}	5×10^{-6}
Engineering control: WP in WSP. Maximum PPE: Chemical-resistant coveralls over long pants, long sleeved shirts, and chemical-resistant gloves. Respirator for all hand held M/L/A.								
Use-site category 5: Greenhouse Food Crops	Tomato	DF, WG	LP Handwand	6.00×10^{-3} (kg a.i./L)	150 L	2.05×10^{-2}	8.98×10^{-4}	5×10^{-8}
			HP Handwand		3750 L	1.38	6.03×10^{-2}	4×10^{-6}
			Backpack		150 L	5.05×10^{-2}	2.21×10^{-3}	1×10^{-7}
		WP in WSP	LP Handwand	6.00×10^{-3} (kg a.i./L)	150 L	1.92×10^{-2}	8.41×10^{-4}	5×10^{-8}
			HP Handwand		3750 L	1.34	5.89×10^{-2}	4×10^{-6}
			Backpack		150 L	4.92×10^{-2}	2.15×10^{-3}	1×10^{-7}

Use Site Category	Crop	Form [a]	Method of Application [b]	Rate [c] (kg a.i./ha) or (kg a.i./L)	Area Treated ha/day [d] (ha) or (L)	ETU Absorbed Daily Dose [e] (µg/kg bw/day)	Lifetime Average Daily Dose [f] (µg/kg bw/day)	Cancer Risk [g]
Engineering control: Wettable Powder in WSP. Maximum PPE: Chemical-resistant coveralls over long pants, long sleeved shirts, and chemical-resistant gloves. Respirator for M/L/A. Restriction on amount handled per day (2.25 kg a.i./day, approx. 375 L at 6 kg a.i. per 1000 L).								
Use-site category 5: Greenhouse Food Crops	Tomato	DF, WG	HP Handwand	6.00×10^{-3} (kg a.i./L)	375 L	1.38×10^{-1}	6.03×10^{-3}	4×10^{-7}
		WP in WSP	HP Handwand		375 L	1.34×10^{-1}	5.89×10^{-3}	4×10^{-7}
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Open cab groundboom.								
Use-site category 07: Terrestrial Crops Grown for Seed Only	Alfalfa grown for seed	DF, WG	Groundboom (f)	1.10	100	6.29×10^{-1}	2.76×10^{-2}	2×10^{-6}
			Groundboom (c)		300	1.89	8.28×10^{-2}	5×10^{-6}
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Respirator for M/L. Open cab groundboom.								
Use-site category 07: Terrestrial Crops Grown for Seed Only	Alfalfa grown for seed	DF, WG	Groundboom (f)	1.10	100	5.20×10^{-1}	2.28×10^{-2}	1×10^{-6}
			Groundboom (c)		300	1.56	6.84×10^{-2}	4×10^{-6}
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves. Open cab airblast.								
Use-site category 14: Terrestrial Food Crops (Orchard and Vine Crops)	Apple	DF, WG	Airblast	4.50	16	1.69	7.43×10^{-2}	4×10^{-6}
		WP	Airblast	4.80	16	6.89	3.02×10^{-1}	2×10^{-5}
		SN	Airblast	4.84	16	1.72	7.54×10^{-2}	5×10^{-6}
	Grape	DF	Airblast	1.50	16	5.65×10^{-1}	2.48×10^{-2}	1×10^{-6}
		WG	Airblast	1.60	16	6.03×10^{-1}	2.64×10^{-2}	2×10^{-6}
		WP	Airblast	5.40	16	7.75	3.40×10^{-1}	2×10^{-5}
	Pears	WP	Airblast	7.20	16	10.3	4.53×10^{-1}	3×10^{-5}
Engineering control: Wettable Powders in WSP. Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves. Respirator for applicators. Open cab airblast.								
Use-site category 14: Terrestrial Food Crops (Orchard and Vine Crops)	Apple	DF, WG	Airblast	4.50	16	1.28	5.62×10^{-2}	3×10^{-6}
		WP in WSP	Airblast	4.80	16	1.11	4.86×10^{-2}	3×10^{-6}
		SN	Airblast	4.84	16	1.28	5.59×10^{-2}	3×10^{-6}
	Grape	WP in WSP	Airblast	5.40	16	1.25	5.47×10^{-2}	3×10^{-6}

Use Site Category	Crop	Form [a]	Method of Application [b]	Rate [c] (kg a.i./ha) or (kg a.i./L)	Area Treated ha/day [d] (ha) or (L)	ETU Absorbed Daily Dose [e] (µg/kg bw/day)	Lifetime Average Daily Dose [f] (µg/kg bw/day)	Cancer Risk [g]
	Pear	WP in WSP	Airblast	7.20	16	1.66	7.29×10^{-2}	4×10^{-6}
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Open cab groundboom.								
Use-site category 14: Terrestrial Food Crops (Low Acreage Field and Vegetable Crops)	Cantaloupe, Cucumber, Melon, Onion including dry bulb (foliar), Pumpkin, Squash, Tomato, Watermelon	DF, WG	Groundboom	2.44	30	4.20×10^{-1}	1.84×10^{-2}	1×10^{-6}
		WP	Groundboom	2.60	30	5.61	2.46×10^{-1}	1×10^{-5}
		SN	Groundboom	2.69	30	3.58×10^{-1}	1.57×10^{-2}	9×10^{-7}
Use-site category 14: Terrestrial Food Crops (Low Acreage Field and Vegetable Crops	Carrot	DF, WG	Groundboom	1.69	30	2.91×10^{-1}	1.28×10^{-2}	8×10^{-7}
	Carrot, Celery	WP	Groundboom	1.80	30	3.89	1.70×10^{-1}	1×10^{-5}
		SN	Groundboom	1.86	30	2.47×10^{-1}	1.08×10^{-2}	7×10^{-7}
	Celery	DF, WG	Groundboom	2.44	30	4.20×10^{-1}	1.84×10^{-2}	1×10^{-6}
	Ginseng	DF, WG	Groundboom	3.30	30	5.69×10^{-1}	2.49×10^{-2}	1×10^{-6}
		WP	Groundboom	3.52	30	7.60	3.33×10^{-1}	2×10^{-5}
		SN	Groundboom	3.57	30	4.76×10^{-1}	2.08×10^{-2}	1×10^{-6}
	Head Lettuce	WG	Groundboom	1.60	30	2.76×10^{-1}	1.21×10^{-2}	7×10^{-7}
		WP	Groundboom	1.61	30	3.48	1.53×10^{-1}	9×10^{-6}
	Onion dry bulb (in-furrow)	DF, WG	Broadcast Spreader	6.60	30	1.20	5.25×10^{-2}	3×10^{-6}
Engineering control: Wettable Powder in WSP. **Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application). Open cab groundboom..**								
Use-site category 14: Terrestrial Food Crops (Low Acreage Field and Vegetable Crops)	Cantaloupe, Cucumber, Melon, Onion including dry bulb (foliar), Pumpkin, Squash, Tomato, Watermelon	WP in WSP	Groundboom	2.60	30	1.87×10^{-1}	8.20×10^{-3}	5×10^{-7}
	Carrots, Celery	WP in WSP	Groundboom	1.80	30	1.30×10^{-1}	5.68×10^{-3}	3×10^{-7}
	Ginseng	WP in WSP	Groundboom	3.52	30	2.53×10^{-1}	1.11×10^{-2}	7×10^{-7}
	Head Lettuce	WP in WSP	Groundboom	1.61	30	1.16×10^{-1}	5.09×10^{-3}	3×10^{-7}

Use Site Category	Crop	Form [a]	Method of Application [b]	Rate [c] (kg a.i./ha) or (kg a.i./L)	Area Treated ha/day [d] (ha) or (L)	ETU Absorbed Daily Dose [e] (µg/kg bw/day)	Lifetime Average Daily Dose [f] (µg/kg bw/day)	Cancer Risk [g]
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves. Respirator for M/L.								
Use-site category 14: Terrestrial Food Crops	Onion dry bulb (in-furrow)	DF, WG	Broadcast Spreader	6.60	30	1.00	4.39×10^{-2}	3×10^{-6}
Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves (except during groundboom application).								
Use-site category 14: Terrestrial Food Crops (High Acreage Field and Vegetable Crops) (also Use-site category 13: Terrestrial Feed Crop (Potato and Wheat)	Lentil	SN	Aerial M/L	2.23	400	2.33	1.02×10^{-1}	6×10^{-6}
			Aerial A			2.72×10^{-1}	1.19×10^{-2}	7×10^{-7}
			Groundboom (f)		100	9.92×10^{-1}	4.35×10^{-2}	3×10^{-6}
			Groundboom (c)		300	2.98	1.30×10^{-1}	8×10^{-6}
	Lentil, Potato, Sugar beet (ground application only), Wheat	DF, WG	Aerial M/L	1.69	400	2.64	1.16×10^{-1}	7×10^{-6}
			Aerial A			2.06×10^{-1}	9.02×10^{-3}	5×10^{-7}
			Groundboom (f)		100	9.70×10^{-1}	4.25×10^{-2}	3×10^{-6}
			Groundboom (c)		300	2.91	1.28×10^{-1}	8×10^{-6}
	Potato, Sugar beet (ground application only), Wheat	WP	Aerial M/L	1.80	400	50.5	2.21	1×10^{-4}
			Aerial A			2.19×10^{-1}	9.62×10^{-3}	6×10^{-7}
			Groundboom (f)		100	12.9	5.68×10^{-1}	3×10^{-5}
			Groundboom (c)		300	38.9	1.70	1×10^{-4}
	Potato (ground application only), Wheat	SN	Aerial M/L	1.86	400	1.94	8.51×10^{-2}	5×10^{-6}
			Aerial A			2.26×10^{-1}	9.92×10^{-3}	6×10^{-7}
			Groundboom (f)		100	8.25×10^{-1}	3.62×10^{-2}	2×10^{-6}
			Groundboom (c)		300	2.48	1.09×10^{-1}	7×10^{-6}
Engineering control: WP in WSP. **Baseline PPE: Long pants, long sleeved shirts, and chemical-resistant gloves. Respirator for Mix/Load (except WSP) and Apply.**								
Use-site category 14: Terrestrial Food Crops (High Acreage Field and Vegetable Crops)	Lentil	SN	Aerial M/L	2.23	400	9.37×10^{-1}	4.11×10^{-2}	2×10^{-6}
			Groundboom (f)		100	4.31×10^{-1}	1.89×10^{-2}	1×10^{-6}
			Groundboom (c)		300	1.29	5.67×10^{-2}	3×10^{-6}

Use Site Category	Crop	Form [a]	Method of Application [b]	Rate [c] (kg a.i./ha) or (kg a.i./L)	Area Treated ha/day [d] (ha) or (L)	ETU Absorbed Daily Dose [e] (µg/kg bw/day)	Lifetime Average Daily Dose [f] (µg/kg bw/day)	Cancer Risk [g]
(also Use-site category 13: Terrestrial Feed Crops (Potato and Wheat)	Lentil, Potato, Sugar beet (ground application only), Wheat	DF, WG	Aerial M/L	1.69	400	1.97	8.64×10^{-2}	5×10^{-6}
			Groundboom (f)	1.69	100	6.42×10^{-1}	2.81×10^{-2}	2×10^{-6}
			Groundboom (c)		300	1.92	8.44×10^{-2}	5×10^{-6}
	Potato, Sugar beet (ground application only), Wheat	WP in WSP	Aerial M/L	1.80	400	4.07×10^{-1}	1.79×10^{-2}	1×10^{-6}
			Groundboom (f)	1.80	100	2.61×10^{-1}	1.14×10^{-2}	7×10^{-7}
			Groundboom (c)		300	7.82×10^{-1}	3.43×10^{-2}	2×10^{-6}
	Potato (ground application only), Wheat	SN	Aerial M/L	1.86	400	7.80×10^{-1}	3.42×10^{-2}	2×10^{-6}
			Groundboom (f)	1.86	100	3.59×10^{-1}	1.57×10^{-2}	9×10^{-7}
			Groundboom (c)		300	1.08	4.72×10^{-2}	3×10^{-6}

Shaded cells indicate cancers risks greater than 1×10^{-5}.
[a] Form. refers to formulation type, WP = Wettable powder; WG = Wettable granules; DF = Dry flowable; SN = Solution; WSP = Water soluble packaging.
[b] M/L = Mixer/Loader; groundboom c) = custom groundboom application; groundboom (f) = farmer groundboom application; HP Handwand = high pressure handwand; LP Handwand = low pressure handwand.
[c] Maximum listed label rate in kilograms of active ingredient per hectare (kg a.i./ha) unless specified as kilograms of active ingredient per litre (kg a.i./L). Rates per litre were calculated assuming the following spray volumes: Trees and ornamentals assumed 1000 L/ha, greenhouse tobacco assumed 2500 L/ha, greenhouse tomatoes assumed 300 L/ha.
[d] Based on default assumptions.
[e] Represents total daily exposure to ETU expressed in µg/kg bw/day, as presented in Appendix II Tables 2 and 3.
[f] LADD, calculated using the following formula: $\frac{\text{Absorbed Daily Dose (mg/kg bw/day)} \times \text{Treatment Frequency (30 days per year)} \times \text{Working Duration (40 yrs)}}{\text{365 days/yrs} \times \text{Life Expectancy (75 yrs)}}$
[g] Calculated using the following formula: LADD (mg/kg bw/day) × q_1* (0.0601 mg/kg bw/day)$^{-1}$.

Table 9 Cancer Exposure and Risk Estimates for Seed and Potato Seed Piece treatment

Use Scenario	Crop	Operation	Form [a]	Rate [b] (g a.i./kg Seed)	Seed Treated per Day (kg seed/day)	Treatment Days per Year	Absorbed Daily Dose [c] (µg/kg bw/day)	Lifetime Average Daily Dose [d] (µg/kg bw/day)	Cancer Risk [e]
PPE: Long sleeved shirt, long plants, and chemical-resistant gloves. Open mix/load									
Commercial Seed Treatment (Slurry)	Barley	Treater/Bagger	WP	1.06	65 000	30	14.36	6.29×10^{-1}	4×10^{-5}
		Stacker/Tagger			65 000		2.69	1.18×10^{-1}	7×10^{-6}
		Forklift Operator			65 000		0.11	4.86×10^{-3}	3×10^{-7}
	Corn	Treater/Bagger	WP	1.79	60 000	30	22.49	9.86×10^{-1}	6×10^{-5}

Use Scenario	Crop	Operation	Form [a]	Rate [b] (g a.i./kg Seed)	Seed Treated per Day (kg seed/day)	Treatment Days per Year	Absorbed Daily Dose [c] (µg/kg bw/day)	Lifetime Average Daily Dose [d] (µg/kg bw/day)	Cancer Risk [e]
		Stacker/Tagger			60 000		4.22	1.85×10^{-1}	1×10^{-5}
		Forklift Operator			60 000		0.17	7.61×10^{-3}	5×10^{-7}
	Oat	Treater/Bagger	WP	1.47	65 000	30	20.02	8.77×10^{-1}	5×10^{-5}
		Stacker/Tagger			65 000		3.76	1.65×10^{-1}	1×10^{-5}
		Forklift Operator			65 000		0.15	6.77×10^{-3}	4×10^{-7}
	Wheat	Treater/Bagger	WP	0.83	65 000	30	11.31	4.96×10^{-1}	3×10^{-5}
		Stacker/Tagger			65 000		2.12	9.30×10^{-2}	6×10^{-6}
		Forklift Operator			65 000		0.09	3.83×10^{-3}	2×10^{-7}
Engineering controls: WP in Water Soluble Packaging (WSP). PPE: Long sleeved shirt, long plants, and chemical-resistant gloves. Respirator.									
Commercial Seed Treatment (Slurry)	Barley	Treater/Bagger	WP in WSP	1.06	65 000	30	1.47	6.47×10^{-2}	4×10^{-6}
		Stacker/Tagger			65 000		3.59×10^{-1}	1.57×10^{-2}	9×10^{-7}
		Forklift Operator			65 000		2.86×10^{-2}	1.25×10^{-3}	8×10^{-8}
	Corn	Treater/Bagger	WP in WSP	1.79	60 000	30	2.31	1.01×10^{-1}	6×10^{-6}
		Stacker/Tagger			60 000		5.63×10^{-1}	2.47×10^{-2}	1×10^{-6}
		Forklift Operator			60 000		4.48×10^{-2}	1.96×10^{-3}	1×10^{-7}
Commercial Seed Treatment (Slurry)	Oat	Treater/Bagger	WP in WSP	1.47	65 000	30	2.06	9.01×10^{-2}	5×10^{-6}
		Stacker/Tagger			65 000		5.01×10^{-1}	2.20×10^{-2}	1×10^{-6}
		Forklift Operator			65 000		3.98×10^{-2}	1.75×10^{-3}	1×10^{-7}
	Wheat	Treater/Bagger	WSP	0.83	65 000	30	1.16	5.09×10^{-2}	3×10^{-6}
		Stacker/Tagger			65 000		2.83×10^{-1}	1.24×10^{-2}	7×10^{-7}
		Forklift Operator			65 000		2.25×10^{-2}	9.87×10^{-4}	6×10^{-8}

Use Scenario	Crop	Operation	Form [a]	Rate [b] (g a.i./kg Seed)	Seed Treated per Day (kg seed/day)	Treatment Days per Year	Absorbed Daily Dose [c] (µg/kg bw/day)	Lifetime Average Daily Dose [d] (µg/kg bw/day)	Cancer Risk [e]
PPE: Long pants, long sleeved shirt, and chemical-resistant gloves. Open cab planter.									
Handling and Planting Treated Seed	Barley	Loader/Planter	WP	1.06	9600	10	3.21	4.70×10^{-2}	3×10^{-6}
	Flax	Loader/Planter	WP	1.79	3600		2.01	2.99×10^{-2}	2×10^{-6}
	Oats	Loader/Planter	WP	1.47	9200		4.29	6.27×10^{-2}	4×10^{-6}
	Wheat	Loader/Planter	WP	0.83	14 000		3.69	5.39×10^{-2}	3×10^{-6}
PPE: Long pants, long sleeved shirt, and chemical-resistant gloves. Open cab planter. Respirator for Loading and Planting.									
Handling and Planting Treated Seed	Barley	Loader/Planter	WP	1.06	9600	10	7.23×10^{-1}	1.06×10^{-2}	6×10^{-7}
	Flax	Loader/Planter	WP	1.79	3600		4.60×10^{-1}	6.73×10^{-3}	4×10^{-7}
	Oats	Loader/Planter	WP	1.47	9200		9.66×10^{-1}	1.41×10^{-2}	8×10^{-7}
	Wheat	Loader/Planter	WP	0.83	14 000		8.31×10^{-1}	1.21×10^{-2}	7×10^{-7}
Engineering Controls: Closed cab planter. PPE: Long pants, long sleeved shirt, chemical-resistant gloves									
Handling and Planting Treated Seed	Corn	Loader/Planter (c)	WP	1.79	2400	10	5.75×10^{-1}	8.40×10^{-3}	5×10^{-7}
		Loader/Planter (f)	WP		1200		2.87×10^{-1}	4.20×10^{-3}	3×10^{-7}
Engineering controls: Closed cab planter. PPE: Long sleeved shirt, long plants, chemical-resistant gloves while loading and treating.									
On-farm Seed Treatment (Planter or Drill Box Treatment, Dry Application)	Barley	Loader/treater/planter	WP	1.06	9600	10	14.29	2.09×10^{-1}	1×10^{-5}
	Corn	Loader/treater/planter (c)	WP	1.79	2400	10	6.06	8.86×10^{-2}	5×10^{-6}
		Loader/treater/planter (f)	WP		1200		3.03	4.43×10^{-2}	3×10^{-6}
	Flax	Loader/treater/planter	WP	1.79	3600	10	9.09	1.33×10^{-1}	8×10^{-6}
	Oat	Loader/treater/planter	WP	1.47	9200	10	19.09	2.79×10^{-1}	2×10^{-5}
	Wheat	Loader/treater/planter	WP	0.83	14 000	10	16.42	2.40×10^{-1}	1×10^{-5}
PPE: Long sleeved shirt, long plants, and chemical-resistant gloves. Open mix/load. Open cab planter.									
On-farm Seed Treatment (Slurry)	Barley	Loader/treater/planter	WP	1.06	9600	10	3.30	4.82×10^{-2}	3×10^{-6}
	Corn	Loader/treater/planter (c)	WP	1.79	2400	10	1.4	2.04×10^{-2}	1×10^{-6}
		Loader/treater/planter (f)			1200		6.99×10^{-1}	1.02×10^{-2}	6×10^{-7}

Use Scenario	Crop	Operation	Form [a]	Rate [b] (g a.i./kg Seed)	Seed Treated per Day (kg seed/day)	Treatment Days per Year	Absorbed Daily Dose [c] (µg/kg bw/day)	Lifetime Average Daily Dose [d] (µg/kg bw/day)	Cancer Risk [e]
	Oat	Loader/treater/planter	WP	1.47	9200	10	4.40	6.43×10^{-2}	4×10^{-6}
	Wheat	Loader/treater/planter	WP	0.83	14000	10	3.79	5.53×10^{-2}	3×10^{-6}
Engineering controls: WP in WSP. PPE: Open mix/load. Long sleeved shirt, long plants, and chemical-resistant gloves. Respirator.									
On-farm Seed Treatment (Slurry)	Barley	Loader/treater/planter	WP in WSP	1.06	9600	10	3.46×10^{-1}	5.06×10^{-3}	3×10^{-7}
	Corn	Loader/treater/planter (c)	WP in WSP	1.79	2400	10	1.47×10^{-1}	2.14×10^{-3}	1×10^{-7}
		Loader/treater/planter (f)			1200		7.34×10^{-2}	1.07×10^{-3}	6×10^{-8}
	Oat	Loader/treater/planter	WP in WSP	1.47	9200	10	4.62×10^{-1}	6.75×10^{-3}	4×10^{-7}
	Wheat	Loader/treater/planter	WP in WSP	0.83	14 000	10	3.98×10^{-1}	5.81×10^{-3}	3×10^{-7}
PPE: Long sleeves, long pants and chemical-resistant gloves. Closed cab planter.									
On-farm Potato Seed Piece Treatment	Potato	Loader/treater/planter	DU	0.8	40 000	10	4.26	6.23×10^{-2}	4×10^{-6}
		Loader/treater/planter			90 000		9.60	1.40×10^{-1}	8×10^{-6}
	Potato	Loader/treater/planter	DU	0.45	40 000	10	2.40	3.51×10^{-2}	2×10^{-6}
		Loader/treater/planter			90 000		5.40	7.89×10^{-2}	5×10^{-6}
PPE: Long sleeves, long pants and chemical-resistant gloves. Respirator for loader/treater. Closed cab planter.									
On-farm Potato Seed Piece Treatment	Potato	Loader/treater/planter	DU	0.8	40 000	10	3.2	4.68×10^{-2}	3×10^{-6}
		Loader/treater/planter			90 000		7.2	1.05×10^{-1}	6×10^{-6}
	Potato	Loader/treater/planter	DU	0.45	40 000	10	1.8	2.63×10^{-2}	2×10^{-6}
		Loader/treater/planter			90 000		4.05	5.92×10^{-2}	4×10^{-6}
PPE: Long sleeves, long pants and chemical-resistant gloves. Respirator for loader/treater. Closed cab planter. Restriction on amount handled per day (7.85 kg a.i./day).									
On-farm Potato Seed Piece Treatment	Potato	Loader/treater/planter	DU	0.8	9800	10	7.84×10^{-1}	1.15×10^{-2}	7×10^{-7}
	Potato	Loader/treater/planter	DU	0.45	17 440	10	7.85×10^{-1}	1.15×10^{-2}	7×10^{-7}

Use Scenario	Crop	Operation	Form [a]	Rate [b] (g a.i./kg Seed)	Seed Treated per Day (kg seed/day)	Treatment Days per Year	Absorbed Daily Dose [c] (µg/kg bw/day)	Lifetime Average Daily Dose [d] (µg/kg bw/day)	Cancer Risk [e]
PPE: Long sleeves, long pants and chemical-resistant gloves. Respirator for loader/treater. Closed cab planter. Restriction on amount handled per day (7.85 kg a.i./day).									
Commercial Potato Seed Piece Treatment	Potato	Loader/treater/planter	DU	0.8	9800	30	7.84×10^{-1}	3.44×10^{-2}	2×10^{-6}
PPE: Long sleeves, long pants and chemical-resistant gloves.									
Seed Potatoes for Storage	Potato	Treater	SN	0.72	64 000	10	8.99×10^{-1}	1.31×10^{-2}	8×10^{-7}
		Cutter/Sorter			64 000	10	9.12×10^{-1}	1.33×10^{-2}	8×10^{-7}
		All tasks			64 000	10	1.23	1.80×10^{-2}	1×10^{-6}
PPE: Long sleeves, long pants and chemical-resistant gloves. Respirator.									
Seed Potatoes for Storage	Potato	Treater	SN	0.72	64 000	10	3.74×10^{-1}	5.47×10^{-3}	3×10^{-7}
		Cutter/Sorter			64 000	10	9.12×10^{-2}	1.33×10^{-3}	8×10^{-8}
		All tasks			64 000	10	4.07×10^{-1}	5.95×10^{-3}	4×10^{-7}

Shaded cell indicate cancer risk is greater than 1×10^{-5}. N/A= not applicable; NM = not measured; c) = custom; (f) = farmer.

[a] Form. refers to formulation type, WP = Wettable powder, DU = Dust, SN = Solution.

[b] Maximum listed label rate of mancozeb in grams of active ingredient per kilogram of seed.

[c] Represents total daily exposure to ETU expressed in µg/kg bw/day, as calculated in Appendix II, Table 7.

[d] Life time average daily dose (LADD), calculated using the following formula: $\frac{\text{Absorbed Daily Dose (mg/kg bw/day)} \times \text{Treatment Frequency (days per year)} \times \text{Working Duration (40 yrs)}}{\text{365 days/yrs} \times \text{Life Expectancy (75 yrs)}}$

[e] Calculated using the following formula: LADD (mg/kg bw/day) × q_1* (0.0601 mg/kg bw/day)$^{-1}$.

Table 10 Dislodgeable Foliar Residue Data Applied to Canadian Crops

Surrogate Crop	Study (Site)	Rate [a] (kg a.i./ha)	Application Regime [b]	Analyte	Slope[c]	Peak Value [d] (µg/cm²)	Peak Value [e] (%)	Half-life [f] (days)	Daily Dissipation [g] (%)	Correlation Coefficient (R^2)	Canadian Crops
Apples	Graves 1999a (Washington)	5.4	2 applications, 7 day apart	MCZ	-0.032	16.5	30.6	21.9	3.1	0.88	Ash, oak, sycamore, hawthorn, arborvitae, juniper, Douglas fir, holly, ivy, honeysuckle, pine, apples, pears
				ETU	-0.025	0.05	0.09	27.7	2.5	0.7	
Grapes	Graves 1999b (California)	2.2	2 applications, 7 days apart	MCZ	-0.039	4.66	21.2	18	3.8	0.91	Grapes
				ETU	-0.068	0.09	0.4	10.1	6.6	0.56	
Field Tomatoes	Honeycutt, 1992 (Florida)	2.6	14 applications, 7 days apart	MCZ	-0.085	10.7 [h]	41.2	8.2	8.2	0.95	Alfalfa, cantaloupe, cucumbers, melons, pumpkins, squash, watermelons, carrots, potatoes, sugar beets, ginseng, head lettuce, celery, lentils, tomatoes, onions, wheat
				ETU	-0.079	0.06 [I]	0.21	8.8	7.6	0.63	
Greenhouse Tomatoes	Graves 1999d (North Carolina)	2.6	2 applications, 7 days apart	MCZ	-0.073	5.36	20.6	9.5	7	0.91	Greenhouse tomatoes, greenhouse tobacco
				ETU	-0.038	0.01	0.05	18.3	3.7	0.62	

MCZ = Mancozeb, ETU = ethylene thiourea

[a] Mean study application rate of mancozeb in kilograms of active ingredient per hectare.

[b] All crops assessed based on the number of applications (or multiples thereof) and application intervals used in the available studies.

[c] Slope of the equation of the line: y = mx + b, calculated by plotting the natural logarithms of DFR versus dissipation time (postapplication interval).

[d] Peak DFR, based on highest mean DFR value, corrected for recovery.

[e] Peak DFR expressed as a percent of the mancozeb application rate per application.

[f] The determined half-life of residue on foliage; derived from the slope of the DFR curve (ln of dislodgeable residue vs. time), assuming 1st order kinetics.

[g] Daily dissipation is the rate at which the dislodgeable foliar residue is lost to the environment; derived from the slope of the DFR curve (ln of dislodgeable residue vs. time).

[h] Rainfall occurred prior and following the 14th application. The peak DFR value which occurred following the 11th application was used to determine peak DFR.

[I] Rainfall occurred prior and following the 14th application. The peak DFR value which occurred following the 8th application was used to determine peak DFR.

Table 11 Mancozeb Short- to Intermediate-term Postapplication Risk Assessment and Restricted-Entry Intervals

Crops	Rate [a] (kg a.i./ha)	Applications [b]		Activity	TC [c] (cm²/hr)	MOE (Day 0) [d]	Target DFR [e] (µg/cm²)	REI [f] (days)
		Number	Interval					
Use-site category 4: Forests and Woodlots & Use-site category 27: Ornamentals Outdoors								
Arborvitae, Ash, Juniper, Douglas fir, Hawthorn, Oak, Sycamore	2.80	6	10	All activities	400	2239	39.38	12 hrs
Holly, Ivy, Pine	2.00	6	7	All activities	400	3135	39.38	12 hrs
Honeysuckle	1.50	3	10	All activities	400	5230	39.38	12 hrs

Crops	Rate [a] (kg a.i./ha)	Applications [b] Number	Applications [b] Interval	Activity	TC [c] (cm^2/hr)	MOE (Day 0) [d]	Target DFR [e] ($\mu g/cm^2$)	REI [f] (days)
Use-site category 5: Greenhouse Food Crops								
Tobacco	8.30	18	7[g]	All activities	400	1473	39.38	12 hrs
Use-site category 7: Industrial Oil Seed Crops and Fibre Crops								
Alfalfa	1.10	3	7	Scouting	1500	2330	10.50	12 hrs
Use-site category 14: Terrestrial Food Crops (Orchard and Vine Fruit)								
Apple	4.80	6	7	Thinning	3000	174	5.25	56
				Hand harvesting	1500	348	10.50	34
				Hand-line irrigation	1100	475	14.32	24
				Hand pruning, scouting, pinching, tying, training	500	1045	31.50	12 hrs
Apple	4.50	6	7	Thinning	3000	186	5.25	54
				Hand harvesting	1500	372	10.50	32
				Hand-line irrigation	1100	507	14.32	22
				Hand pruning, scouting, pinching, tying, training	500	1115	31.50	12 hrs
Use-site category 14: Terrestrial Food Crops (Orchard and Vine Fruit)								
Grape	1.50	6	10	Gridling, cane turning	19300	134	0.82	53
				Hand harvesting, training, thinning, hand pruning, tying, leaf pulling	8500	304	1.85	31
				Hand-line irrigation	1100	2346	14.32	12 hrs
				Scouting, hand weeding and other minor contact activities	700	3687	22.50	12 hrs
Grape	5.40	4	10	Gridling, cane turning	19300	45	0.82	81
				Hand harvesting, training, thinning, hand pruning, tying, leaf pulling	8500	102	1.85	60
				Hand-line irrigation	1100	791	14.32	7
				Scouting, hand weeding and other minor contact activities	700	1244	22.50	12 hrs
Grape	1.60	1	10	Gridling, cane turning	19300	241	0.82	37
				Hand harvesting, training, thinning, hand pruning, tying, leaf pulling	8500	547	1.85	16
				Hand-line irrigation	1100	4225	14.32	12 hrs
				Scouting, hand weeding and other minor contact activities	700	6639	22.50	12 hrs
Pear	7.20	4	7	Thinning	3000	145	5.25	62
				Hand harvesting	1500	291	10.50	40
				Hand-line irrigation	1100	396	14.32	30
				Hand pruning, scouting, pinching, tying, training	500	872	31.50	5
Use-site category 14: Terrestrial Food Crops (Orchard and Vine Fruit)								
Pear	5.40[h]	4	7	Thinning	3000	194	5.25	53
				Hand harvesting	1500	387	10.50	31
				Hand-line irrigation	1100	528	14.32	21
				Hand pruning, scouting, pinching, tying, training	500	1162	31.50	12 hrs
Use-site category 14: Terrestrial Food Crops (Field and Vegetable Crops)								
Cantaloupe, Cucumber, Melon, Pumpkin, Squash, Watermelon	2.69	8	7	Hand harvesting, hand pruning, thinning, leaf pulling	2500	570	6.30	7
				Hand weeding, irrigating, scouting	1500	950	10.50	1
Cantaloupe, Cucumber, Melon,	2.44	8	7	Hand harvesting, hand pruning, thinning, leaf pulling	2500	628	6.30	6

Crops	Rate [a] (kg a.i./ha)	Applications [b] Number	Applications [b] Interval	Activity	TC [c] (cm²/hr)	MOE (Day 0) [d]	Target DFR [e] (µg/cm²)	REI [f] (days)
Pumpkin, Squash, Watermelon				Hand weeding, irrigating, scouting	1500	1047	10.50	12 hrs
Carrot	1.86	6	7	Hand harvest	2500	825	6.30	3
				Irrigating, scouting, hand weeding	300	6877	52.50	12 hrs
Celery	2.44	6	7	Hand harvesting	2500	628	6.30	6
				All other activities	1500	1047	10.50	12 hrs
Celery	1.86	6	7	Hand harvesting	2500	825	6.30	3
				All other activities	1500	1375	10.50	12 hrs
Ginseng	3.57	6	14	Hand harvesting	2500	429	6.30	10
				Irrigation, scouting	1500	716	10.50	4
				Hand weeding, thinning	300	3578	52.50	12 hrs
Use-site category 14: Terrestrial Food Crops (Field and Vegetable Crops)								
Lentil	2.23	3	10	Hand harvesting	2500	686	6.30	5
				Irrigation, scouting	1500	1144	10.50	12 hrs
Lentil	1.69	3	10	Hand harvesting	2500	907	6.30	2
				Irrigation, scouting	1500	1511	10.50	12 hrs
Head lettuce	1.61	3	14	Hand harvesting	2500	950	6.30	1
				All other activities	1500	1583	10.50	12 hrs
Onion (foliar)	2.69	10	10	Irrigation, scouting, thinning, hand weeding	300	4749	52.50	12 hrs
Potato, Wheat, Sugar beet	1.86	2–10	3–10	All activities	1500	1375	10.50	12 hrs
Tomato	2.69	7	10	All activities	1000	1425	15.75	12 hrs

Shaded cells indicate MOEs that are less than the target; REI = Restricted-Entry Interval; N/A=Not Applicable; NS = Not Specified.

[a] Maximum listed label rates expressed in kilograms a.i./ha.

[b] Maximum number of applications per season and application interval for registered crops. Maximum number of applications was not specified on labels for all uses. For these uses, registrants have indicated the maximum number of applications and interval between applications. Dislodgeable foliar residue data based from studies conducted with two applications were modelled to the nearest multiple of 2 applications (i.e., 4 or 6 applications) assuming cumulative addition of DFR curves.

[c] Transfer coefficients are based on PMRA default values. Soybean TCs were used as a surrogate to estimate exposure for lentils. Greenhouse lettuce TCs were used as a surrogate to estimate exposure for greenhouse tobacco. Sweet potato TCs were used as a surrogate to estimate exposure for ginseng.

[d] Dermal MOE on Day 0 is the margin of exposure on the day of application. If there are multiple applications, the dermal MOE is presented for the day of the last application to account for any possible accumulation of mancozeb. Calculated using the dermal short- to intermediate-term NOAEL of 18 mg/kg bw/day from the oral modified reproductive toxicity study, target MOE of 1000.

[e] Target dislodgeable foliar residues (DFR) refers the residue level where entry into a treated area to perform a specific activity will result in a margin of exposure above the Agency target. Calculated using the following formula: Target DFR (µg/cm²) = [NOAEL × Body Weight (70 kg)]/[TC (cm²/hr) × Duration (8 hrs/day) × Target MOE (1000) × DA (1%)]

[f] Restricted-entry interval refers to the day following application that mancozeb residues are less than the target DFR and calculated MOEs exceed the target of 1000.

[g] Registrants proposed a minimum application interval of 3 to 4 days. However, the study used to estimate DFR was conducted with a 7 day application interval and cannot be used to support an application interval of less than 7 days.

[h] Lower rate proposed by technical registrants. For pears, the maximum seasonal rate proposed by all registrants collectively is based on 4 applications at 5.4 kg/ha.

Table 12 Mancozeb Long-term Postapplication Risk Assessment and Restricted-Entry Intervals

Crop	Rate [a] (kg a.i./ha)	Applications [b] Number	Applications [b] Interval	Activity	TC[c] (cm²/hr)	Day 0[d] MOE	Target DFR[e] (µg/cm²)	REI [f] (days)
Use-site category 5: Greenhouse Food Crops								
Tomato	1.80	4	7	All activities	1800	222	0.53	5
Tomato	1.80	2	7	All activities	1800	301	0.53	0.5

Shaded cells indicate MOEs that are less than the target. REI = Restricted-Entry Interval; N/A = Not Applicable; NS = Not Specified.

[a] Maximum listed label rates expressed in kilograms a.i./ha.

[b] Registrants proposed a maximum of 5 applications, 7 days apart. Postapplication risk was assessed for 2 and 4 applications, which resulted in REIs which are not considered agronomically feasible; therefore, additional applications were not considered.
[c] Transfer coefficients are based on PMRA default values.
[d] Dermal MOE on Day 0 is the margin of exposure on the day of application. If there are multiple applications, the dermal MOE is presented for the day of the last application to account for any possible accumulation of mancozeb. Calculated using the dermal long-term NOAEL of 2.3 mg/kg bw/day from the oral chronic toxicity study and target MOE of 300.
[e] Calculated using the following formula: Target DFR (µg/cm^2) = [LOAEL × Body Weight (70 kg)]/[TC (cm^h/hr) × Duration (8 hrs/day) × Target MOE (300) × DA (1%)]
[f] Restricted-entry interval refers to the day following application that mancozeb residues are less than the target DFR and calculated MOEs exceed the target of 300.

Table 13 ETU Short- to Intermediate-term Postapplication Risk Assessment and Restricted Entry-Intervals

Crop	Rate[a] (kg a.i./ha)	Number of Applications[b]	Activity	TC[c] (cm^2/hr)	MCZ REI[d] (days)	MCZ Exposure[e]	ETU Exposure (µg/kg bw/day)			MOE[i]	ETU REI[j]
							Dermal[f]	Metabolic Conversion from MCZ[g]	Total[h]		
Use-site category 4: Forests and Woodlots & Use-site category 27: Ornamentals outdoors											
Arborvitae, Ash, Juniper, Douglas fir, Hawthorn, Oak, Sycamore	2.8	6	All activities	400	12 hrs	8.04	1.25	0.60	1.85	2703	N/A
Holly, Ivy, Pine	2.00	6	All activities	400	12 hrs	5.74	0.89	0.43	1.32	3784	N/A
Honeysuckle	1.50	3	All activities	400	12 hrs	3.44	0.52	0.26	0.77	6452	N/A
Use-site category 7: Industrial Oil Seed Crops and Fibre Crops											
Alfalfa	1.10	3	Scouting	1500	12 hrs	7.73	1.79	0.58	2.37	2113	N/A
Use-site category 14: Terrestrial Food Crops											
Apple	4.80	6	Thinning	3000	56	17.61	4.00	1.32	5.32	940	59
			Hand harvesting	1500	34	17.65	3.45	1.32	4.77	1047	N/A
			Hand-line irrigation	1100	24	17.75	3.24	1.33	4.57	1093	N/A
			Hand pruning, scouting, etc.	500	12 hrs	17.23	2.67	1.29	3.96	1261	N/A
Apple	4.50	6	Thinning	3000	54	17.59	3.94	1.32	5.26	951	56
			Hand harvesting	1500	32	17.62	3.40	1.32	4.72	1059	N/A
			Hand-line irrigation	1100	22	17.73	3.19	1.33	4.52	1105	N/A
			Hand pruning, scouting, etc.	500	12 hrs	16.15	2.51	1.21	3.72	1345	N/A
Grape	1.50	6	Gridling, cane turning	19300	53	17.40	2.32	1.31	3.62	1380	N/A
			Hand harvesting, training, thinning, etc.	8500	31	17.92	4.66	1.34	6.00	833	34
			Hand-line irrigation	1100	12 hrs	7.67	5.12	0.58	5.69	878	2
			Scouting, hand weeding, etc.	700	12 hrs	4.88	3.26	0.37	3.62	1380	N/A
Grape	5.40	4	Gridling, cane turning	19300	81	17.50	1.09	1.31	2.41	2078	N/A
			Hand harvesting, training, thinning, etc.	8500	60	17.34	2.05	1.30	3.35	1491	N/A
			Hand-line irrigation	1100	7	17.36	10.29	1.30	11.59	431	20
			Scouting, hand weeding, etc.	700	12 hrs	14.47	10.61	1.09	11.70	427	13
Grape	1.60	1	Gridling, cane turning	19300	37	17.92	4.89	1.34	6.23	802	41
			Hand harvesting, training, thinning, etc.	8500	16	17.75	9.17	1.33	10.50	476	28
			Hand-line irrigation	1100	12 hrs	4.26	3.58	0.32	3.90	1282	N/A
			Scouting, hand weeding, etc.	700	12 hrs	2.71	2.28	0.20	2.48	2015	N/A
Pear	7.20	4	Thinning	3000	62	17.47	4.00	1.31	5.31	942	65

Crop	Rate [a] (kg a.i./ha)	Number of Applications [b]	Activity	TC [c] (cm^2/hr)	MCZ REI [d] (days)	MCZ Exposure [e]	ETU Exposure (µg/kg bw/day)			MOE[i]	ETU REI[j]
							Dermal [f]	Metabolic Conversion from MCZ[g]	Total [h]		
			Hand harvesting	1500	40	17.50	3.45	1.31	4.76	1050	N/A
			Hand-line irrigation	1100	30	17.60	3.24	1.32	4.56	1096	N/A
			Hand pruning, scouting, etc.	500	5	17.63	2.74	1.32	4.06	1231	N/A
Pear	5.40 [k]	4	Thinning	3000	53	17.41	3.75	1.31	5.05	989	54
			Hand harvesting	1500	31	17.44	3.23	1.31	4.54	1101	N/A
			Hand-line irrigation	1100	21	17.55	3.04	1.32	4.36	1148	N/A
			Hand pruning, scouting, etc.	500	12 hrs	15.49	2.33	1.16	3.49	1434	N/A
Cantaloupe, Cucumber, Melon, Pumpkin, Squash, Watermelon	2.69	8	Hand harvesting, hand pruning, thinning, leaf pulling	2500	7	17.38	4.22	1.30	5.52	906	9
			Hand weeding, irrigating, scouting	1500	1	17.40	4.05	1.31	5.36	933	2
Cantaloupe, Cucumber, Melon, Pumpkin, Squash, Watermelon	2.60	8	Hand harvesting, hand pruning, thinning, leaf pulling	2500	7	16.83	4.08	1.26	5.34	936	8
			Hand weeding, irrigating, scouting	1500	1	16.84	3.92	1.26	5.19	964	2
Cantaloupe, Cucumber, Melon, Pumpkin, Squash, Watermelon	2.44	8	Hand harvesting, hand pruning, thinning, leaf pulling	2500	6	17.18	4.14	1.29	5.43	921	8
			Hand weeding, irrigating, scouting	1500	12 hrs	17.19	3.98	1.29	5.27	949	1
Carrot	1.86	6	Hand harvest	2500	3	16.89	3.99	1.27	5.25	952	4
			Irrigating, scouting, hand weeding	300	12 hrs	2.62	0.61	0.20	0.80	6237	N/A
Celery	2.44	6	Hand harvesting	2500	6	17.18	4.14	1.29	5.43	921	8
			Irrigating, scouting	1500	12 hrs	17.20	3.98	1.29	5.27	949	1
			Hand weeding	500	12 hrs	5.73	1.33	0.43	1.76	2847	N/A
Celery	1.86	6	Hand harvesting	2500	3	16.89	3.99	1.27	5.25	952	4
			Irrigating, scouting	1500	12 hrs	13.09	3.03	0.98	4.01	1247	N/A
			Hand weeding	500	12 hrs	4.36	1.01	0.33	1.34	3742	N/A
Ginseng	3.57	6	Hand harvesting	2500	10	17.86	4.42	1.34	5.76	868	12
			Irrigation, scouting	1500	4	17.88	4.25	1.34	5.59	894	6
			Hand weeding, thinning	300	12 hrs	5.03	1.16	0.38	1.54	3245	N/A
Ginseng	3.30	6	Hand harvesting	2500	10	16.53	4.09	1.24	5.33	937	11
			Irrigation, scouting	1500	4	16.55	3.93	1.24	5.18	966	5
			Hand weeding, thinning	300	12 hrs	4.66	1.08	0.35	1.43	3506	N/A
Lentil	2.23	3	Hand harvesting	2500	5	17.12	4.10	1.28	5.38	929	6
			Irrigation, scouting	1500	12 hrs	15.73	3.64	1.18	4.82	1038	N/A
Lentil	1.69	3	Hand harvesting	2500	2	16.73	3.92	1.26	5.18	965	3
			Irrigation, scouting	1500	12 hrs	11.91	2.75	0.89	3.65	1371	N/A
Head lettuce	1.61	3	Hand harvesting	2500	1	17.40	4.05	1.31	5.36	933	2
			All other activities	1500	12 hrs	11.37	2.63	0.85	3.48	1435	N/A
Onion (foliar)	2.69	10	All activities	300	12 hrs	3.79	0.88	0.28	1.16	4307	N/A
Tomato	2.69	7	All activities	1000	12 hrs	12.63	2.92	0.95	3.87	1292	N/A
Potato, Sugar beet, Wheat	1.86	2–10	All activities	1500	12 hrs	13.09	3.03	0.98	4.01	1247	N/A

Shade cells indicate MOEs are less than the target. MCZ = Mancozeb; REI = Restricted-Entry Interval; MOE = Margin of Exposure; N/A= Not Applicable.
[a] Maximum rates expressed in kilograms a.i./ha.
[b] Maximum number of applications per season for registered crops. Maximum number of applications was not specified on labels for all uses. For these uses, registrants have indicated the maximum number of applications. Dislodgeable foliar residue data based from studies conducted with two application were modelled to the nearest multiple of 2 applications (i.e., 4 or 6 application) assuming cumulative addition of DFR curves.
[c] Transfer coefficients are based on PMRA default values. Soybean TCs were used as a surrogate to estimate exposure for lentils. Greenhouse lettuce TCs were used as a surrogate to estimate exposure for greenhouse tobacco. Sweet potato TCs were used as a surrogate to estimate exposure for ginseng.
[d] Mancozeb REI refers to the day following application that mancozeb residues are less than the target DFR and calculated MOEs exceed the target of 1000, as presented in Appendix II, Table 11.
[e] Refers to mancozeb dermal exposure on the REI day, calculated as Dermal exposure = [MCZ DFR × TC × MCZ Dermal absorption (1%) × 8 hr]/70 kg.
[f] Refers to ETU dermal exposure on the REI day, calculated as Dermal exposure = [ETU DFR × TC × ETU Dermal absorption (45%) × 8 hr]/70 kg.
[g] Refers to ETU exposure from metabolic conversion of mancozeb, calculated by multiplying mancozeb exposure on the REI day by 7.5%.
[h] Refers to total ETU exposure on the mancozeb REI day, calculated as the sum of dermal and metabolic ETU exposure on the REI day.
[I] Refers to ETU margin of exposure (MOE) on mancozeb REI day, calculated using the short- to intermediate-term NOAEL of 5 mg/kg bw/day from the oral developmental toxicity study and target MOE of 1000.
[j] Extended REI refers to the day following application that ETU MOE for total exposure exceed the target of 1000 if target is not met of the mancozeb REI day.
[k] Lower rate purposed by technical registrants. For pears, the maximum seasonal rate proposed by all registrants collectively is based on 4 applications at 5.4 kg/ha.

Table 14 ETU Long-term Postapplication Risk Assessment and Restricted-Entry Intervals

Crop	Rate [a] (kg a.i./ha)	Number of Applications [b]	Activity	TC[c] (cm^2/hr)	MCZ REI [d] (days)	ETU MOE based on MCZ REI	ETU Exposure (µg/kg bw/day)			MOE[i]
							Dermal [f]	Metabolic Conversion from MCZ[g]	Total [h]	
Use-site category 5: Greenhouse Food Crops										
Tomato	1.80	4	All activities	1800	5	111	0.47	0.08	0.58	27
Tomato	1.80	2	All activities	1800	0.5	129	0.43	0.08	0.60	17

N/A=Not Applicable
[a] Maximum listed label rates expressed in kilograms a.i./ha.
[b] Registrants proposed a maximum of 5 applications, 7 days apart. Postapplication risk was assessed for 2 and 4 applications, which resulted in REIs which are not considered agronomically feasible; therefore, additional applications were not considered.
[c] Transfer coefficients are based on PMRA default values.
[d] Mancozeb REI refers to the day following application that mancozeb residues are less than the target DFR and calculated MOEs exceed the target of 300, as presented in Appendix II, Table 12.
[e] Refers to ETU margin of exposure (MOE) based on mancozeb REI day, calculated using the dermal long-term NOAEL of 2.3 mg/kg bw/day and target MOE of 300.
[f] Refers to ETU dermal exposure on the ETU REI day, calculated as Dermal exposure = [ETU DFR × TC × ETU Dermal absorption (45%) × 8 hr]/70 kg.
[g] Refers to ETU exposure from metabolic conversion of mancozeb, calculated by multiplying mancozeb exposure on the ETU REI day by 7.5%.
[h] Total ETU exposure, calculated as the sum of dermal and metabolic ETU exposure on the ETU REI day.
[I] Restricted-entry interval refers to the day following application that calculated MOEs exceed the target of 300.

Table 15 Cancer Postapplication Risk Assessment

Crop	Rate [a] (kg a.i./ha)	Number of Applications	Activity	TC [b] (cm^2/hr)	REI [c] (days)	ETU Absorbed Daily Dose [d] (µg/kg/day)	ETU LADD [e] (µg/kg bw/day)	Cancer Risk [f]
Use-site category 4: Forests and Woodlots & Use-site category 27: Ornamentals Outdoors								
Arborvitae, Ash, Juniper, Douglas fir, Hawthorn, Oak, Sycamore	2.8	6	All activities	400	12 hrs	1.29	5.64×10^{-2}	3×10^{-6}
Holly, Ivy, Pine	2.00	6	All activities	400	12 hrs	0.92	4.03×10^{-2}	2×10^{-6}

Crop	Rate [a] (kg a.i./ha)	Number of Applications	Activity	TC [b] (cm²/hr)	REI [c] (days)	ETU Absorbed Daily Dose [d] (µg/kg/day)	ETU LADD [e] (µg/kg bw/day)	Cancer Risk [f]
Honeysuckle	1.50	3	All activities	400	12 hrs	0.54	2.36×10^{-2}	1×10^{-6}
Use-site category 5: Greenhouse Food Crops								
Tobacco	8.3	18	All activities	400	12 hrs	1.62	7.09×10^{-2}	4×10^{-6}
Tomatoes	1.8	4	All activities	1800	31	0.28	1.22×10^{-2}	7×10^{-7}
Tomatoes	1.8	2	All activities	1800	27	0.21	9.34×10^{-3}	6×10^{-7}
Use-site category 7: Industrial Oil Seed Crops and Fibre Crops								
Alfalfa	1.1	3	Scouting	1500	12 hrs	0.93	4.09×10^{-2}	2×10^{-6}
Use-site category 14: Terrestrial Food Crops (Orchard and Vine Crops)								
Apple	4.80	6	Thinning	3000	59	3.44	1.51×10^{-1}	9×10^{-6}
			Hand harvesting	1500	34	3.33	1.46×10^{-1}	9×10^{-6}
			Hand-line irrigation	1100	24	3.19	1.40×10^{-1}	8×10^{-6}
			Hand pruning, scouting	500	12 hrs	2.76	1.21×10^{-1}	7×10^{-6}
Apple	4.50	6	Thinning	3000	56	3.49	1.53×10^{-1}	9×10^{-6}
			Hand harvesting	1500	32	3.29	1.44×10^{-1}	9×10^{-6}
			Hand-line irrigation	1100	22	3.15	1.38×10^{-1}	8×10^{-6}
			Hand pruning, scouting	500	12 hrs	2.58	1.13×10^{-1}	7×10^{-6}
Use-site category 14: Terrestrial Food Crops (Orchard and Vine Crops)								
Grape	1.50	6	Gridling, cane turning	19 300	53	1.80	7.89×10^{-2}	5×10^{-6}
			Hand harvesting, training, thinning, hand pruning, tying, leaf pulling	8500	34	2.38	1.04×10^{-1}	6×10^{-6}
			Hand-line irrigation	1100	2	2.27	9.95×10^{-2}	6×10^{-6}
			Scouting, hand weeding and other minor contact activities	700	12 hrs	1.64	7.21×10^{-2}	4×10^{-6}
Grape	5.40	4	Gridling, cane turning	19 300	81	1.27	5.57×10^{-2}	3×10^{-6}
			Hand harvesting, training, thinning, hand pruning, tying, leaf pulling	8500	60	1.68	7.37×10^{-2}	4×10^{-6}
			Hand-line irrigation	1100	16	2.97	1.30×10^{-1}	8×10^{-6}
			Scouting, hand weeding and other minor contact activities	700	13	2.29	1.00×10^{-1}	6×10^{-6}
Grape	1.60	1	Gridling, cane turning	19 300	41	2.32	1.02×10^{-1}	6×10^{-6}
			Hand harvesting, training, thinning, hand pruning, tying, leaf pulling	8500	28	2.26	9.89×10^{-2}	6×10^{-6}
			All other activities	1100	12 hrs	1.76	7.70×10^{-2}	5×10^{-6}
Pear	7.20	4	Thinning	3000	65	3.43	1.50×10^{-1}	9×10^{-6}
			Hand harvesting	1500	40	3.33	1.46×10^{-1}	9×10^{-6}
			Hand-line irrigation	1100	30	3.18	1.39×10^{-1}	8×10^{-6}
			Hand pruning, scouting	500	5	2.82	1.24×10^{-1}	7×10^{-6}
Pear	5.40 [g]	4	Thinning	3000	54	3.44	1.51×10^{-1}	9×10^{-6}
			Hand harvesting	1500	31	3.17	1.39×10^{-1}	8×10^{-6}
			Hand-line irrigation	1100	21	3.03	1.33×10^{-1}	8×10^{-6}
			Hand pruning, scouting	500	0	2.42	1.06×10^{-1}	6×10^{-6}
Use-site category 14: Terrestrial Food Crops (Field and Vegetable Crops)								
Cantaloupe, Cucumber, Melon, Pumpkin, Squash, Watermelon	2.69	8	Hand harvesting, hand pruning, thinning, leaf pulling	2500	9	1.85	8.13×10^{-2}	5×10^{-6}

Crop	Rate [a] (kg a.i./ha)	Number of Applications	Activity	TC [b] (cm^2/hr)	REI [c] (days)	ETU Absorbed Daily Dose [d] (µg/kg/day)	ETU LADD [e] (µg/kg bw/day)	Cancer Risk [f]
			Hand weeding, irrigating, scouting	1500	2	1.95	8.54×10^{-2}	5×10^{-6}
Cantaloupe, Cucumber, Melon, Pumpkin, Squash, Watermelon	2.60	8	Hand harvesting, hand pruning, thinning, leaf pulling	2500	8	1.94	8.52×10^{-2}	5×10^{-6}
			Hand weeding, irrigating, scouting	1500	2	1.89	8.27×10^{-2}	5×10^{-6}
Cantaloupe, Cucumber, Melon, Pumpkin, Squash, Watermelon	2.44	8	Hand harvesting, hand pruning, thinning, leaf pulling	2500	8	1.82	7.99×10^{-2}	5×10^{-6}
			Hand weeding, irrigating, scouting	1500	1	1.91	8.39×10^{-2}	5×10^{-6}
Carrot	1.86	6	Hand harvest	2500	4	1.91	8.37×10^{-2}	5×10^{-6}
			Irrigating, scouting, hand weeding	300	12 hrs	0.32	1.38×10^{-2}	8×10^{-7}
Celery	2.44	6	Hand harvesting	2500	8	1.82	7.99×10^{-2}	5×10^{-6}
			Irrigating, scouting	1500	1	1.92	8.40×10^{-2}	5×10^{-6}
			Hand weeding	500	12 hrs	0.69	3.03×10^{-2}	2×10^{-6}
Celery	1.86	6	Hand harvesting	2500	4	1.91	8.37×10^{-2}	5×10^{-6}
			All other activities	1500	12 hrs	1.58	6.92×10^{-2}	4×10^{-6}
			Hand weeding	500	12 hrs	0.53	2.31×10^{-2}	1×10^{-6}
Ginseng	3.57	6	Hand harvesting	2500	12	1.94	8.48×10^{-2}	5×10^{-6}
			Irrigation, scouting	1500	6	1.88	8.23×10^{-2}	5×10^{-6}
			Hand weeding, thinning	300	12 hrs	0.61	2.66×10^{-2}	2×10^{-6}
	3.30	6	Hand harvesting	2500	11	1.94	8.51×10^{-2}	5×10^{-6}
			Irrigation, scouting	1500	5	1.88	8.25×10^{-2}	5×10^{-6}
			Hand weeding, thinning	300	12 hrs	0.56	2.46×10^{-2}	1×10^{-6}
Use-site category 14: Terrestrial Food Crops (Field and Vegetable Crops)								
Lentil	2.23	3	Hand harvesting	2500	6	1.96	8.58×10^{-2}	5×10^{-6}
			Irrigation, scouting	1500	12 hrs	1.90	8.32×10^{-2}	5×10^{-6}
Lentil	1.69	3	Hand harvesting	2500	3	1.88	8.26×10^{-2}	5×10^{-6}
			Irrigation, scouting	1500	12 hrs	1.44	6.30×10^{-2}	4×10^{-6}
Head lettuce	1.61	3	Hand harvesting	2500	2	1.95	8.54×10^{-2}	5×10^{-6}
			Irrigation, scouting	1500	12 hrs	1.37	6.01×10^{-2}	4×10^{-6}
			Hand weeding	500	12 hrs	0.46	2.00×10^{-2}	1×10^{-6}
Onion (foliar)	2.69	10	Irrigation, scouting, thinning, hand weeding	300	12 hrs	0.46	2.00×10^{-2}	1×10^{-6}
Tomatoes	2.69	7	All activities	1000	12 hrs	1.52	6.68×10^{-2}	4×10^{-6}
Potato, Sugar beet, Wheat	1.86	2–10	Irrigating, scouting	1500	12 hrs	1.58	6.92×10^{-2}	4×10^{-6}

[a] Maximum listed label rates expressed in kilograms a.i./ha. REI = Restricted-Entry Interval.
[b] Transfer coefficients are based on PMRA default values. Soybean TCs were used to estimate exposure for lentils. Greenhouse lettuce TCs were used as a surrogate to estimate exposure for greenhouse tobacco. Sweet potato TCs were used as a surrogate to estimate exposure for ginseng.
[c] REI day refers to the day following application that mancozeb and ETU exposure exceed the target MOE, as presented in Appendix II, Table 13 and Table 14.
[d] ETU Absorbed Daily Dose (ADD) expressed in µg/kg bw/day, calculated by averaging the total daily ETU exposure (as described in Appendix II, Table 13 and Table 14) for the duration of exposure (30 days) following the REI.
[e] ETU LADD (Lifetime Average Daily Dose, mg/kg/bw/day) calculated using the following formula:

$$\text{LADD} = \frac{\text{Absorbed Daily Dose ETU (mg/kg bw/day)} \times \text{Exposure Days (30 days/yr)} \times \text{Working Duration (40 yrs/lifetime)}}{\text{365 days/yrs} \times \text{Life Expectancy (75 yrs)}}$$

[f] Lifetime cancer risk, calculated using the following formula: Cancer Risk = LADD (mg/kg bw/day) × q_1* (0.0601 (mg/kg bw/day)$^{-1}$
[g] Lower rate purposed by technical registrants. For pears, the maximum seasonal rate proposed by all registrants collectively is based on 4 applications at 5.4 kg/ha.

Appendix V Non-occupational Risk Assessment

Table 1 Mancozeb Acute Risk Assessment for Harvesting at PYO Operations

Subpopulation	Application Rate (kg a.i./ha) [a]	MCZ DFR (µg/cm^2) [b]	PHI (days)	TC [c] (cm^2/hr)	Dermal Exposure (µg/kg bw/day) [d]	Dermal MOE [e]
Apples (6 applications)						
Adults (70 kg)	4.80	7.27	45	1500	3.12	5777
Youth (39 kg)				1034	3.85	129703
Toddler (15 kg)				534	5.18	96595

[a] Maximum label rate expressed in kilograms a.i./hectare
[b] Mancozeb dislodgeable foliar residue at the pre-harvest interval (45 days after application) for apples.
[c] Transfer coefficients for hand harvesting based on PMRA defaults are expressed in cm^2/hr. For adults the TC for hand harvesting orchards is 1500 cm^2/hr. Since this TC is based on a body weight of 70 kg, it was scaled for the surface area of a youth (correction factor 12700 cm^2/hr/18440 cm^2/hr = 68.9%) and children (correction factor 6565 cm^2/hr/18440 cm^2/hr=35.6%). As such, the TC for youth and toddlers are 1034 and 534 cm^2/hr, respectively.
[d] Dermal exposure = (DFR (µg/cm^2) × TC (cm^2/hr) × Exposure Duration (2 hr) × Dermal Absorption (1%))/Body Weight.
[e] Dermal MOE for adults was calculated using dermal acute NOAEL of 18 mg/kg bw/day from the oral modified reproductive toxicity study, target MOE of 1000. For youth and toddlers, dermal MOEs were calculated using a dermal acute LOAEL of 500 mg/kg bw/day from the oral neurotoxicity study, target MOE of 1000.

Table 2 ETU Acute and Cancer Risk Assessment for Harvesting at PYO Operations

Subpopulation	ETU DFR (µg/cm^2) [a]	TC [b] (cm^2/hr)	ETU Exposure (µg/kg bw/day)			Acute MOE [f]	LADD [g] (µg/kg bw/day)	Cancer Risk [h]
			Dermal	Metabolic Conversion from MCZ [d]	Total [e]			
Apples (6 applications)								
Adults (70 kg)	0.034	1500	0.66	0.23	0.89	5622	1.02×10^{-2}	7×10^{-7}
Youth (39 kg)		1034	0.81	0.29	1.10	NA	1.21×10^{-3}	
Toddler (15 kg)		534	1.09	0.39	1.48	NA	6.48×10^{-4}	

NA = Not Applicable
[a] ETU dislodgeable foliar residue at the pre-harvest interval (45 days after application) for apples.
[b] Transfer coefficients for hand harvesting based on PMRA defaults are expressed in cm^2/hr. For adults the TC for hand harvesting orchards is 1500 cm^2/hr. Since this TC is based on a body weight of 70 kg, it was scaled for the surface area of a youth (correction factor 12 700 cm^2/hr/18440 cm^2/hr = 68.9%) and children (correction factor 6565 cm^2/hr/18440 cm^2/hr = 35.6%). As such, the TC for youth and toddlers are 1034 and 534 cm^2/hr, respectively.
[c] Dermal exposure to ETU = (DFR (µg/cm^2) × TC (cm^2/hr) × Exposure Duration (2 hr) × Dermal Absorption (45%))/Body Weight
[d] ETU exposure from the metabolic conversion of mancozeb, calculated using the following equation: mancozeb exposure (see Table 1) × 7.5%.
[e] Calculated by summing dermal exposures expected from direct exposure to ETU residues and metabolic conversion of mancozeb.
[f] Acute Margin of Exposure (MOE). For adults, MOEs were calculated using the acute NOAEL (Females aged 13 to 49 years) of 5.0 mg/kg bw day from the oral developmental toxicity study, target MOE of 1000. For toddlers and youth, an ARfD for the general population was not established and therefore a risk assessment was not performed.
[g] Lifetime Average Daily Dose (LADD) expressed in µg/kg bw/day, calculated using the following formula: LADD = (Total Daily ETU Exposure × Exposure Frequency (2 days for toddlers, 5 days for youth and adults) × Exposure Duration (6 years for toddlers and youth, and 63 years for adults)/(365 days/year × Life Expectancy (75 yrs)).
[h] Lifetime cancer risk calculated using the following formula: Cancer risk = Total LADD (Adult + Youth + Toddler) × q_1* (0.0601 (mg/kg bw/day)$^{-1}$.

Table 3 Bystander Inhalation Exposure and Short-term Risk Assessment

Population	Air Concentration [a] (µg/m^3)	Inhalation Rate (m^3/hr)	Exposure Time (hrs)	MCZ Daily Inhalation Exposure [b] (µg/kg bw/day)	MCZ MOE [c]	ETU Daily Dose [d] (µg/kg bw/day)	LADD [e] (µg/kg bw/day)	Total LADD (µg/kg bw/day)	Lifetime Cancer Risk [f]
Adult (70 kg)	4.76	1	1.5	0.10	51667	7.65×10^{-3}	1.76×10^{-4}	3.17×10^{-4}	2×10^{-8}
Youth (39 kg)		1	2	0.24	21589	1.83×10^{-2}	4.01×10^{-5}		
Toddler (15 kg)		0.7	3	0.66	7908	5.00×10^{-2}	1.10×10^{-4}		

[a] Maximum concentrations from Garron et al 2009, measured at fields edge during spraying.
[b] Where inhalation exposure (µg/kg bw/day) = air concentration × inhalation rate(based on the USEPA Exposure Factors Handbook, 1997) × exposure time (based on the USEPA Exposure Factors Handbook, 1997)/body weight.
[c] Mancozeb margin of exposure (MOE), based on the dermal short- to intermediate-term inhalation NOAEL of 5.27 mg/kg bw/day from the inhalation developmental toxicity study, target 1000.
[d] ETU Daily Dose expressed in µg/kg bw/day from the metabolic conversion of mancozeb, calculated using the following equation: mancozeb daily exposure × 7.5%.
[e] Lifetime Average Daily Dose expressed in µg/kg bw/day, calculated using the following formula: LADD = (ETU Daily Dose × Exposure Frequency (10 day per year) × Exposure Duration (6 years for toddlers and youth each, and 63 years for adults))/(365 days/year × Life Expectancy (75 years)).
[f] Cancer risk calculated using the following formula: Cancer risk = Total LADD × q_1* (0.0601 (mg/kg bw/day)$^{-1}$

Appendix VI Dietary Exposure and Risk Estimates for Mancozeb and Ethylene thiourea

Table 1 Dietary Exposure and Risk Estimates for Mancozeb

Population Subgroup	Acute Dietary[1] (99.9th Percentile)		Chronic Dietary[2]	
	Exposure (mg/kg/day)	% ARfD	Exposure (mg/kg/day)	%ADI
General Population (total)	NA		0.000202	2.5
Children 1–2 years old	0.020112	1.20	0.000796	10
Children 3–5 years old	0.019084	1.14	0.000611	7.6
Children 6–12 years old	0.012505	0.75	0.00032	4
Youth 13–19 years old	NA		0.000141	1.8
Adults 20–49 years old			0.000136	1.7
Adults 50+ years old			0.000139	1.7
Females 13–49 years old	0.006602	37	0.00014	1.75

[1]Acute Reference Dose (ARfD) of 0.018 mg/kg/day for females 13–49 years old. [1]Acute Reference Dose (ARfD) of 0.5 mg/kg/day for the general population, including infants and children.
[2]Acceptable Daily Intake (ADI) of 0.008 mg/kg/day applies to the general population and all population subgroups.
Note: The mancozeb risk estimates are from food alone as mancozeb is not expected to occur in drinking water.

Table 2 Acute and Chronic Dietary Exposure and Risk Estimates for ETU

Population Groups	Acute assessment[1]				Chronic assessment[2]					
	Food Exposure		Food + water exposure		Food Exposure		Food + water exposure		Water exposure	
	Exposure (mg/kg bw/day)	% ARfD	Exposure (mg/kg bw/day)	% ARfD	Exposure (mg/kg bw/day)	% ADI	Exposure (mg/kg bw/day)	% ADI	Exposure (mg/kg bw/day)	% ADI
General Population	N/A	N/A	N/A	N/A	0.00071	12	0.000132	22	0.000061	10
All Infants (<1 year old)	N/A	N/A	N/A	N/A	0.000129	21	0.000329	55	0.000200	33
Children 1–2 years old	N/A	N/A	N/A	N/A	0.000255	43	0.000346	58	0.000091	15
Children 3–5 years old	N/A	N/A	N/A	N/A	0.000186	31	0.000271	45	0.000085	14
Children 6–12 years old	N/A	N/A	N/A	N/A	0.000105	18	0.000164	27	0.000059	10
Youth 13–19 years old	N/A	N/A	N/A	N/A	0.000058	10	0.000103	17	0.000044	7
Adults 20–49 years old	N/A	N/A	N/A	N/A	0.000053	9	0.000110	18	0.000057	10
Adults 50+ years old	N/A	N/A	N/A	N/A	0.000048	8	0.000108	18	0.000060	10
Females 13–49 years old	0.001231	25	0.002459	49	0.000052	9	0.000109	18	0.000057	10

[1]Acute Reference Dose (ARfD) of 0.005 mg/kg/day for females 13–49 years old
[2]Acceptable Daily Intake (ADI) of 0.0006 mg/kg/day applies to the general population and all population subgroups.

Table 3 Cancer Dietary Exposure and Risk Estimates for ETU

Population Group	Food exposure		Food and water exposure		Water exposure	
	Exposure (mg/kg bw/day)	Lifetime risk	Exposure (mg/kg bw/day)	Lifetime risk	Exposure (mg/kg bw/day)	Lifetime risk
General Population	0.000071	4.3×10^{-6}	0.000132	8×10^{-6}	0.000061	3.7×10^{-6}

Cancer unit risk = Exposure (mg/kg bw/day) × q_1* $(0.0601 \text{ mg/kg bw/day})^{-1}$

Appendix VII Food Residue Chemistry Summary

1.0 Metabolism

The residue chemistry database for mancozeb is complete for the currently registered uses. The nature and the magnitude of the residue in plant and livestock commodities are adequately understood based on acceptable metabolism studies in lactating cows and goats, laying hens, potatoes, soybean, sugar beet, tomato and wheat. The residue of mancozeb in all livestock and plant commodities is expressed as the parent compound mancozeb and ETU.

Plant and animal metabolism studies were reviewed to identify the major components of the total terminal residues, to provide an estimate of these residues and to indicate their distribution between relevant plant and animal parts. The nature of mancozeb residues in animals and plants is well understood and the terminal residues are defined for risk assessment purposes as the parent compound mancozeb and its metabolite ETU. A brief description of the available metabolism studies or summaries is presented below.

The metabolism of mancozeb has been extensively investigated. The general metabolic degradation pathways for mancozeb are identical in both plants and animals. Some of the ^{14}C compounds identified in plants, rats and livestock metabolism studies are the same (ETU, EU, EDA). The residue of toxicological concern, ETU, has been found in all the matrices. Mancozeb initially breaks down to either EDA or ETU. Acidic conditions favour the initial formation of EDA whereas neutral or basic environment favours formation of ETU. EDA is formed via the evolution of two CS_2 molecules from mancozeb and can form N-acetyl, N,N-diacetyl and N-formyl derivatives. Following oxidative de-amination, EDA is metabolized to glycine which is the intermediate through which carbon atoms (from mancozeb) enter the natural product pool. As well, ETU is formed from Mancozeb via a simple cyclisation reaction or from the intermediate EBIS in a reducing environment. It may be noted that the reaction to form Jaffe's base is reversible, although ETU primarily oxidizes to EU following enzymatic attack.

1.1 Plant Metabolism

The PMRA has reviewed potato, soybean, sugar beet, tomato and wheat radiolabelled metabolism studies to identify the nature of the major decomposition products and metabolites of Mancozeb in plants.

The major metabolites were identified as natural products (proteins, carbohydrates and lipids) while minor degradates such as ETU, EU, ethylene di-isothiocyanate, EDA and Jaffe's base were found. Plants treated with radiolabelled mancozeb showed that ^{14}C was incorporated into the carbon pool of natural products with ethylene-urea as the major primary metabolite.

It should be noted that the application rates and PHIs described in this document are representative of the American use pattern.

Review of the JMPR document published in 1974 indicated that studies on the metabolism of mancozeb on and in several other plants, including leafy plants such as sugar beet, lettuce and turnip were conducted using ^{3}H, ^{14}C and ^{35}S applied at exaggerated rates to facilitate identification of metabolites. Ethyleneurea and EDA were detected as the predominant metabolites, representing 17% and 11% of the percentage of ^{3}H activity.

1.2 Animal Metabolism

During the re-evaluation process, the PMRA reviewed hen, cow and goat radiolabelled metabolism studies to determine the fate of mancozeb ingested by animals and to identify the major decomposition products and metabolites of mancozeb in tissues, milk and egg.

In goats, the distribution of metabolites in milk, muscle and liver showed that the absorbed radiolabelled mancozeb was metabolized to produce a wide variety of labelled degradates, including ETU, EU, EDA, N-formylglycine and N-acetylethylenediamine.

In cows, the determination of ETU and EU in milk has been investigated using a reverse isotope dilution method. When ^{14}C mancozeb was administered at 25 ppm, results indicated that milk contained ETU at 24% of the total radioactive residues and EU at 10% of total radioactive residues. Radioactive residues identified in urine were ETU, EU, and natural components. When ^{14}C mancozeb was administered to lactating dairy cows in feed at levels of 1 ppm, 5 ppm and 25 ppm, residues in milk reached a plateau in 3 to 9 days, the time increasing as the dose level increased. It was also noted that the total ^{14}C residues increased as the feed level increased and that the vast majority of the dose fed daily was recovered in excreta (urine & faeces). ^{14}C residues were found in all tissues examined from the cow at the 25 ppm feeding level.

In hens orally dosed with ^{14}C-mancozeb at 0 (control), 3, 14, 36 ppm in the feed and at 36 ppm with a 10 day depuration period in the feed for 7 consecutive days, the recovered activity indicated that 99% was found in the excreta at all doses while the remaining 1% was distributed among egg and tissues. In tissue, the highest radiolabelled mancozeb equivalent residues were found in liver and kidney. Residue levels in eggs were approximately equally divided between the egg yolk and white. The 10 day depuration period typically reduced residue levels by a factor of 2 in fat, of 4 in muscle and heart, of 6, 7 and 12 in kidney, liver and gizzard respectively. However, the residue level stayed identical in eggs. Low levels of radioactivity were detected in poultry food commodities and eggs.

1.3 Residue Definition

The qualitative nature of mancozeb residues in plant and animal is well understood based on reviews of acceptable plant and animal metabolism studies. As the cancer potency factor for all the EBDCs is derived from ETU, the PMRA has concluded that both the mancozeb and its ETU metabolite must be included in the risk assessment. As it is well known that the analytical methods convert most of the metabolites of the EBDCs to CS_2 and that the amount of ETU in raw and processed commodities can not be considered as a reliable indicator, the PMRA has concluded that for enforcement purpose, the MRLs should be expressed in CS_2.

The current residue definition for all EBDCs in all commodities is expressed as manganese and zinc ethylenebis(dithiocarbamate) (polymeric), also known as zineb. Expressing EBDC residues as such a surrogate chemical is no longer consistent with international practice. The United States, Codex and the European Union establish their MRLs on total dithiocarbamates, determined as CS_2 and expressed as mg CS_2/kg.

2.0 Analytical Methods

2.1 Methods for Residues Analysis in Plants

Methodologies for EBDC fungicide residues have been reviewed by several authors. Different analytical methods, measuring EDA, ETU and CS_2 may be used to determine mancozeb residues.

EDA

This method by Rohm and Haas is described in the 1970 JMPR document. Ethylene diamine is liberated from known components of residues (mancozeb, EU, ETU, EBIS and N-acetyl ethylenediamine). EDA is isolated, after hydrolysis of the residues with acid containing stannous chloride, by ion exchange chromatography and quantified by gas liquid chromatography of its bis(triflouroacetate). Overall recoveries at levels of 0.16–1.3 mg/kg parent compound mancozeb were greater than 80% and generally more than 95%. The limit of detection in terms of mancozeb is approximately 0.1 mg/kg. The sensitivity of detection for the method is 0.01 ppm (as EDA) or 0.05 ppm (as mancozeb).

ETU

ETU residues may be determined by a multiresidue methodology as it is the common metabolite of all the EBDC fungicides. As mentioned previously, ETU is the residue of greatest toxicological concern. For information, it should be noted that the EBDCs may be used as vulcanization accelerators in the production of a wide range of elastomers. As a result, contamination of head-space analysis bottles and rubber gloves may occur. Samples handled with these gloves or that have been in contact with rubber objects prior to arrival at a laboratory could make it difficult to be certain that residues are ONLY derived from the use of agricultural pesticides. The importance of characterizing the magnitude of the ETU component in the residue, a separate method was developed (Rohm and Haas, 1970) that is sensitive to 0.01 ppm for milk and cow tissues and originally 0.05 ppm for potatoes.

The Keppel method (or CS_2 method) is not suitable to determine ETU as this compound does not degrade to carbon disulfide. Also, thin layer chromatography (TLC) would not provide a precise quantification of ETU as this compound may undergo decomposition on the TLC plate. Gas-liquid cromatography (GLC) is also not a satisfactory method due to inadequate recovery.

Results from American field trials on almond, asparagus, banana, celery, cucumber, orange, peanut, potato, tomato and wheat were obtained using GLC flame photometric detector in sulphur mode (JMPR - Larese 1988). High pressure liquid chromatography (HPLC) without derivatization is the preferred methodology for the detection and quantification of ETU residues, using C8 or C18 reversed-phase silica based columns with little or no organic solvent in the mobile phase. UV detectors may also be used but would not provide an adequate selectivity due to a multitude of UV absorbing crop co-extractives and pesticides. The official AOAC method (Onley and Yip) was revised to increase ETU recoveries and to improve consistency. The derivatization step was eliminated and ETU was determined by an HPLC Hg/Au EC system. Sodium chloride was replaced by sodium acetate to control the pH. The PMRA laboratory has proposed to treat samples with sodium sulfite to prevent the oxidation of ETU to its metabolites of sulphone and sulphoxide forms. The process requires an extraction from fruits/vegetables with methanol before partitioning from basic aqueous solution into dichloromethane.

The sample is then concentrated and analysed by HPLC-UV. The mean recovery was 62% when samples were spiked at 0.05 ppm. This method is still under development.

CS_2

Analytical methods converting all EBDCs and some metabolites to carbon disulfide were reviewed. The decomposition of EBDC under acidic conditions leads to the formation of carbon disulfide. At high temperatures, 2 mol of CS_2 may be produced by mol of EBDC while at low temperatures, production of CS_2, H_2S and ETU may be observed.

It is also well known that several plants produce CS_2, either naturally (for example, cabbage) or under reaction conditions. The PMRA has on file (PMRA# 1272210) the description of method ETU-89AM-001, ETU-89AM-002 and ETU-89AM-003, used to determine the concentration of EBDC in crops and processed crops, meat, and milk respectively. The detection limits were determined to be 0.02 ppm for crops and processed crops, 2 ppb for meat and milk. It should be noted that the reaction with a mixture of HCl/stannous chloride converts all the EBDCs to a common moiety, CS_2, preventing to distinguish between residues of specific EBDCs.

The PMRA has also reviewed (PMRA# 708528) an analytical method (ETL method MS 133.02) to determine residues of mancozeb (as CS_2) in plant tissue by GC/MS. A limit of quantitation of 0.02 ppm to 0.04 ppm was established for most plants.

The USEPA has also reviewed the MTF-88AM-005 and ETU-89AM-001 methods. The validated limits of quantitation from field trials were 0.05 ppm in banana, cranberry, grape, pear, sugar beet root and top, 0.02 ppm in cottonseed and 0.4 ppm in dry bulb onion.

The Pesticide Analytical Manual (PAM) Vol. II lists Methods I, II, III, IV, and A for the determination of dithiocarbamate residues in/on plant commodities. These methods are based on the decomposition of dithiocarbamates with release of carbon disulfide Using these methods, the CS_2 is swept through a trap to remove any H_2S and into a reaction tube containing a solution of copper acetate and an amine. A coloured copper dithiocarbamate complex is formed, and its absorbance is read as a measure of the original dithiocarbamate.

CS_2/zineb

Analytical methods for determining ethylenebis(dithiocarbamates) in fruits and vegetables using GC headspace and CS_2 evolution were provided by Agriculture Canada (LSD # P-RE-044-090-EBDC & P-RE-053-95-EBDC). For analysis of mancozeb, the limits of quantitation was 0.3 ppm in apple when using the GC-headspace method. In fresh vegetables, the limit of quantitation was set at 0.1 ppm zineb equivalents with an average recovery of 88% and a standard deviation of 6.2% when using the CS_2 evolution method.

Lentil

The PMRA has also previously reviewed the analytical method (ETL Rep No. 98RHC35.REP) was used to analyse mancozeb in lentils. The method is a common moiety method (CS_2) in which samples were analysed by GC/MSD using selected ion monitoring (SIM). The limit of detection (LOD) was 0.02 ppm and the limit of quantitation (LOQ) was established at 0.05 ppm. The method validation indicated that the average recoveries of mancozeb residues (as CS_2) ranged from 71%–125% when samples were spiked with mancozeb at 0.0495 mg/kg to 6.92 mg/kg with a standard deviation of less than 20% (13 January 2001).

The ETL Rep No 97RHC20A.REP has also been reviewed during the course of the re-evaluation process. Also, the method is a common moiety method (CS_2) in which samples were analysed by GC/MSD using selected ion monitoring (SIM). The limit of detection (LOD) was 0.05 ppm. The average percent recovery of Mancozeb (as CS,) in lentils for the validation was 120% ± 9.5%. The average % recovery of fortifications during analysis was 114% ± 13%. Residues of Mancozeb in lentils ranged from 0.053 ppm to 0.45 ppm.

2.2 Methods for Residues Analysis of Food of Animal Origin

Method 135 was amended to extend the UV spectroscopic method also to animal samples (eggs, cow urine and molasses). The initial LOD of 0.02–0.2 ppm cannot be achieved with animal matrices, therefore the LOD in eggs is 0.12 ppm and 1 ppm in urine and molasses. The average recovery is 90.7, 97.7, and 88.4% in eggs, cow urine and molasses, respectively.

As the method extension 135/1 was not effective in the determination of animal matrices, an amended method 135/2 was proposed for their determination, using GC-FPD. The method can be used for the analysis of poultry eggs, muscle, skin + fat, liver, feed and cow milk, muscle, fat, liver, kidney, urine, molasses.

The method follows the same procedures in which the samples are distilled with a solution of stannous chloride and hydrochloric acid yielding CS_2 in a stream of nitrogen. The stream is purified from H_2S and other volatile impurities by sequential absorption in a lead acetate solution, a concentrated sulphuric acid solution and a sodium hydroxide solution. The liberated CS_2 is absorbed in two traps (to improve the recovery) with ice-cooled methanol from which the carbon disulfide is analysed by GC-FPD. Since no standard reagent is available, the technical product, with a known content of CS_2, must be used for analysis. The use of ethanol, instead of methanol, for the CS_2 absorption will not increase the determined recoveries.

2.3 Enforcement Analytical Methodology

The Keppel colorimetric method (designated as Method III in PAM Vol. II; JAOAC, 54:528-532) may be used for enforcement purpose. The Keppel method, which analyses EBDCs as a group, and so is not specific to Mancozeb residues but to its common moiety, by degradation to carbon disulfide, is proposed as the official method for dithiocarbamates including Mancozeb.

2.4 Inter-Laboratory Analytical Methodology Validation

An independent laboratory validation study describing the determination of Mancozeb in lentils by gas chromatography with mass selective detection has been reviewed by the PMRA. Method has been described in the ETL report # 98RHC35.REP and the validation was conducted at Morse Laboratories. The limit of quantitation was established at 0.05 ppm. Recoveries ranged from 98% to 123% and averaging 111 ±7.6% (n =14) over the concentration range of 0.05 to 6 ppm.

The PMRA has concluded that the method was applicable for the determination of Mancozeb in lentils.

2.5 Multi-Residue Analytical Methodology

No multi-residue analytical method is on file. Mancozeb or any other EBDCs are not listed in the Canadian Food Inspection Agency's Pesticide Multiresidues Analytical method manual (Volume 7). The PMRA requests the registrant to provide an acceptable study.

The USEPA stated that the behaviour of Mancozeb has been investigated through FDA's Multiresidue Method Testing Protocols but was not recovered. There is a small recovery (<50%) of ETU using Method 302 (Luke method; Protocol D) but ETU is not recovered using Method 303 (Mills, Onley, and Gaither method; Protocol E) and 304 (Mills method for fatty food).

3.0 Food Residues

3.1 Freezer Storage

3.1.1 Freezer Storage Stability in Plants

It has been determined that oxygen plays a role in the conversion of ETU to EU. As a result, surface residues may be more susceptible to degradation. The PMRA concludes that mancozeb and ETU residues were stable under frozen storage conditions.

Control samples representative of commodities were fortified with known concentrations of EBDC and ETU using both finely and coarsely ground commodities. This method was chosen based on the fact that previous studies with finely ground commodities fortified with ETU were subject to ETU loss. Ground matrices were used in order to facilitate accurate fortification of the samples. Degradation appears to be a function of the degree of cell rupture and release of enzymes, natural chemicals, or other cellular materials capable of facilitating EBDC and/or ETU degradation.

Therefore, the degradation rate of ETU on commodities stored at -20 ± 5 °C was determined in both finely and coarsely ground matrices. Also, short term storage stability (up to 12 days) were conducted to test the stability of ETU on finely ground matrices since the analytical protocol required samples to be extracted for analysis within this period.

The results from these studies summarized thereafter confirm that both EBDC and ETU residues in frozen stored commodities were stable between the time of preparation and analysis of the survey samples.

For Mancozeb, less than 30% degradation was seen for all commodities for three months except for raw potatoes.

For ETU, the studies showed that residues were stable in coarsely ground matrices. Less than 30% degradation in one month was demonstrated in all commodities except for raw potato which showed 36% degradation. At the three month interval, all commodities showed less than 30% degradation except for raw potato and lettuce.

3.1.2 Freezer Storage Stability in Animals

The PMRA has reviewed a storage stability study for mancozeb and ETU in meat and poultry products. These data indicate that residues of mancozeb are stable (>80% recovered) under frozen storage conditions in the milk, muscle, fat, liver, and kidney of cows and the eggs, liver, fat, gizzard, and muscle of chickens for 180 days, and in chicken kidney for 120 days of frozen storage. The data also indicate that residues of ETU are stable (>70% recovered) in chicken muscle for 750 days, in chicken liver and kidney for 540 days, in beef liver for up to 450 days, in beef kidney and chicken gizzard for 360 days, in beef muscle and chicken eggs for up to 270 days, in beef fat for 180 days, in chicken fat for 60 days, and in milk for 30 days of frozen storage. No additional data are required unless samples in the required meat and milk study are stored for longer periods.

3.1.3 Storage Stability of Working Solutions in Analytical Methodology

There are no storage stability studies for working solutions submitted by the registrant. The registrant is required to submit such storage stability studies for any expansion of use of mancozeb.

3.2 Crop Residues

Residue decline studies are on file for apple, grape, oat, potato, sugar beet and summer squash. Results indicated that Mancozeb residues decreased with increasing PHI . However, these studies were conducted in the United States and might not be representative of the Canadian use conditions.

3.3 Livestock, Poultry, Egg and Milk Residue Data

Dairy Cattle

Feeding of field aged mancozeb residues on alfalfa hay to lactating dairy cattle was investigated by the PMRA. Four groups of cows were fed diet containing mancozeb residues at 0 (control), 5 ppm (onefold), 15 ppm (threefold) and 45 ppm (ninefold) for a period of 28 days.

No residues of mancozeb (<0.04 ppm) were found in the heart or muscle tissues, but residues ranging from 0.06 to 0.22 ppm were found in fat, kidney and liver samples from the highest feeding level group. Discrepancy was determined since depurated cows from both the 5 and 15 ppm feeding groups had apparent residues of 5 ppm whereas the depurated cow from the 45 ppm group had only 0.78 ppm. No logical explanation was provided.

No residues of ETU were found in the fat from the highest feed level. Heart, muscle, liver and kidney from this group showed residues ranging from 0.011 to 0.039 ppm. However, no residues were detected from the epurated cow. ETU residues found in the thyroid from each treated cow tend to diminish after a week of depuration but do not totally disappear.

Results indicated that aged mancozeb residues orally ingested by lactating cow were eliminated mainly via the faeces. There were no measurable mancozeb and ETU residues in the milk. Because of the slow depuration of ETU from the thyroid, the higher level may be the result of an accumulation of dosed ETU or due to the decomposition of mancozeb.

Concentrations of ETU found in milk (avg 0.032 ppm) and urine (0.064 ppm) were very low considering the large amount (25 ppm) of mancozeb fed to the cow. However, it was also noted that the ETU accounted for a substantial fraction of the total ^{14}C activity in milk (avg 23%). It may also be noted that less EU than ETU were found in milk, however, EU was 10 times greater than ETU in urine. As residues of mancozeb and ETU found in potato field trials were lower than 0.2 ppm and 0.02 ppm respectively, it is expected that no finite residue or really low concentrations of either mancozeb or ETU will be detected in animal food commodities when animals were fed with potatoes.

The maximum theoretical dietary burden calculated by USEPA and the EBDC/ETU TF show differences in the choice of the feed items. The anticipated residues of the commodities as well as the percentage in the diet were different. As restrictions stated under Canadian labels prevent feeding or grazing activities with treated food/feed, the PMRA did not calculate a MTDB.

This information has to be compared with metabolism reviews that indicated that a very large proportion of mancozeb were excreted in the faeces and urine. Also, as the Canadian labels restrict the use of treated feed to animals, it is expected that no secondary residues would be found in edible tissues of livestock.

Poultry and Eggs

As indicated in the metabolism review, low levels of radioactive residues were detected in poultry food commodities and eggs. In a feeding study, laying hens were fed with field-aged mancozeb residues (alfalfa) at nominal levels of 0 ppm (control), 5 ppm (4.2 ppm of mancozeb and 0.082 ppm of ETU), 15 ppm (14 ppm of mancozeb and 0.19 ppm of ETU) or 50 ppm (43 ppm of mancozeb and 0.68 ppm of ETU) for a period of 28 days. Alfalfa meal, treated or untreated, comprising approximately 14% of the diet.

Results showed that no mancozeb residues (<0.082 ppm) were found in the whole eggs. Consequently, the egg white and egg yolk fractions were not analysed. There were no measurable ETU residues in the whole eggs except in the highest level dose group at day 20 (0.013 ppm) and day 27 (0.017 ppm).

Mancozeb residues in tissues were found at low concentrations in liver, heart and breast muscle. Higher levels were found in the thigh muscle and gizzard. No ETU residues were detected in the tissues.

Based on review of metabolism and feeding studies, the PMRA concluded that mancozeb residues are eliminated via the excreta with very little deposition in the eggs or tissues.

The maximum theoretical dietary burden calculated by USEPA and the EBDC/ETU TF show differences. The anticipated residues of the commodities as well as the percentage in the diet were different. As restrictions stated under Canadian labels prevent feeding or grazing activities with treated food/feed, the PMRA did not calculate a MTDB.

This information has to be compared with metabolism reviews that indicated that a very large proportion of mancozeb were excreted in the faeces and urine. Also, as the Canadian labels restrict the use of treated feed to animals, it is expected that no secondary residues would be found in edible tissues of hen.

3.4 Confined Crop Rotation Trial Study

The PMRA has reviewed plant back residue study to determine crop and soil residues from 30 and 60 day plant-back crops. In this study, ^{14}C Dithane M-45 was applied at a treatment rate of 6.7 kg a.i./ha. Thirty and sixty days later, after retotalling, plant-back crops of barley, potato, radish and Swiss chard were planted.

^{14}C residues at harvest for the 30 day plant-back were 0.075 ppm for barley grain, 0.072 ppm for potato tubers, 0.038 ppm for radish root and 0.019 ppm for Swiss chard leaves.

^{14}C residues at harvest for the 60 day plant-back were 0.060 ppm for barley grain, 0.007 for radish root and 0.009 ppm for Swiss chard leaves.

No residues of ETU were detected at harvest for the 30 day crops.

Information stated on labels indicated that rotation of fields treated with Mancozeb to cereal grains (wheat, barley and oat) is acceptable after a minimum plant-back interval of 30 days and to peas and beans after a minimum plant-back interval of 9 months. Rotation to all other food and feed crops will require a 12 month plant-back interval. Also, green manure and other cover crops not intended for human or animal consumption are acceptable rotational crops which do not require a plant-back interval following treatment. The statement of “Do not graze or harvest such cover crops for food or feed” is also included.

3.5 Processed Food/Feed

Little information is available in the scientific literature regarding the formation of ETU during the process of food treated with EBDCs. It is of importance to highlight the discrepancies in the results of different reviewed studies (for example, washing factor of apple ranging from 0.4 to 2.4).

The PMRA review of 8 Dec 1974 presented the results of zineb, mancozeb, maneb, metiram and ETU residues in cooked carrots, spinach, apples and tomatoes and concluded: “Cooking of crops containing dithiocarbamate residues results in the formation of significant amounts of ETU.” and “Studies should be conducted on the effects of washing, peeling, etc. on residues since even if high residues are found on the harvested crops these may be significantly reduced by processing.

During the re-evaluation process and review of the scientific literature, it was determined that generally, mancozeb residues remain on the surface of the raw agricultural commodity. Some conversion of mancozeb to ETU may occur, but most of the residues on the Raw Agricultural Commodity are the parent. If some conversion to ETU has occurred, the ETU residues are able to transfer across the surface of the edible commodity and are able to spread throughout the plant. Therefore, washing, trimming and peeling the raw commodity causes considerable reduction of surface mancozeb residues, but not for “systemic” ETU residues. However, peeling has been found to reduce ETU residues on thick-skinned commodities such as bananas, mangoes and melons. Heating commodities reduces ETU slightly and causes some conversion of mancozeb residues to ETU. Processes involving cooking of commodities result in a conversion of the EBDC to ETU.

As some commodities may be subjected to multiple steps during processing, an overall factor combines the multiple processing steps (individual factors are multiplied) to yield a single factor.

The PMRA has reviewed several processing studies submitted by the Mancozeb Task Force to support the registration of mancozeb. These studies clearly show discrepancies between the processing factor values. The PMRA also concluded that the majority of the ETU residues formed after processing may be avoided by a sound washing of the EBDC residues present on the Raw Agricultural Commodity.

To conduct the Dietary Exposure Assessment, the PMRA has followed recommendations adopted in the OECD guideline for the testing of chemicals describing the magnitude of the pesticide residues in processed commodities. The processing studies should simulate industrial or domestic practices as closely as possible. Raw Agricultural Commodies used in processing studies should contain field-treated quantifiable residues, at sufficient levels that concentration/reduction factors for the various consumed products can be determined. However, results from the PMRA review showed that some studies did not comply to such recommendation.

Processing studies reviewed indicate that mancozeb and more generally the EBDCs residues in food commodities are reduced through typical industrial/commercial/consumer practices such as washing, peeling. However, it has been noted that residues concentrate in processed fractions of grains such as bran as well as in potatoes processed food forms such as flakes and flour.

Appendix VIII Supplemental Maximum Residue Limit Information – International Situation and Trade Implications

As per Table 1, the MRLs in Canada differ from the corresponding tolerances established in the United States (40 CFR Part 180) and differ from Codex MRLs (Codex Pesticides Residues in Food Online Database). Common Canadian MRLs are established for the all ethylenebis-dithiocarbamate fungicides, while the Codex MRLs are set collectively for all dithiocarbamate compounds. Specific American tolerances are set for mancozeb.

Specific MRLs for animal commodities have not been established but are covered under the general provisions of B.15.002(1) of the *Food and Drug Regulations*. This requires that residues do not exceed 0.1 ppm when no specific MRL has been established.

Residues of ETU are relevant to the ethylenebis-dithiocarbamate fungicides. Residues of ETU on commodities are regulated. There are no specific MRLs established for ETU under the *Pest Control Products Act*. However, residues in food from all sources are regulated separately under sections B.01.046 and B.01.047 of the *Food and Drug Regulations*, where a maximum limit of 0.05 ppm is specified for ETU in fruits, vegetables and cereals. No change to this maximum limit is proposed. Neither American tolereances nor Codex MRLs are established for ETU.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For livestock commodities, differences in MRLs can be due to different livestock feed items and practices.

Table 1 Difference Between Canadian MRLs and Other Jurisdictions

Raw Agricultural Commodity	Current Canadian MRL (ppm)[a]	American established tolerance for mancozeb (ppm)[b]	American reassessed tolerance (ppm CS2)	Codex MRL (ppm CS2)[c]
Apple	7	7	0.6 (see 6.6)	5
Asparagus	-	0.1	0.1 (see 6.6)	0.1 (see 6.6)
Avocado	-	-	-	-
Banana	-	4	2	2
Barley grain	-	5	1	1
Barley straw	-	25	20	25
Currant	-	-	-	10
Broccoli	7	-	-	-
Brussel sprouts	7	-	-	-
Cabbage	7	-	-	5
Cauliflower	7	-	-	-
Carrot	-	2	1	1
Celery	5	5	2	-
Corn pop grain	-	0.5	0.06	-
Corn (sweet corn, kernels plus cob with husk removed)	-	0.5	0.1	-
Corn grain (except popcorn grain)	-	0.1	0.06	-
Cottonseed	-	0.5	TBD	-

Raw Agricultural Commodity	Current Canadian MRL (ppm)[a]	American established tolerance for mancozeb (ppm)[b]	American reassessed tolerance (ppm CS2)	Codex MRL (ppm CS2)[c]
Crabapple	-	10	0.6	-
Cranberry	-	7	5	5
Cucumber	4	4	reassign to cucurbit	2
Cucurbit	-	-	2	-
Eggplant	7	-	-	-
Endive	7	-	-	-
Fennel	-	10	25	-
Garlic	-	-	-	0.5
Ginseng	-	2	12	-
Grape	7	7	15	5
Brassica	-	-	2	-
Kale	-	-	-	15
Kidney	-	0.5	TBD	-
Leek	-	-	-	0.5
Lentil	6	-	-	-
Lettuce	7	-	-	10
Liver	-	0.5	TBD	-
Mango	-	-	-	2
Melon	-	4	Reassign to cucurbit	0.5 (except watermelon)
Milk	-	-	-	0.05
Mushroom	7	-	-	-
Oat grain	-	5	0.6	-
Oat straw	-	25	20	-
Onion dry	0.5	0.5	1.5	0.5
Onion green	7	-	-	-
Orange	-	-	-	2
Papaya	-	10	9	5
Peanut	-	0.5	0.1	0.1 (LOD)
Pear	7	10	0.6	5
Pepper	7	-	-	1
Potato	-	1	0.2	0.2
Poultry meat	-	-	-	0.1
Poultry, edible offal	-	-	-	0.1
Pumpkin	-	-	-	0.2
Quince	-	10	0.6	-
Rye grain	-	5	0.6	-
Rye straw	-	25	20	-
Squash	-	4	Reassign to cucurbit	1 (summer) 0.1 (winter)
Sugar beet root	-	2	12	0.5
Sugar beet top	-	65	60	-
Tomato	4	4	2.5	2
Watermelon	-	-	-	1
Wheat grain	-	5	1	1
Wheat straw	-	25	25	25

[a] The Canadian residue definition for compliance with MRLs in plant and estimation of the dietary intake in plant and animal commodities: manganese and zinc ethylenebis(dithiocarbamate) (polymeric).

[b] The United States residue definition for compliance with the tolerance levels is to be determined by measuring only those mancozeb residues convertible to and expressed in terms of the degradate carbon disulfide. American tolerances list accessed [CFR 180.176, July 20, 2011].

[c] Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.The Codex residue definition for compliance with MRLs in plant and estimation of dietary intake in plant and animal commodities: total dithiocarbamates, determined as CS_2, evolved during acid digestion and expressed as mg CS_2/kg.

Appendix IX Environment Assessment

Table 1 Fate and Behaviour of Mancozeb in the Environment

Process	Substance	$t_{½}$ or DT_{50} (d)	DT_{90} (d)	Kinetics[1]	Comments	PMRA #
Abiotic Transformation						
Hydrolysis	Parent mancozeb	0.8 d pH 5 0.7 d pH 7 1.4 d pH 9	NR	SFO	From USEPA 2005 Regristration Eligibility Decision	1807553
Phototransformation soil	Parent mancozeb	CND			Mancozeb is not shown to photolytically degrade on dry soil, however, rapid decomposition would be expected in moist soil due to hydrolysis.	1215599
Biotic Transformation						
Aerobic sandy loam soil	Parent mancozeb	< 1h	CND		The dissipation of parent mancozeb in soil under aerobic biotransformation is attribuatable to hydrolysis, as such, parent mancozeb is considered non-persistent.	1729981
	Mancozeb complex	8.3 d	27.4 d	SFO	The mancozeb complex was determined to be non-persistent in soil under aerobic conditions. The DT_{50}/DT_{90} was determined based on extractable radioactivity. The major transformation products identified were ETU, EU and EBIS. Non-extractable residues increased to a maximum of 59.1% of AR (Aoolied Radiation) (day 28) and decreased to 49% at study termination (day 120).	
Aerobic loamy sand soil	Parent mancozeb	< 1 h	CND		The dissipation of parent mancozeb in soil under aerobic biotransformation is attribuatable to hydrolysis, as such, parent mancozeb is considered non-persistent.	
	Mancozeb complex	1.8 d	27.2 d	DFOP	The mancozeb complex was determined to be non-persistent in soil under aerobic conditions. The DT_{50}/DT_{90} was determined based on extractable radioactivity. The major transformation products identified were ETU, EU and EBIS. Non-extractable residues increased to a maximum of 69.8% of AR (day 28) and decreased to 58% at study termination (day 120).	

Process	Substance	$t_{½}$ or DT_{50} (d)	DT_{90} (d)	Kinetics[1]	Comments	PMRA #
Aerobic silt loam	Parent mancozeb	< 1 h	CND		The dissipation of parent mancozeb in soil under aerobic biotransformation is attribuatable to hydrolysis, as such, parent mancozeb is considered non-persistent.	
	Mancozeb complex	4.84 d	16.1 d	SFO	The mancozeb complex was determined to be non-persistent in soil under aerobic conditions. The DT_{50}/DT_{90} was determined based on extractable radioactivity. The major transformation products identified were ETU, EU and EBIS. Non-extractable residues increased to a maximum of 70.7% of AR (day 7) and decreased to 52% at study termination (day 120).	
Aerobic water/river system	Parent mancozeb	0.72 d	7.11	DFOP	The dissipation of parent mancozeb in water under aerobic biotransformation is attributable to hydrolysis, as such, parent mancozeb is considered non-persistent. Major transformation products EBIS, ETU and EU which were found predominantly in the water phase.	1728579
	Mancozeb complex	19.9	66.3	SFO		
Aerobic Water/pond system	Parent	0.81	7.23	SFO	The dissipation of parent mancozeb in water under aerobic biotransformation is attribuatable to hydrolysis, as such, parent mancozeb is considered non-persistent. Major transformation products EBIS, ETU and EU which were found predominantly in the water phase.	
	Complex	40.5	135	SFO	The mancozeb complex was determined to be slightly persistent under aquatic aerobic conditions. Non-extractable residues were determined to range from 5.4 to 35.4% at study termination.	
Aerobic Water/river system	Parent	< 1 day	CND	SFO	The dissipation of parent mancozeb in water under aerobic biotransformation is attribuatable to hydrolysis, as such, parent mancozeb is considered non-persistent.	1764935
	Complex	25.1	83.4	SFO	The mancozeb complex was determined to be slightly persistent under aquatic aerobic conditions. Non-extractable residues were determined to increase from 1.2 to 39.5 at study termination.	

Process	Substance	$t_{½}$ or DT_{50} (d)	DT_{90} (d)	Kinetics[1]	Comments	PMRA #
Aerobic Water/pond system	Parent	< 1 day	CND	SFO	The dissipation of parent mancozeb in water under aerobic biotransformation is attribuatable to hydrolysis, as such, parent mancozeb is considered non-persistent.	
	Complex	62.4	207	SFO	The mancozeb complex was determined to be slightly persistent under aquatic aerobic conditions. Non-extractable residues were determined to range from 2.2 to 43.6% at study termination.	
Anaerobic water	Parent	80	267	SFO	DT50 for mancozeb complex could not be determined as a mass balance was not conducted for study. Only parent mancozeb was determined via CS_2 generation/spectrophotometric analysis; (a procedure similar to that of the Keppel method).	1728580
Foliar dissipation	Parent mancozeb	20 d (90th centile) 10 d (50th centile)	NR		Half-lives based on a dataset of mancozeb dislodgeable residue on foliage.	1807553
Mobility						
Adsorption	Sand	Kd = 11.4	Koc = 2279		Slight mobility	1215600
	Sandy Loam	Kd = 8.8	Koc = 551		Low mobility	
	Silt Loam	Kd = 5.7	Koc = 283		Moderate mobility	
	Clay loam	Kd = 8.4	Koc = 562		Low mobility	
Leaching	Radioactivity recovered in the leachate was 19.1, 8.7 and 4.2 % of AR in sandy loam and two silt loam soil, respectively. The majority of the residues remained in the soil – 77.8, 98.9 and 90.2% of AR, respectively. The greatest concentration of ^{14}C residues left in the soils were in the top 1 inch, 56.8, 84.2 and 83% of AR, respectively. No significant ^{14}C volatiles were formed. Radioactivity in leachates and remaining in soil was not characterized.					1132308
Field Studies						
Terrestrial Field Dissipation (California)	Parent mancozeb	31–66 d	NR		The data used to calculated these DT_{50}s included the concentration data for the period after the first application, between all 10 applications and thereafter. The half-life calculations provided by the author are based on first order	1699407
	ETU	41–89	NR			

Process	Substance	$t_{½}$ or DT_{50} (d)	DT_{90} (d)	Kinetics[1]	Comments	PMRA #
					exponential decay. The DT_{50} for ETU are only apparent half-lives since formation of ETU is continuing at the same time as the degradation of ETU. Half-lives representative of the period after the final application, (application 10), were not calculated due to the limited number of sampling events after the 10th application.	

CND = could not determine
NR = not reported
1 – SFO: single first order; DFOP: double first order in parallel

Table 2 Fate and Behaviour of ETU in the Environment

Study type	Test material	Value	Transformation products	Comments	Reference PMRA #
Abiotic transformation					
Hydrolysis	ETU	$t_{1/2}$= 96.7 d (pH 7) stable (pH 5,7,9)	None detected because little transformation	From dark control of photolysis study	1580898 1744702
Phototransformation on soil	ETU	EU and 2-imidazoline, Amounts unknown		Rapid phototransformation	1744702
Phototransformation in water	ETU	$t_{1/2}$ = 2.35 d sensitized $t_{1/2}$ = 358 d unsensitized	EU and two unknowns at 31,10 and 36% of applied at study termination	In natural water (non-sterile) phototransformation is rapid	1580898
Phototransformation in air	Maneb and Zineb	$t_{1/2}$ = 8 and 9 d $t_{1/2}$ = <1 day	Not measured n/a	In microagroecosystem Calculated by EPI Suite	1750246 1744702
Biotransformation					
Biotransformation in aerobic soil	ETU	$t_{1/2}$ = 1.6-3.2 d	EU < 1 to 3.4% of applied	Slight decrease in rates with decreased soil	1744702

Study type	Test material	Value	Transformation products	Comments	Reference PMRA #
	ETU Parent EBDCs	$t_{1/2}$ = <2 d ETU $t_{1/2}$ = 0.2-6.6 d	EU 54-94%, 2 unknowns No info	moisture	1216524 1744708, 1744712, 1744713
Biotransformation in anaerobic soil	No information				
Biotransformation in aerobic water systems	Nabam	ETU Apparent DT_{50}= 21 d	EBIS: <0.1-19%; EU: 5-16%*	Slightly persistent	1580892
Biotransformation in anaerobic water systems	Maneb Nabam	ETU Apparent DT_{50} = 149 d ETU Apparent DT_{50} = 499 d	No Information EBIS: <0.1- 27%; EU: 9-16%*	Moderately persistent Persistent	1744702 1580894
Mobility					
Adsorption/desorption in soil	ETU	K_f = 0.51 clay loam K_f = 0.67 sandy loam K_f = 0.73 sand K_f = 1.14 silt loam $K_{oc\text{-}ads}$ = 35-141 (all soils)	EU 0-14% of applied	High to very high mobility	1580895
	ETU	Koc = 54, 165, 276, 464, 783, 855	Not provided	Low to Very high mobility	1744702
Soil leaching	ETU residues	22-91% of AR in leachate	No characterization	Very to very highly mobile residues	1580902
Volatilization	Maneb and zineb	$t_{1/2}$ = 8 or 9 d	Not determined	Not persistent in air	1750246
Field studies					
Field dissipation	Metiram - New York Mancozeb – California EBDC –	Apparent DT_{50} = 21 d Apparent DT_{50} = 41, 93 d DT50 <7 days	Not determined Not determined Not determined	Slightly to moderately persistent Slightly to moderately persistent Non persistent	1589667 1699407 1744708, 1744712, 1744713

Study type	Test material	Value	Transformation products	Comments	Reference PMRA #
	European rev.				
Field leaching	Metiram New York Mancozeb - California	ND >15.2 cm soil depth ND >15.2 cm soil depth	Not determined Not determined	Could not be detected below 15cm, however, could have leached through the soil profile between sampling dates or was just below the level of detection	1589667 1699407

* These transformation products may not be a result of transformation from ETU to EBIS and EU. They could have formed as a result of the transformation of the parent EBDC that was initially used in the study.

Table 3 Toxicity of Mancozeb and ETU to Non-Target Species

Organism	Study type	Species	Test material	Endpoint	Value (nominal/mean measured)	Effect of concern	Reference
Terrestrial Organisms							
Earthworm	Acute	*Eisenia foetida*	84.6% mancozeb	14-d LC_{50}	>299.1 mg a.i./kg soil	mortality	PMRA# 1132316
	Chronic		81.7% mancozeb	NOEC	1000 mg a.i./kg soil	reproduction	PMRA# 1699413
Bee	Contact	*Apis mellifera*	Technical (% a.i. not reported)	LD_{50}	> 179 µg a.i./bee	mortality	PMRA# 1807553
			69% mancozeb 8.26% zoxamide	72-h LD_{50}	> 200 µg formulation/bee		PMRA# 1699414
	Oral		69% mancozeb 8.26% zoxamide	72-h LD_{50}	> 153 µg formulation/bee		
Predatory arthropod	Contact (extended lab)	*Typhlodromus pyri*	Dithane M-45 (% mancozeb not reported)	7-d LR_{50}	112.1 g a.i./ha	Mortality	PMRA# 1699434
Birds	Acute	mallard duck (*Anas platyrhynchos*)	86% mancozeb	10-d LD_{50}	> 1600 mg a.i./kg/day	Mortality	PMRA# 1699431
		English sparrow (*Passer domesticus*)	Not reported	10-d LD_{50}	1500 mg a.i./kg		PMRA# 1807553
	Reproduction	northern bobwhite quail (*Colinus virginuanus*)	86.2 – 88.5% mancozeb	NOEL[1]	25.5 mg a.i./kg bw/day	Endpoints affected: the proportion of normal hatchlings of fertile eggs set, the proportion of 14-day survivors of eggs set and of eggs laid.	PMRA# 1788050
			81.9% mancozeb	NOEL[2]	**13.2** mg a.i./kg bw/day	Endpoints affected: reductions in the percentage of 14-day old survivors of normal hatchlings and reductions in hatchling and 14-day old survivor bodyweights	PMRA# 1788051
		mallard duck (*Anas platyrhynchos*)	80.1% mancozeb	NOEL[1]	18.1mg a.i./kg bw/day	Endpoints affected: egg production, early and late embryo viability, hatchability, and offspring weight at hatch and 14-days of age.	PMRA# 1788049
Mammals	Acute	Rat	95% mancozeb	LD_{50}	> 5000 mg/kg bw	Survival	PMRA# 1570258
			ETU	LD_{50}	545 – 1832 mg/kg bw (600 mg/kg bw for pregnant rats)	Survival	PMRA# 1570258, 1805631, 1805563, 1805536

Organism	Study type	Species	Test material	Endpoint	Value (nominal/mean measured)	Effect of concern	Reference
		Mouse	ETU	LD_{50}	2400 – 4000 mg/kg bw	Survival	PMRA# 1805563, 1805631, 1570258
	90-d dietary	Rat	84% mancozeb	NOEL	14.98 (♂); 17.82 (♀) (mg a.i./kg bw/day)	Endpoints affected: Based on reduced body weight	PMRA# 1570229
			ETU	NOEL	1.7 mg/kg bw/day		PMRA# 1831764
		Mice	83% mancozeb	NOEL	166.9 (♂); 233.8 (♀) (mg a.i./kg bw/day)		PMRA# 1570228
			ETU	NOEL	1.7 mg/kg bw/day	hyperaemia of thyroid, increased thyroid wt., decreased thyroid binding globulin (TBG) T_3 and T_4	PMRA# 1570233
	120-d dietary	Rat	ETU	NOEL	2.5 mg/kg bw/day	↑ rel thyroid wt at ≥30 days, ↓ ^{131}I uptake at 24 h, slight hyperplasia of the thyroid gland.	PMRA# 1805536
	Developmental	Rat	ETU	NOEL	Maternal: 40 Developmental: 5 (mg a.i./kg bw/day)	Dams **at**80 mg/kg bw/d: lethal to 9/11 dams. Fetal ≥5 mg/kg bw/d: ↑ in delayed ossification of the parietal bone (groups I and II). ≥10 mg/kg bw/d: (all groups): ↑ meningoencephalocele, meningorrhagia, meningorrhea, hydrocephalus, obliterated neural canal, abnormal pelvic limb posture with equinovarus, and short or kinked tail.	PMRA# 1805649, 1805557

Organism	Study type	Species	Test material	Endpoint	Value (nominal/mean measured)	Effect of concern	Reference
		Rat	ETU	NOEL	Maternal: 35 Developmental: 15 (mg a.i./kg bw/day)	Dams No maternal toxicity noted. Fetal ≥25 mg/kg bw/d: ↑ dilated brain ventricles (33.5%). **at3**5 mg/kg bw/d: ↑ cranial meningocele and meningorrhea, severe hindlimb talipes, hydroureter and dilated ureter, and ↓ ossification of skull bones. 43.5% of fetuses had short or kinky tails, 93% had ELV, 33.5% had dumbell-shaped or bilobed vertebral centra.	PMRA# 1805574
		Rat, mice, hamster and guinea pigs	ETU	NOEL	5 mg/kg bw/day rats	Maternal: **at** 80 mg/kg bw/d: ↓ bwg and 25% mortality. DEV: ≥10 mg/kg bw/d: ↓ bw ≥20 mg/kg bw/d: ↑ hydrocephalus ≥40 mg/kg bw/d: ↓ ossification, ↑ encephalocele, kyphosis and digit defects. **at** 80 mg/kg bw/d: ↑ mortality, edema, gross defects of the skeletal system and CNS. No apparent effects in hamsters or guinea pigs	PMRA# 1805604
	2 generation reproduction	Rat	88.4% mancozeb	NOEL	Repro > 110 offspring: 2.5 parental: 15 (mg a.i./kg bw/day)	Endpoints affected: Based on reduced body weight	PMRA# 1624102
			84% mancozeb	NOEL	Repro: 69/79 offspring: 69/79 parental: 7.0/7.5 (mg a.i./kg bw/day)		PMRA# 1173163
Vascular plants	Seedling emergence	4 monocot species: corn, oat, onion,	60% mancozeb 9% dimethomorph	Most sensitive monocot: Onion – 12% plant dw inhibition Most sensitive dicot: Soybean + tomato – 4% plant dw inhibition			PMRA# 1807553

Organism	Study type	Species	Test material	Endpoint	Value (nominal/mean measured)	Effect of concern	Reference
	Vegetative vigour	ryegrass 6 dicot species: cabbage, cucumber, lettuce, soybean, tomato, radish	Tier I study: (155/0.20 kg a.i./ha)	Most sensitive monocot: Corn + onion – 2% plant dw inhibition Most sensitive dicot: Cucumber – 10% plant dw inhibition			
Freshwater Organisms							
Invertebrates	Acute	*Daphnia magna*	80.0% mancozeb	48-h LC_{50}	580 µg/L (nominal)	immobility	PMRA# 1807553
			Formulated product (37%)	48-h LC_{50} NOEC	8500 µg g a.i./L (nominal)		PMRA# 1788052
			66.6% mancozeb 4.09% benalaxyl	48-h LC_{50} NOEC	1800 µg total product/L 980 µg total product/L (mean measured)		PMRA# 1788053
			69 % mancozeb 8.26% zoxamide	48-h LC_{50} NOEC	3300 µg total product/L 820 µg total product/L (mean measured)		PMRA# 1699415
			82.4% mancozeb	48-h LC_{50} NOEC	1040 µg a.i/L 460 µg a.i/L (nominal)		PMRA# 1132317
			99.6% ETU	48-h LC_{50}	26900 µg a.i/L (measured)		PMRA# 1744702
	Chronic	*Daphnia magna*	82.4% mancozeb	21-d LC_{50} (survival) NOEC (reproductive effects)	>50 µg a.i./L (nominal) > 31.1 µg a.i/L (mean measured) 5.9 µg a.i/L (nominal) 2.4 µg a.i/L (mean measured)	mortality mean young/adult reproduction day	PMRA# 1169756
			77.1% mancozeb	21-d LC_{50} (survival) NOEC (reproductive effects)	24 µg a.i/L (mean measured) 63 µg a.i./L (nominal) 18 µg a.i/L (mean measured)	mortality mean young/adult reproduction day	PMRA# 1699416
			ETU (% not reported)	21-d NOEC	2000 µg a.i/L (not reported)	Not reported	PMRA# 1744708
Fish	Acute	Rainbow trout (*Oncorhynchus mykiss*)	>90% mancozeb	96-h LC_{50} NOEC 96-h LC_{50} NOEC	210 µg a.i/L 180 µg a.i/L (nominal) 74 µg a.i/L 41 µg a.i/L (mean measured)	mortality	PMRA# 1699424 or PMRA# 1726834
			86% mancozeb	48-h LC_{50}	1860 µg a.i/L (nominal)		PMRA# 1699421
			Formulated product (37%)	96-h LC_{50}	1100 µg a.i./L (nominal)		PMRA# 1788055

Organism	Study type	Species	Test material	Endpoint	Value (nominal/mean measured)	Effect of concern	Reference
			81.3% mancozeb	96-h LC_{50} NOEC 96-h LC_{50} NOEC	990 µg a.i./L 250 µg a.i./L (nominal) 910 µg a.i./L 270 µg a.i./L (mean measured)		PMRA# 1788057
			80% mancozeb	96-h LC_{50}	640µg a.i./L (not reported)		Environmental Fate and Effects Division Reregistration Eligibility Decision
					460 µg a.i./L (mean measured)		
			8.9% dimethomorph/59.7% mancozeb	96-h LC_{50}	550 µg a.i./L (nominal)		
			8.9% dimethomorph/59.7% mancozeb		680 µg a.i./L (nominal)		
			7.5% dimethomorph/67.7% mancozeb		390 µg a.i./L (nominal)		
			8.26 zoxamide/69.0% mancozeb		1900 µg a.i./L (not reported)		
			99.6% ETU	96-h LC_{50}	>502000 µg a.i/L (not reported)		PMRA# 1744702
		Bluegill sunfish (*Lepomis macrochirus*)	81.3% mancozeb	96-h LC_{50} NOEC 96-h LC_{50} NOEC	4000 µg a.i./L 500 µg a.i./L (nominal) 3600 µg a.i./L 440 µg a.i./L (mean measured)		PMRA# 1699425
			80% mancozeb	96-h LC_{50}	3850 µg a.i./L (nominal)		Environmental Fate and Effects Division Reregistration Eligibility Decision
					1350 µg a.i./L (not reported)		
					1540 µg a.i./L (not reported)		
					2040 µg a.i./L (mean measured)		
			100% ETU	96-h LC_{50}	>990000 µg a.i/L (not reported)		PMRA# 1619167
	Chronic	Fathead minnow (*Pimephales promelas*)	79.3% mancozeb	NOEC LOEC (28 day early life stage)	4.65 µg a.i/L 9.57 µg a.i/L (LSC mean measured)		PMRA# 1171150
		Rainbow trout (*Oncorhynchus mykiss*)	77.1% mancozeb	21 day LC_{50} NOEC	149 µg a.i./L 13 µg a.i./L (nominal) 102 µg a.i./L 8 µg a.i./L (mean measured)		PMRA# 1699422

Organism	Study type	Species	Test material	Endpoint	Value (nominal/mean measured)	Effect of concern	Reference
Algae	Acute	Green algae (*Selenastrum capricornutum*)	82.4% mancozeb	120-h EC_{50} NOEC 120-h EC_{50} NOEC	63 µg a.i./L 33 µg a.i./L (nominal) 21.9 µg a.i/L 9.5 µg a.i/L (mean measured)	Biomass/growth rate	PMRA# 1169755
			69.0% mancozeb 8.26% zoxamide	96-h EC_{50} NOEC	31.4 µg a.i/L 234 µg a.i/L 8.43 µg a.i./L (mean measured total product)	biomass/growth rate	PMRA# 1699433
			62.9% mancozeb 3.96% CGA 329351 (unknown active)	72-h EC_{50} NOEC	31.4 µg a.i/L 234 µg a.i/L 8.43 µg a.i./L (mean measured total product)	Biomass growth rate biomass and growth rate	PMRA# 1171060
			89.14% mancozeb	120-h EC_{50} 48-h EC_{50} NOEC	390 µg a.i/L 430 µg a.i/L 200 µg a./L (nominal)	Biomass/growth rate biomass and growth rate	PMRA# 1169754
			67.7% mancozeb 7.5% dimethomorph	72-h EC_{50} NOEC	19 µg total product/L 4.3 µg total product/L	biomass	PMRA# 1807553
			60% mancozeb 9% dimethomorph	120-h EC_{50} NOEC	112 µg total product/L 28 µg total product/L		
		freshwater diatom *(Navicula pelliculosa)*		120-h EC_{50} NOEC	13.71 µg total product/L 2.88 µg total product/L		
		freshwater blue-green algae *(Anabaena flos-aquae)*		120-h EC_{50} NOEC	130 µg total product/L 28 µg total product/L		
		Green Algae (*Pseudokirchneriella subcapitata*)	99.6% ETU	72-h EC_{50} NOEC	23000 µg a.i/L 12500 µg a.i/L (not reported)	Biomass	PMRA# 1744702
Vascular Plants	Acute	Duckweed (*Lemna gibba*)	100% ETU	7-d EC_{50} NOEC	>960000 µg a.i/L 960000 µg a.i/L (nominal)	Frond biomass, growth rate, density	PMRA# 1619169

Organism	Study type	Species	Test material	Endpoint	Value (nominal/mean measured)	Effect of concern	Reference
Amphibians	Acute	*Bufo Americanus*	Dithane DG (76-80% mancozeb)	96-h LC_{50}	1400 µg a.i/L (nominal)	Hatching success (Exposure at Gosner stage 8 – embryo stage)	PMRA# 2137153
		Rana pipiens			200 µg a.i/L (nominal)		
		Rana pipiens	Dithane DG (guarantee: 76-80% mancozeb) and Manzate		> 1000 µg a.i/L (nominal)	Mortality Stage 25 tadpoles	PMRA# 2137165
		Rana clamitans	Dithane DG (76-80% mancozeb)	Continuous exposure 96 hour LC_{50} 13-day LC_{50}	2210 µg a.i/L 23 µg a.i/L (nominal)	96 hour LC_{50} based on hatching success; 13 day LC_{50} based on tadpole survival. Exposure began at stage 8 (embryo stage).	PMRA# 2137156
				Discontinuous exposure 96 hour LC_{50} 16-day LC_{50} EC_{50} 16-d NOEC	960 µg a.i/L 200 µg a.i/L 40 µg a.i/L 7.8 µg a.i/L (nominal)	96 hour LC_{50} based on hatching success; 16 day LC_{50} based on tadpole survival; EC_{50} based on deformities at hatching (day 8); NOEC based on growth inhibition observed at 78 ug a.i./L treatment. Exposure began at stage 8 (embryo stage).	
	Chronic	*Bofu americanus*		Sex ratio NOEC LOEC	0.8 µg a.i./L 80 µg a.i./L (nominal)	Exposure at stage 8 (embryo) for 96 hours then again at stage 42 (limb emergence) for 48 hours. Note: the NOEC may be 8 ug/L; sex ratio was not reported for this treatment level.	PMRA# 2137153
				NOEC LOEC	8.0 µg a.i./L 80 µg a.i./L (nominal)	Based on 14% skeletal deformities at stage 20 and 5% deformities (abnormal eye) at 80 ug a.i./L. Exposure at stage 8 (embryo) for 96 hours then again at stage 42 (limb emergence) for 48 hours.	
		Rana pipiens	Manzate 75 DF (guarantee: 75 % mancozeb)	49 day NOEC 49 day LOEC	Could not determine 16 µg a.i./L (nominal)	Survival and growth rate Post hatch exposure	PMRA# 2137159

Organism	Study type	Species	Test material	Endpoint	Value (nominal/mean measured)	Effect of concern	Reference
Aquatic mesocosm			Penncozeb 80 WP/L (81.7% mancozeb)	EC_{20} EC_{50}	4.5 µg a.i./L 7.5 µg a.i./L (nominal)		PMRA# 1788072
Amphibians	Acute	*X. laevis*	ETU (purity not reported)	28-d NOEC	10000 µg a.i./L (not reported)	Endpoint not specified	PMRA# 1744712
	Chronic		ETU (purity not reported)	90-d NOEC	10000 µg a.i./L 1000 µg a.i./L (nor reported)	Developmental effects Histological alterations (thyroid)	PMRA# 1722137 PMRA# 1744709
Marine and estuarine Organisms							
Invertebrates	Acute	Mysid shrimp (*Mysidopsis bahia*)	82.4% mancozeb	96-h LC_{50}	21.9 µg a.i/L (nominal) 10.5 µg a.i/L (mean measured)	Mortality	PMRA# 1788059
			Formulated product (37%)	96-h LC_{50} NOEC 96-h LC_{50} NOEC	21.9 µg a.i/L 3.7 µg a.i/L (nominal) 9.5 µg a.i/L 1.9 µg a.i/L (mean measured)		PMRA# 1788061
			100% ETU	96-h LC_{50} NOEC	9200 µg a.i/L 6400 µg a.i/L (mean measured)		PMRA# 1616165
		Eastern oysters (*Crassostrea virginica*)	Formulated product (37%)	96-h EC_{50}	1850 µg a.i/L (nominal) 1530 µg a.i/L (mean measured)	Shell deposition	PMRA# 1788062
			82.4% mancozeb	96-h EC_{50}	2100 µg a.i/L (nominal) 1600 µg a.i/L (mean measured)		PMRA# 1788063
			100% ETU	96-h EC_{50} NOEC	>110000 µg a.i/L 42 000µg a.i/L (mean measured)		PMRA# 1619166
Fish	Acute	Sheepshead minnow (*Cypronodon variegates*)	Formulated product (% a.i. not reported)	96-h LC_{50} NOEC 96-h LC_{50} NOEC	5660 µg a.i/L 1700 µg a.i/L (nominal) 1100 µg a.i/L 560 µg a.i/L (mean measured)	Mortality	PMRA# 1788064

Organism	Study type	Species	Test material	Endpoint	Value (nominal/mean measured)	Effect of concern	Reference
			82.4% mancozeb	96-h LC_{50} NOEC 96-h LC_{50} NOEC	2300 µg a.i/L 1700 µg a.i/L (nominal) 1700 µg a.i/L 820 µg a.i/L (mean measured)		PMRA# 1788065
			Formulated product (% a.i. not reported)	96-h LC_{50}	4200 µg a.i/L (nominal)		PMRA# 1788071
			82.4% mancozeb	96-h LC_{50}	4200 µg a.i/L (nominal)		PMRA# 1788070
			100% ETU	96-h LC_{50} NOEC	>900 µg a.i/L 900 µg a.i/L (mean measured)		PMRA# 1619168
Algae	Acute	*Skeletonema costatum*	Formulated product (60% mancozeb, 9% dimethomorph)	120-h EC_{50} NOEC	139 µg total product/L 104 µg total product/L	Growth inhibition	PMRA# 1807553

1 - NOEL calculated using (concentration in diet × FIR)/BW; FIR = food ingestion rate reported in study, BW = mean body weight reported in study
2 - NOEL calculated using (concentration in diet × FIR)/BW; default FIR for bobwhite quail (Nagy, 1987): 18.9 g diet/bird/day = 0.0189 kg diet/bird/day; default Body weight for bobwhite quail (BW; Dunning, 1993): 0.178 kg/bird
NA –not applicable

Table 4 Screening Level Risk Assessment for Earthworms and Bees

Organisms	Exposure	Endpoint Value	Application Rate	EEC[1]	RQ[2]	LOC[3] exceeded
Earthworm	Acute	14-day LC_{50} ÷ 2: 149.6 mg a.i./kg soil	4800 g a.i./ha × 6	4.68 mg a.i./kg	<0.1	No
	Chronic	28-d NOEC: 1000 mg a.i./kg soil	4800 g a.i./ha × 6	4.68 mg a.i./kg	<0.01	No
Bee	Acute	48-h LD_{50} : > 179 µg a.i./bee[4]	5400 g a.i./ha	5400 g a.i./ha	<0.1	No
Atkins EL; Kellum D; Atkins KW. 1981. Reducing pesticide hazards to honey bees: mortality prediction techniques and integrated management techniques. Univ Calif, Div Agric Sci, Leaflet 2883. 22 pp						

1 - Environmental Exposure Concentration (Soil: calculated based on a soil density of 1.5 g/cm^3, soil depth of 15 cm and the maximum cumulative application rate taking into consideration dissipation between applications; Bee: maximum single application rate (application rate × no. of applications).
2 - Risk Quotient (RQ) = exposure/toxicity
3 - Level of Concern (LOC) = RQ = 1; a calculated RQ > 1 exceeds the LOC
4 - Toxicity in µg/bee converted to the equivalent kg a.i./ha using a conversion factor of 1.12 (Atkins et al., 1981)

Table 5 Risk Assessment for Predatory Arthropods

Organism/endpoint	Crop	Application rate (g a.i./ha)/method	On field			Off-field		
			EEC[1] (g a.i./ha)	RQ	LOC exceeded	EEC[2] (g a.i./ha)	RQ	LOC exceeded
predatory mite *T. pyri* LR_{50} 112.1 kg a.i./ha	Apples	4800 × 6 at 7-d Airblast	13669	**122**	Yes	1008	**9.0**	Yes

1 - In-field EEC = cumulative rate × crop interception factor (80%); the cumulative application is based on a 20 d foliar half-life: this value is representative of the 90th percentile of foliar residue data for mancozeb.
2 - Off-field EEC = cumulative rate × drift factor (59% late airblast application) × vegetation distribution factor of 10%. The vegetation distribution factor is applied since drift is overestimated to the lower or interior portions of a three-dimensional habitat structure. Most of the drift would be intercepted by the top or side portions of the habitat.
Risk quotients shown in bold exceed the level of concern (RQ > 1) which is applicable to extended lab tests for beneficial arthropods.

Table 6 Summary of Screening Level Risk Assessment of Mancozeb to Birds

Toxicity endpoint (mg a.i./kg bw/d)	Feeding Guild (food item)	On-field		Off Field	
		EDE[1] (mg a.i./kg bw)	RQ[2]	EDE (mg a.i./kg bw)	RQ[2]
Birds (20 g)					
Acute 150 mg a.i./kg bw/d	Insectivore (small insects)	861	5.7	637	4.2
	Granivore (grain and seeds)	215	1.4	159	1.1
	Frugivore (fruit)	430	2.9	319	2.1
Reproduction 13.2 mg a.i./kg bw/d	Insectivore (small insects)	861	65.2	637	48.3
	Granivore (grain and seeds)	215	16.3	159	12.1
	Frugivore (fruit)	430	32.6	319	24.1
Birds (100 g)					
Acute 150 mg a.i./kg bw/d	Insectivore (small insects)	672	4.5	497	3.3
	Insectivore (large insects)	168	1.1	124	0.8
	Granivore (grain and seeds)	168	1.1	124	0.8
	Frugivore (fruit)	336	2.2	249	1.7
Reproduction 13.2 mg a.i./kg bw/d	Insectivore (small insects)	672	50.9	497	37.7
	Insectivore (large insects)	168	12.7	124	9.4
	Granivore (grain and seeds)	168	12.7	124	9.4
	Frugivore (fruit)	336	25.5	249	18.8

Toxicity endpoint (mg a.i./kg bw/d)	Feeding Guild (food item)	On-field		Off Field	
		EDE[1] (mg a.i./kg bw)	RQ[2]	EDE (mg a.i./kg bw)	RQ[2]
Birds (1000 g)					
Acute 150 mg a.i./kg bw/d	Insectivore (small insects)	196	1.3	145	1.0
	Herbivore (short grass)	701	4.7	519	3.5
	Herbivore (long grass)	428	2.9	317	2.1
	Herbivore (forage crops)	649	4.3	480	3.2
	Herbivore (leafy foliage)	1321	8.8	978	6.5
Reproduction 13.2 mg a.i./kg bw/d	Insectivore (small insects)	196	14.9	145	11.0
	Insectivore (large insects)	49	3.7	36	2.7
	Granivore (grain and seeds)	49	3.7	36	2.7
	Frugivore (fruit)	98	7.4	73	5.5
	Herbivore (short grass)	701	53.1	519	39.3
	Herbivore (long grass)	428	32.4	317	24.0
	Herbivore (forage crops)	649	49.1	480	36.4
	Herbivore (leafy foliage)	1321	100.1	978	74.1

[1] – EDEs based on maximum residue values.
[2] - Risk quotients shown in bold exceed the level of concern (RQ > 1).

Table 7 Summary of Screening Level Risk Assessment of Mancozeb to Mammals

Toxicity endpoint (mg a.i./kg bw/d)	Food Guild	On-field		Off Field	
		EDE[1] (mg a.i./kg bw)	RQ[2]	EDE[1] (mg a.i./kg bw)	RQ[2]
Small mammals (15 g)					
Dietary 14.98 mg a.i./kg bw/d	Insectivore (small insects)	495	33.1	30	2.0
	Granivore (grain and seeds)	124	8.3	7	0.5
	Frugivore (fruit)	248	16.5	15	0.9
Reproduction 2.5 mg a.i./kg bw/d	Insectivore (small insects)	495	198.1	30	11.9
	Granivore (grain and seeds)	124	49.5	7	3.0
	Frugivore (fruit)	248	99.0	15	5.9

Toxicity endpoint (mg a.i./kg bw/d)	Food Guild	On-field		Off Field	
		EDE[1] (mg a.i./kg bw)	RQ[2]	EDE[1] (mg a.i./kg bw)	RQ[2]
Small mammals (35 g)					
Acute 500 mg a.i./kg bw/d	Herbivore (short grass)	1551	3.1	93	0.2
	Herbivore (long grass)	947	1.9	57	0.1
	Herbivore (forage crops)	1435	2.9	86	0.2
	Herbivore (leafy foliage)	2924	5.8	175	0.4
Dietary 14.98 mg a.i./kg bw/d	Insectivore (small insects)	434	29.0	26	1.7
	Insectivore (large insects)	109	7.2	7	0.4
	Granivore (grain and seeds)	109	7.2	7	0.4
	Frugivore (fruit)	217	14.5	13	0.9
	Herbivore (short grass)	1551	103.6	93	6.2
	Herbivore (long grass)	947	63.2	57	3.8
	Herbivore (forage crops)	1435	95.8	86	5.7
	Herbivore (leafy foliage)	2924	195.1	175	11.7
Reproduction 2.5 mg a.i./kg bw/d	Insectivore (small insects)	434	173.6	26	10.4
	Insectivore (large insects)	109	43.4	7	2.6
	Granivore (grain and seeds)	109	43.4	7	2.6
	Frugivore (fruit)	217	86.8	13	5.2
	Herbivore (short grass)	1551	620.6	93	37.2
	Herbivore (long grass)	947	378.9	57	22.7
	Herbivore (forage crops)	1435	574.2	86	34.4
	Herbivore (leafy foliage)	2924	1169.6	175	70.2
Small mammals (1000 g)					
Acute 500 mg a.i./kg bw/d	Herbivore (short grass)	829	1.7	50	<0.1
	Herbivore (long grass)	506	1.0	30	<0.1
	Herbivore (forage crops)	767	1.5	46	<0.1
	Herbivore (leafy foliage)	1562	3.1	94	0.2
Dietary 14.98 mg a.i./kg bw/d	Insectivore (small insects)	232	15.5	14	0.9
	Insectivore (large insects)	58	3.9	3	0.2
	Granivore (grain and seeds)	58	3.9	3	0.2
	Frugivore (fruit)	116	7.7	7	0.5
	Herbivore (short grass)	829	55.3	50	3.3

Toxicity endpoint (mg a.i./kg bw/d)	Food Guild	On-field		Off Field	
		EDE[1] (mg a.i./kg bw)	RQ[2]	EDE[1] (mg a.i./kg bw)	RQ[2]
	Herbivore (long grass)	506	33.8	30	2.0
	Herbivore (forage crops)	767	51.2	46	3.1
	Herbivore (leafy foliage)	1562	104.3	94	6.3
Reproduction 2.5 mg a.i./kg bw/d	Insectivore (small insects)	232	92.8	14	5.6
	Insectivore (large insects)	58	23.2	3	1.4
	Granivore (grain and seeds)	58	23.2	3	1.4
	Frugivore (fruit)	116	46.4	7	2.8
	Herbivore (short grass)	829	331.6	50	19.9
	Herbivore (long grass)	506	202.5	30	12.1
	Herbivore (forage crops)	767	306.8	46	18.4
	Herbivore (leafy foliage)	1562	624.9	94	37.5

[1] – EDEs based on maximum residue values.
[2] - Risk quotients shown in bold exceed the level of concern (RQ > 1).

Table 8 Refined Risk Assessment of Mancozeb to Birds

Toxicity endpoint (mg a.i./kg bw/d)	Food Guild	On-field				Off Field			
		EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC	EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC
APPLES (4800 g a.i./ha × 6 at 7 day intervals, airblast application)									
Small birds (20 g)									
Acute 150 mg a.i./kg bw/d	Insectivore (small insects)	332	2.2	45	39	246	1.6	61	28
Reproduction 13.2 mg a.i./kg bw/d	Insectivore (small insects)	332	25	4	82	246	19	5	78
	Granivore (grain and seeds)	71	5.4	19	60	52	3.9	25	55
	Frugivore (fruit)	142	11	9	70	105	8.0	13	65
Medium sized birds (100 g)									
Acute 150 mg a.i./kg bw/d	Insectivore (small insects)	259	1.7	58	29	192	1.3	78	12
Reproduction 13.2 mg a.i./kg bw/d	Insectivore (small insects)	259	20	5	78	192	15	7	74
	Insectivore (large insects)	55	4.2	24	56	41	3.1	32	49
	Granivore (grain and seeds)	55	4.2	24	56	41	3.1	32	49

Toxicity endpoint (mg a.i./kg bw/d)	Food Guild	On-field				Off Field			
		EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC	EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC
	Frugivore (fruit)	111	8.4	12	66	82	6.2	16	62
Large birds (1000 g)									
Acute 150 mg a.i./kg bw/d	Herbivore (short grass)	172	1.1	87	5	127	0.8	-	
	Herbivore (leafy foliage)	302	2.0	50	38	223	1.5	67	21
Reproduction 13.2 mg a.i./kg bw/d	Insectivore (small insects)	76	5.8	17	61	56	4.2	24	56
	Insectivore (large insects)	16	1.2	82	8	12	0.9	-	
	Granivore (grain and seeds)	16	1.2	82	8	12	0.9	-	
	Frugivore (fruit)	32	2.4	41	41	24	1.8	55	32
	Herbivore (short grass)	172	13	8	73	127	9.6	10	68
	Herbivore (long grass)	97	7.3	14	64	71	5.4	18	60
	Herbivore (forage crops)	148	11	9	70	110	8.3	12	66
	Herbivore (leafy foliage)	302	23	4	82	223	17	6	77
Lettuce (1612 g a.i./ha × 3 at 14 day intervals, groundboom application)									
Small birds (20 g)									
Reproduction 13.2 mg a.i./kg bw/d	Insectivore (small insects)	69	5.2	19	52	4	0.3	-	
	Granivore (grain and seeds)	15	1.1	90	3	1	<0.1	-	
	Frugivore (fruit)	29	2.2	45	29	2	0.1	-	
Medium sized birds (100 g)									
Reproduction 13.2 mg a.i./kg bw/d	Insectivore (small insects)	54	4.1	25	49	3	0.2	-	
	Frugivore (fruit)	23	1.7	57	18	1	<0.1	-	
Large birds (1000 g)									
Reproduction 13.2 mg a.i./kg bw/d	Insectivore (small insects)	16	1.2	84	5	1	0.1	-	
	Herbivore (short grass)	36	2.7	37	37	2	0.2	-	
	Herbivore (long grass)	20	1.5	66	12	1	<0.1	-	
	Herbivore (forage crops)	31	2.3	43	31	2	0.2	-	
	Herbivore (leafy foliage)	63	4.8	21	52	4	0.3	-	

Toxicity endpoint (mg a.i./kg bw/d)	Food Guild	On-field				Off Field			
		EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC	EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC
Lettuce (1612 g a.i./ha × 1)									
Small birds (20 g)									
Reproduction 13.2 mg a.i./kg bw/d	Insectivore (small insects)	45	3.4	29	18	3	0.2	-	
	Frugivore (fruit)	19	1.4	68	6	1	<0.1	-	
Medium sized birds (100 g)									
Reproduction 13.2 mg a.i./kg bw/d	Insectivore (small insects)	35	2.7	37	15	2	0.2	-	
	Frugivore (fruit)	15	1.1	87	2	1	<0.1	-	
Large birds (1000 g)									
Reproduction 13.2 mg a.i./kg bw/d	Herbivore (short grass)	23	1.7	56	9	1	<0.1	-	
	Herbivore (forage crops)	20	1.5	65	7	1	<0.1	-	
	Herbivore (leafy foliage)	41	3.1	32	18	2	0.2	-	

[1] – EDEs based on mean residue values.
[2] - Risk

Table 9 Refined Risk Assessment of Mancozeb to Mammals

Toxicity endpoint (mg a.i./kg bw/d)	Food Guild	On-field				Off Field			
		EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC	EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC
APPLES (4800 g a.i./ha × 6 at 7 day intervals, airblast application)									
Small mammals (15 g)									
Dietary 14.98 – 57.34 mg a.i./kg bw/d	Insectivore (small insects)	191	3.3 - 13	8 - 30	51 - 72	141	2.5 - 9.4	11 - 41	43 - 68
	Granivore (grain and seeds)	41	0.7 - 2.7	37	50	30	0.5 - 2.0	50	46
	Frugivore (fruit)	82	1.4 - 5.4	18 - 70	18 - 60	60	1.1 - 4.0	25 - 95	2 - 56
Reproduction 2.5 – 110 mg a.i./kg bw/d	Insectivore (small insects)	191	1.7 - 76	1 - 58	29 - 98	141	1.3 - 56	2 - 78	12 - 94
	Granivore (grain and seeds)	41	0.4 - 16	6	76	30	0.3 - 12	8	72
	Frugivore (fruit)	82	0.7 - 33	3	86	60	0.5 - 24	4	81

Toxicity endpoint (mg a.i./kg bw/d)	Food Guild	On-field				Off Field			
		EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC	EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC
Small mammals (35 g)									
Acute 500 mg a.i./kg bw/d	Herbivore (leafy foliage)	668	1.3	75	14	494	0.9	-	
Dietary 14.98 – 57.34 mg a.i./kg bw/d	Insectivore (small insects)	167	2.9 - 11	9 - 34	47 - 70	124	2.2 - 8.2	12 - 46	39 – 66
	Insectivore (large insects)	36	0.6 - 2.4	42	41	26	0.5 - 1.7	57	32
	Granivore (grain and seeds)	36	0.6 - 2.4	42	41	26	0.5 - 1.7	57	32
	Frugivore (fruit)	72	1.2 - 4.8	21 - 80	10 - 58	53	0.9 - 3.5	28	53
	Herbivore (short grass)	381	6.6 - 25	4 - 15	63 - 82	282	4.9 - 19	5 - 20	58 - 78
	Herbivore (long grass)	214	3.7 - 14	7 - 27	53 - 74	158	2.8 - 11	9 - 36	45 - 70
	Herbivore (forage crops)	328	5.7 - 22	5 - 17	61 - 80	243	4.2 - 16	9 - 24	56 - 70
	Herbivore (leafy foliage)	668	12 - 45	2 - 9	71 - 90	494	8.6 - 33	3 - 12	67 - 86
Reproduction 2.5 – 110 mg a.i./kg bw/d	Insectivore (small insects)	167	1.5 - 67	1 - 34	47 - 96	124	1.1 - 50	2 - 89	5 - 92
	Insectivore (large insects)	36	0.3 - 14	7	74	26	0.2 - 11/	9	70
	Granivore (grain and seeds)	36	0.3 - 14	7	74	26	0.2 - 11	9	70
	Frugivore (fruit)	72	0.6 - 29	21	58	53	0.5 - 21	5	80
	Herbivore (short grass)	381	3.5 - 152	1 - 29	51 - 108	282	2.6 - 113	5 - 39	43 – 78
	Herbivore (long grass)	214	1.9 - 86	1 - 51	35 - 100	158	1.4 - 63	9 - 70	18 – 70
	Herbivore (forage crops)	328	3.0 - 131	1 - 34	47 - 106	243	2.2 - 97	6 - 45	39 – 76
	Herbivore (leafy foliage)	668	6.1 - 267	<1 - 16	62 - 116	494	4.5 - 198	3 - 22	57 - 86
Small mammals (1000 g)									
Dietary 14.98 – 57.34 mg a.i./kg bw/d	Insectivore (small insects)	89	1.6 - 5.9	17 - 64	23 - 61	66	1.2 - 4.4	23 - 87	6 - 57
	Insectivore (large insects)	19	0.3 - 1.3	78	11	14	0.2 - 0.9	-	
	Granivore (grain and seeds)	19	0.3 - 1.3	78	11	14	0.2 - 0.9	-	
	Frugivore (fruit)	38	0.7 - 2.5	39	43	28	0.5 - 1.9	53	35
	Herbivore (short grass)	203	3.5 - 14	7 - 28	53 - 73	151	2.6 - 10	10 - 38	43 - 69
	Herbivore (long grass)	114	2.0 - 7.6	13 - 50	35 - 65	85	1.5 - 5.6	18 - 68	20 - 67
	Herbivore (forage crops)	175	3.0 - 12	9 - 33	49 - 71	130	2.3 - 8.7	12 - 44	39 - 67
	Herbivore (leafy foliage)	357	6.2 - 24	4 - 16	62 - 81	264	4.6 - 18	6 – 22	58 - 77
Reproduction 2.5 – 110 mg a.i./kg bw/d	Insectivore (small insects)	89	0.8 - 36	3	87	66	0.6 - 26	4	83
	Insectivore (large insects)	19	0.2 - 7.6	13	65	14	0.1 -5.6	18	61
	Granivore (grain and seeds)	19	0.2 - 7.6	13	65	14	0.1 - 5.6	18	61

Toxicity endpoint (mg a.i./kg bw/d)	Food Guild	On-field				Off Field			
		EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC	EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC
	Frugivore (fruit)	38	0.3 - 15	7	75	28	0.3 - 11	9	71
	Herbivore (short grass)	203	1.8 - 81	1 - 54	32 - 99	151	1.4 - 60	2 - 73	16 - 95
	Herbivore (long grass)	114	1.0 - 46	2 - 96	2 - 91	85	0.8 - 34	3	86
	Herbivore (forage crops)	175	1.6 - 70	1 - 63	25 - 97	130	1.2 - 52	62 - 85	6 - 92
	Herbivore (leafy foliage)	357	3.2 - 143	1 - 31	49 - 107	264	2.4 - 106	1 - 42	41 - 103
Lettuce (1612 g a.i./ha x3 at 14 day intervals, groundboom application)									
Small mammals (15 g)									
Dietary 14.98 – 57.34 mg a.i./kg bw/d	Insectivore (small insects)	40	0.7 - 2.6	38	36	2	<0.1 - 0.1	-	
	Frugivore (fruit)	17	0.3 - 1.1	88	3	1	<0.1	-	
Reproduction 2.5 – 110 mg a.i./kg bw/d	Insectivore (small insects)	40	0.3 - 16	6	68	2	<0.1 - 0.9	-	
	Granivore (grain and seeds)	8	0.1 - 3.4	29	47	1	<0.1 - 0.2	-	
	Frugivore (fruit)	17	0.2 - 6.8	15	56	1	<0.1 - 0.4	-	
Small mammals (35 g)									
Dietary 14.98 – 57.34 mg a.i./kg bw/d	Insectivore (small insects)	35	0.6 - 2.3	43	31	2	<0.1 - 0.1	na	
	Herbivore (short grass)	79	1.4 - 5.3	19 - 72	9 - 53	5	<0.1 - 0.3	-	
	Herbivore (long grass)	44	0.8 - 3.0	34/40	40	3	<0.1 - 0.2	-	
	Herbivore (forage crops)	68	1.2 - 4.6	22 - 84	5 - 50	4	<0.1 -0.3	-	
	Herbivore (leafy foliage)	139	2.4 - 9.3	11 - 41	32 - 61	8	0.1 - 0.6	-	
Reproduction 2.5 – 110 mg a.i./kg bw/d	Insectivore (small insects)	35	0.3 - 14	7	66	2	<0.1 -0.8	-	
	Insectivore (large insects)	7	0.6 - 3.0	34	40	0.4	<0.1 -0.2	-	
	Granivore (grain and seeds)	7	0.6 - 3.0	34	40	0.4	<0.1 -0.2	-	
	Frugivore (fruit)	14	0.1 - 5.9	17	54	1	<0.1 -0.4	-	
	Herbivore (short grass)	79	0.7 - 32	3	78	5	<0.1 -1.9	53	22
	Herbivore (long grass)	44	0.4 - 18	6	70	3	<0.1 -1.1	94	1
	Herbivore (forage crops)	68	0.6 - 27	4	76	4	<0.1 -1.6	61	16
	Herbivore (leafy foliage)	139	1.3 - 56	2 - 79	6 - 86	8	<0.1 -3.3	30	44
Small mammals (1000 g)									
Dietary 14.98 – 57.34 mg a.i./kg bw/d	Insectivore (small insects)	19	0.3 - 1.2	81	6	1	<0.1	-	
	Herbivore (short grass)	42	0.7 - 2.8	35	38	3	<0.1 - 0.2	-	

Toxicity endpoint (mg a.i./kg bw/d)	Food Guild	On-field				Off Field			
		EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC	EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC
	Herbivore (long grass)	24	0.4 - 1.6	63	14	1	<0.1	-	
	Herbivore (forage crops)	36	0.6 - 2.4	41	32	2	<0.1 - 0.1	-	
	Herbivore (leafy foliage)	74	1.3 - 4.9	20 - 77	7 - 52	4	<0.1 - 0.3	-	
Reproduction 2.5 – 110 mg a.i./kg bw/d	Insectivore (small insects)	19	0.1 - 7.4	13	57	1	<0.1 - 0.4	-	
	Insectivore (large insects)	4	<0.1 -1.6	63	14	0.2	<0.1	-	
	Granivore (grain and seeds)	4	<0.1 -1.6	63	14	0.2	<0.1	-	
	Frugivore (fruit)	8	<0.1 -3.2	31	42	0.5	<0.1 - 0.2	-	
	Herbivore (short grass)	42	0.4 - 17	6	69	3	<0.1 -1.0	99	1
	Herbivore (long grass)	24	0.2 - 9.5	11	61	1	<0.1 - 0.6	-	
	Herbivore (forage crops)	36	0.3 - 15	7	67	2	<0.1 -0.8		
	Herbivore (leafy foliage)	74	0.7 - 30	3	77	4	<0.1 -1.8	56	19
Lettuce (1612 g a.i./ha x1)									
Small mammals (15 g)									
Dietary 14.98 – 57.34 mg a.i./kg bw/d	Insectivore (small insects)	26	0.4 - 1.7	57	8	2	<0.1 - 0.1	-	
Reproduction 2.5-110 mg a.i./kg bw/d	Insectivore (small insects)	26	0.2 - 10	10	34	2	<0.1 - 0.6	-	
	Granivore (grain and seeds)	6	<0.1 -2.2	45	22	0.3	<0.1 - 0.1	-	
	Frugivore (fruit)	11	0.1 - 4.5	22	22	0.7	<0.1 - 0.3	-	
Small mammals (35 g)									
Dietary 14.98 – 57.34 mg a.i./kg bw/d	Insectivore (small insects)	22	0.3 - 1.5	66	7	1	<0.1	-	
	Herbivore (short grass)	51	0.9 - 3.5	29	18	3.1	<0.1 - 0.3	-	
	Herbivore (long grass)	29	0.5 - 1.9	51	10	2	<0.1 - 0.1	-	
	Herbivore (forage crops)	45	0.8 - 3.0	33	16	3	<0.1 - 0.2	-	
	Herbivore (leafy foliage)	91	1.6 - 6.1	16 - 63	7 – 27	5	<0.1 - 0.4	-	
Reproduction 2.5 – 110 mg a.i./kg bw/d	Insectivore (small insects)	22	0.2 - 9.1	11	32	1	<0.1 - 0.5	-	
	Insectivore (large insects)	5	<0.1 -1.9	51	10	0.3	<0.1 - 0.1	-	

Toxicity endpoint (mg a.i./kg bw/d)	Food Guild	On-field				Off Field			
		EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC	EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC
	Granivore (grain and seeds)	5	<0.1 -2.0	51	10	0.3	<0.1 - 0.1	-	
	Frugivore (fruit)	10	<0.1 -2.0	26	20	0.6	<0.1 - 0.2	-	
	Herbivore (short grass)	51	0.5 - 21	5	44	3.1	<0.1 -1.2	80	4
	Herbivore (long grass)	29	0.3 - 12	9	36	2	<0.1 - 0.7	-	
	Herbivore (forage crops)	45	0.4 - 18	6	42	3	<0.1 -1.1	93	2
	Herbivore (leafy foliage)	91	0.8 - 36	3	52	5	<0.1 -2.2	46	12
Small mammals (1000 g)									
Dietary 14.98 – 57.34 mg a.i./kg bw/d	Herbivore (short grass)	28	0.5 - 1.9	54	9	2	<0.1 - 0.1	-	
	Herbivore (long grass)	16	0.3 - 1.0	96	1	0.9	<0.1	-	
	Herbivore (forage crops)	24	0.4 - 1.6	63	7	1	<0.1	-	
	Herbivore (leafy foliage)	49	0.8 - 3.3	31	18	3	0.2	-	
Reproduction 2.5 – 110 mg a.i./kg bw/d	Insectivore (small insects)	12	0.1 - 4.9	20	23	0.7	<0.1 - 0.3	-	
	Insectivore (large insects)	3	<0.1 -1.0	96	1	0.2	<0.1	-	
	Granivore (grain and seeds)	3	<0.1 -1.0	96	1	0.2	<0.1	-	
	Frugivore (fruit)	5	<0.1 -2.1	48	11	0.3	<0.1 - 0.1	-	
	Herbivore (short grass)	28	0.3 - 11	9	35	2	<0.1 - 0.7	-	
	Herbivore (long grass)	16	0.1 - 6.2	16	27	0.9	<0.1 - 0.4	-	
	Herbivore (forage crops)	24	0.2 - 9.6	10	33	1	<0.1 - 0.6	-	
	Herbivore (leafy foliage)	49	0.4 - 19	5	43	3	<0.1 -1.2	86	3

na – not applicable
[1] – EDEs based on mean residue values.
[2] - Risk quotients shown in bold exceed the level of concern (RQ > 1).

Table 10 Refined Risk Assessment of ETU to Mammals

Toxicity endpoint (mg a.i./kg bw/d)	Food Guild	On-field				Off Field			
		EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC	EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC
APPLES (4800 g a.i./ha × 6 at 7 day intervals, airblast application)									
Small mammals (15 g)									
Dietary 1.7mg a.i./kg bw/d	Insectivore (small insects)	7.1	4.2	24	71	5.3	3.1	32	66
	Frugivore (fruit)	4.4	2.6	38	55	3.3	1.9	53	45
Reproduction 5 mg a.i./kg bw/d	Insectivore (small insects)	7.1	1.4	71	47	5.3	1.1	91	39
Small mammals (35 g)									
Dietary 1.7mg a.i./kg bw/d	Insectivore (small insects)	6.2	3.7	27	69	4.6	2.7	37	64
	Herbivore (short grass)	22.7	13.4	7	83	16.8	9.9	10	78
	Herbivore (long grass)	12.7	7.5	13	73	9.4	5.5	18	68
	Herbivore (forage crops)	21.8	12.8	8	81	16.1	9.5	11	75
	Herbivore (leafy foliage)	49.9	29.3	3	93	36.9	21.7	5	87
Reproduction 5 mg a.i./kg bw/d	Insectivore (small insects)	6.2	1.2	81	44	4.6	0.9	na	
	Herbivore (short grass)	22.7	4.5	22	65	16.8	3.4	29	60
	Herbivore (long grass)	12.7	2.5	40	51	9.4	1.9	53	43
	Herbivore (forage crops)	21.8	4.4	23	62	16.1	3.2	31	55
	Herbivore (leafy foliage)	49.9	10.0	10	74	36.9	7.4	14	69
Small mammals (1000 g)									
Dietary 1.7mg a.i./kg bw/d	Insectivore (small insects)	3.3	2.0	50	59	2.5	1.5	67	49
	Frugivore (fruit)	2.1	1.2	83	29	1.5	0.9	na	
	Herbivore (short grass)	12.2	7.1	14	72	9.0	5.3	19	67
	Herbivore (long grass)	6.8	4.0	25	63	5.0	3.0	33	57
	Herbivore (forage crops)	11.6	6.8	15	70	8.6	5.1	20	65
	Herbivore (leafy foliage)	26.7	15.7	6	82	19.7	11.6	9	77
Reproduction 5 mg a.i./kg bw/d	Herbivore (short grass)	12.2	2.4	42	49	9.0	1.8	56	41
	Herbivore (long grass)	6.8	1.4	71	30	5.0	1.0	100	10
	Herbivore (forage crops)	11.6	2.3	43	45	8.6	1.7	59	36
	Herbivore (leafy foliage)	26.7	5.3	19	64	19.7	3.9	26	59

Toxicity endpoint (mg a.i./kg bw/d)	Food Guild	On-field				Off Field			
		EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC	EDE [1] (mg a.i./kg bw)	RQ[2]	% diet to reach LOC	# days residues above LOC
Onion (2600 g a.i./ha × 10 at 7 day intervals, groundboom application)									
Small mammals (15 g)									
Dietary 1.7mg a.i./kg bw/d	Insectivore (small insects)	4.2	2.4	42	90	0.3	0.2	na	
	Frugivore (fruit)	2.6	1.5	67	65	0.2	0.1	na	
Small mammals (35 g)									
Dietary 1.7mg a.i./kg bw/d	Insectivore (small insects)	3.6	2.1	48	88	0.2	0.1	na	
	Frugivore (fruit)	2.3	1.3	77	59	0.1	0.1	na	
	Herbivore (short grass)	13.2	7.8	13	102	0.8	0.5	na	
	Herbivore (long grass)	7.4	4.3	23	92	0.4	0.3	na	
	Herbivore (forage crops)	12.7	7.5	13	99	0.8	0.4	na	
	Herbivore (leafy foliage)	29.0	17.1	6	111	1.7	1.0	100	3
Reproduction 5 mg a.i./kg bw/d	Herbivore (short grass)	13.2	2.7	37	80	0.8	0.2	na	
	Herbivore (long grass)	7.4	1.5	67	60	0.4	0.1	na	
	Herbivore (forage crops)	12.7	2.5	40	74	0.8	0.2	na	
	Herbivore (leafy foliage)	29.0	5.8	17	93	1.7	0.4	na	
Small mammals (1000 g)									
Dietary 1.7mg a.i./kg bw/d	Insectivore (small insects)	1.9	1.1	91	68	0.1	<0.1	na	
	Herbivore (short grass)	7.1	4.2	24	91	0.4	0.3	na	
	Herbivore (long grass)	4.0	2.3	43	76	0.2	0.1	na	
	Herbivore (forage crops)	6.8	4.0	25	89	0.4	0.2	na	
	Herbivore (leafy foliage)	15.5	9.1	11	101	0.9	0.6	na	
Reproduction 5 mg a.i./kg bw/d	Herbivore (short grass)	7.1	1.4	71	58	0.4	<0.1	na	
	Herbivore (forage crops)	6.8	1.4	71	47	0.4	<0.1	na	
	Herbivore (leafy foliage)	15.5	3.1	32	78	0.9	0.2	na	

na – not applicable
[1] – EDEs based on mean residue values and lower limits of ratio wet/dry moisture contents of food items.
[2] - Risk quotients shown in bold exceed the level of concern (RQ > 1).

Table 11 The Number of Seeds Treated with Mancozeb Required to Reach the Bird and Mammalian Endpoints

Endpoint	Weight (g)	Number of seeds to reach endpoint[1]				
		Barley	Corn	Flax	Oats	Wheat
Birds						
Acute 150 mg a.i./kg bw	20	63	4	250	45	79
	100	313	22	1250	224	395
	1000	3125	220	12500	2239	3947
Reproduction 13.2 mg a.i./kg bw/day	20	6	1	22	4	7
	100	28	2	110	20	35
	1000	275	19	1100	197	347
Mammals						
Acute 500 mg a.i./kg bw	15	156	11	625	112	197
	35	365	26	1458	261	461
	1000	10417	734	41667	7463	13157
Dietary 14.98 - 57.34 mg a.i./kg bw/day	15	5 – 18	1	19 – 72	3 – 13	6 – 23
	35	11 – 42	1 – 3	44 – 167	8 – 30	14 – 53
	1000	312 – 1195	22 – 84	1248 – 4778	224 – 856	394 – 1509
Reproduction 2.5 - 110 mg a.i./kg bw/day	15	1 – 34	1 – 3	3 – 138	1 – 25	1 – 43
	35	2 – 80	1 – 6	7 – 321	1 – 57	2 – 101
	1000	52 - 2292	4 – 162	208 - 9167	37 – 1642	66 – 2895

[1] - # seeds/day to reach endpoint = Dose-based endpoint × BW (kg bw) ÷ concentration per seed (mg a.i./seed)

Table 12 Generic Bird and Mammal Seed Consumption Per Day

Species	FIR (g dw/day)	(# seeds consumed/day)[1]		
		Barley, oats and Wheat	Corn	Flax
Small bird – 20 g	5.1	112	13	784
Medium bird – 100 g	19.9	438	52	3061
Large bird – 1000 g	58.1	1278	153	8936
Small mammal – 15 g	2.2	48	6	338
Medium mammal – 35 g	4.5	99	12	692
Large mammal – 1000 g	68.7	1511	181	10566

[1] - The number of seeds normally consumed per day was calculated as: # seeds consumed/day = FIR (g dw/day) × # seeds/g; for each body weight, the food ingestion rate is based on equations from Nagy (1987).

Table 13 Screening Level Risk Quotients for Birds and Mammals Consuming Treated Seeds.

Endpoint	Weight (g)	Risk quotients[1]				
		Barley	Corn	Flax	Oats	Wheat
Birds						
Acute 150 mg a.i./kg bw	20	**1.8**	**3.3**	**3.1**	**2.5**	**1.4**
	100	**1.4**	**2.4**	**2.4**	**2.0**	**1.1**
	1000	0.4	0.7	0.7	0.6	0.3
Reproduction 13.2 mg a.i./kg bw/day	20	**19**	**13**	**36**	**28**	**16**
	100	**16**	**26**	**28**	**22**	**13**
	1000	**4.6**	**8.0**	**8.1**	**6.5**	**3.7**
Mammals						
Acute 500 mg a.i./kg bw	15	0.3	0.5	0.5	0.4	0.2
	35	0.3	0.5	0.5	0.4	0.2
	1000	0.1	0.2	0.3	0.2	0.1
Dietary 14.9 – 57.3mg a.i./kg bw/day	15	**2.7 - 9.6**	**6.0**	**4.7 - 18**	**3.7 - 16**	**2.1 – 8.0**
	35	**2.4 - 9.0**	**4.0 - 12**	**4.1 - 16**	**3.3 - 12**	0.9 - **7.1**
	1000	**1.3 - 4.8**	**2.2 - 8.2**	**2.2 - 8.5**	**1.8 - 6.7**	**1.0 - 3.8**
Reproduction 2.5 - 110 mg a.i./kg bw/day	15	**1.4 - 48**	**2.0 - 6**	**2.4 - 113**	**1.9 - 48**	**1.1 - 48**
	35	**1.2 - 50**	**2.0 - 12**	**2.2 - 99**	**1.7 - 99**	0.9 - **50**
	1000	0.7 - **29**	**1.1 - 45**	**1.2 -51**	0.9 - **41**	0.5 - **23**

[1] – Risk quotients calculated as: # of seeds normally consumed per day (Table 15) ÷ # of seeds to the endpoint (Table 14).

Table 14 Area Covered Necessary to Reach Toxic Quantities Assuming Only 3.3% of Planted Seeds Are Available to Birds and Mammals

Endpoint	Weight (g)	#seeds to reach LOC/m² required to reach LOC [1]				
		Barley	Corn	Flax	Oats	Wheat
Birds						
Acute 150 mg a.i./kg bw	20	63/6	4/20	250/13	45/3	79/9
	100	313/27	22/110	1250/65	224/16	395/46
Reproduction 13.2 mg a.i./kg bw/day	20	6/<1	1/5	22/1	4/<1	7/<1
	100	28/2	2/10	110/6	20/1	35/4
	1000	275/24	19/95	1100/57	197/14	347/41
Mammals						
Dietary 14.9 – 57.3 mg a.i./kg bw/day	15	5 – 18/<1 - 2	1/5	19 - 72/<1 – 4	3 - 13/<1	6 - 23/<1 – 3
	35	11 - 42/<1 – 4	1 - 3/5 – 13	44 - 167/2 – 9	8 - 30/<1 – 2	14 – 53/2 – 6
	1000	312 - 1195/27 - 105	22 – 84/110 – 375	1248 - 4778/65 – 249	224 – 856/16 – 63	394 - 1509/46 – 179
Reproduction 2.5 – 110 mg a.i./kg bw/day	15	1 – 34/<1 – 3	1 – 3/5 – 13	3 - 138/<1 – 7	1 - 25/<1 – 2	1 - 43/<1 – 5
	35	2 – 80/<1 – 7	1 - 6/5 – 27	7 - 321/<1 – 17	1 - 57/<1 – 4	2 – 101/<1 – 12
	1000	52 - 2292/5 - 202	4 162/20 - 723	208 - 9167/11 - 478	37 - 1642/3 - 121	66 - 2895/8 - 343

[1] m² required to reach LOC = number seeds to reach LOC/maximum seed density available in spring (3.3%); m² values are rounded off to nearest m².

Table 15 Summary of Screening Level Risk Assessment of Mancozeb to Aquatic Organisms

Organism	Exposure	Species	Endpoint value (µg a.i./L)	Endpoint for RA[1] (µg a.i./L)	Use Rate[2] (g a.i./ha)	EEC[3] (µg a.i./L)	RQ[4]
Freshwater species							
Invertebrate	Acute	*Daphnia magna*	48-hLC$_{50}$ = 580	290	1612	200	0.7
					4800 × 6	2990	**10**
	Chronic	*Daphnia magna*	21-d NOEC = 5.9	5.9	1612	200	**34**
					4800 × 6	2990	**507**
Fish	Acute	Rainbow trout *Onkorynchus mykiss*	96 –h LC$_{50}$ = 210	21	1612	200	**10**
					4800 × 6	2990	**142**
	Chronic	Fathead minnow *Pimephales promelas*	28-d ELS NOEC = 4.65	4.65	1612	200	**43**
					4800 × 6	2990	**643**
Amphibians	Acute	*Rana pipiens*	96 –h LC$_{50}$ = 200	20	1612	1070	**54**
					4800 × 6	15950	**798**
	Chronic	*Bufo americanus*	NOEC = 8.0	8.0	1612	1070	**134**
					4800 × 6	15950	**1994**
Freshwater alga	Acute	Green algae *(Selenastrum capricornitum)*	120-h EC$_{50}$ = 63	31.5	1612	200	**6.3**
					4800 × 6	2990	**95**
Freshwater aquatic community	Chronic	rotifier *Brachionus leydigi*	EC$_{20}$ = 4.5	4.5	1612	200	**44**
					4800 × 6	2990	**664**

Organism	Exposure	Species	Endpoint value (µg a.i./L)	Endpoint for RA[1] (µg a.i./L)	Use Rate[2] (g a.i./ha)	EEC[3] (µg a.i./L)	RQ[4]
Vascular plant	No data available						
Estuarine and marine species							
Invertebrate	Acute	Mysid shrimp *(Mysidopsis bahia)*	96-h LC_{50} = 21.9	11.0	1612	200	**18**
					4800 × 6	2990	**272**
Fish	Acute	Sheepshead minnow *(Cypronodon variegates)*	96-h LC_{50} = 2300	230	1612	200	0.9
					4800 × 6	2990	**13**

1 - Endpoints used in the acute exposure risk assessment (RA) are derived by dividing the EC_{50} or LC_{50} from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of ten (10) for fish and amphibians.
2 – Application rate represents the lowest single application for lettuce (1612 g a.i./ha) and highest cumulative application rate for apples (4800 g a.i./ha × 6 at 7 day intervals).
3 - EEC based on a 15 cm water body depth for amphibians and a 80 cm water depth for all other aquatic organisms.
4 - Risk quotients shown in bold exceed the level of concern (RQ > 1).

Table 16 Spray Drift Assessment of Mancozeb to Non-target Aquatic Organisms Using Deposition for Late Airblast Applications (59%)

Organism	Exposure	Species	Endpoint reported (µg a.i./L)	Endpoint for RA[1] (µg a.i./L)	Use Scenario (rate- g a.i./ha)[2]	EEC Exposure from drift (µg a.i./L)	RQ[3]	LOC exceeded
Freshwater Invertebrate	Acute	*Daphnia magna*	48-hLC_{50} = 580	290	Grapes (5400)	398	**1.3**	Yes
					Apples (4800 × 6, 7d)	1684	**5.8**	Yes
	Chronic	*Daphnia magna*	21-d NOEC = 5.9	5.9	Grapes (5400)	398	**67**	Yes
					Apples (4800 × 6, 7d)	1684	**285**	Yes
Freshwater fish	Acute	*Onkorynchus mykiss*	96 –h LC_{50} = 210	21	Grapes (5400)	398	**19**	Yes
					Apples (4800 × 6, 7d)	1684	**80**	Yes
	Chronic	*Pimephales promelas*	28-d ELS NOEC = 4.65	4.65	Grapes (5400)	398	**86**	Yes
					Apples (4800 × 6, 7d)	1684	**362**	Yes
Amphibian	Acute	*Rana pipiens*	96 –h LC_{50} = 200	20	Grapes (5400)	2124	**106**	Yes
					Apples (4800 × 6, 7d)	8983	**449**	Yes
	Chronic	*Bufo americanus*	NOEC = 8.0	8.0	Grapes (5400)	2124	**266**	Yes
					Apples (4800 × 6, 7d)	8983	**1123**	Yes
Freshwater alga	Acute	Green algae *(Selenastrum capricornitum)*	120-h EC_{50} = 63	31.5	Grapes (5400)	398	**13**	Yes
					Apples (4800 × 6, 7d)	1684	**53**	Yes
Freshwater aquatic community	Chronic	rotifier *Brachionus leydigi*	EC_{20} = 4.5	4.5	Grapes (5400)	398	**88**	Yes
					Apples (4800 × 6, 7d)	1684	**374**	Yes
Plant	**No data available**							
Invertebrate	Acute	Mysid shrimp *(Mysidopsis bahia)*	96-h LC_{50} = 21.9	11.0	Grapes (5400)	398	**36**	Yes
					Apples (4800 × 6, 7d)	1684	**153**	Yes
Fish	Acute	Sheepshead minnow *(Cypronodon variegates)*	96-h LC_{50} = 2300	230	Grapes (5400)	398	**1.7**	Yes
					Apples (4800 × 6, 7d)	1684	**7.3**	Yes
plant	No data available							

1- Endpoints used in the acute exposure risk assessment (RA) are derived by dividing the EC50, LC50 from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants,

and by a factor of ten (10) for fish and amphibians.
2 - The assessment of potential risk from drift was assessed for the lowest single and highest cumulative application rates specific to airblast application (grapes and apples, respectively).
3 - Risk quotients shown in bold exceed the level of concern
(RQ > 1).

Table 17 Spray Drift Risk Assessment of Mancozeb to Aquatic Organisms Using - Percent Drift Deposition for Ground Boom Applications (6%)

Organism	Exposure	Species	Endpoint reported (µg a.i./L)	Endpoint for RA[1] (µg a.i./L)	Use Scenario (rate- g a.i./ha)[2]	EEC Exposure from drift (µg a.i./L)	RQ[3]	LOC exceeded
Freshwater Invertebrate	Acute	*Daphnia magna*	48-hLC_{50} = 580	290	Lettuce (1612)	12.1	<0.1	No
					Onions (2686 × 10, 7d)	134	0.5	No
	Chronic	*Daphnia magna*	21-d NOEC = 5.9	5.9	Lettuce (1612)	12.1	**2.1**	Yes
					Onions (2686 × 10, 7d)	134	**23**	Yes
Freshwater fish	Acute	*Onkorynchus mykiss*	96 –h LC_{50} = 210	21	Lettuce (1612)	12.1	0.6	No
					Onions (2686 × 10, 7d)	134	**6.4**	Yes
	Chronic	*Pimephales promelas*	28-d ELS NOEC = 4.65	4.65	Lettuce (1612)	12.1	**2.6**	Yes
					Onions (2686 × 10, 7d)	134	**29**	Yes
Amphibian	Acute	*Rana pipiens*	96 –h LC_{50} = 200	20	Lettuce (1612)	64	**3.2**	Yes
					Onions (2686 × 10, 7d)	717	**36**	Yes
	Chronic	*Bufo americanus*	NOEC = 8.0	8.0	Lettuce (1612)	64	**8.0**	Yes
					Onions (2686 × 10, 7d)	717	**90**	Yes
Freshwater alga	Acute	Green algae *(Selenastrum capricornitum)*	120-h EC_{50} = 63	31.5	Lettuce (1612)	12.1	0.4	No
					Onions (2686 × 10, 7d)	134	**4.3**	Yes
Freshwater aquatic community	Chronic	rotifier *Brachionus leydigi*	EC_{20} = 4.5	4.5	Lettuce (1612)	12.1	**2.6**	Yes
					Onions (2686 × 10, 7d)	134	**30**	Yes
Plant	No data available							
Invertebrate	Acute	Mysid shrimp *(Mysidopsis bahia)*	96-h LC_{50} = 21.9	11.0	Lettuce (1612)	12.1	**1.1**	Yes
					Onions (2686 × 10, 7d)	134	**12**	Yes
Fish	Acute	Sheepshead minnow *(Cypronodon variegates)*	96-h LC_{50} = 2300	230	Lettuce (1612)	12.1	<0.1	No
					Onions (2686 × 10, 7d)	134	0.6	No
plant	No data available							

1- Endpoints used in the acute exposure risk assessment (RA) are derived by dividing the EC50, LC50 from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of ten (10) for fish and amphibians.
2 - The assessment of potential risk from drift was assessed for the lowest single and highest cumulative application rates specific to ground boom application (lettuce and onions, respectively).
3 - Risk quotients shown in bold exceed the level of concern (RQ > 1).

Table 18 Spray Drift Risk Assessment of Mancozeb to Aquatic Organisms Using Percent Drift Deposition for Aerial Applications (23%)

Organism	Exposure	Species	Endpoint reported (µg a.i./L)	Endpoint for RA[1] (µg a.i./L)	Use Scenario (rate- g a.i./ha)[2]	EEC Exposure from drift (µg a.i./L)	RQ[3]	LOC exceeded
Freshwater Invertebrate	Acute	*Daphnia magna*	48-hLC_{50} = 580	290	Potato/lentils/wheat (1688)	49	0.2	No
					Potato (1688 × 10, 7d)	259	0.9	No
	Chronic	*Daphnia magna*	21-d NOEC = 5.9	5.9	Potato/lentils/wheat (1688)	49	**8.3**	Yes
					Potato (1688 × 10, 7d)	259	**44**	Yes
Freshwater fish	Acute	*Onkorynchus mykiss*	96 –h LC_{50} = 210	21	Potato/lentils/wheat (1688)	49	**2.3**	Yes
					Potato (1688 × 10, 7d)	259	**12**	Yes
	Chronic	*Pimephales promelas*	28-d ELS NOEC = 4.65	4.65	Potato/lentils/wheat (1688)	49	**11**	Yes
					Potato (1688 × 10, 7d)	259	**56**	Yes
Amphibian	Acute	*Rana pipiens*	96 –h LC_{50} = 200	20	Potato/lentils/wheat (1688)	324	**16**	Yes
					Potato (1688 × 10, 7d)	1729	**86**	Yes
	Chronic	*Bufo americanus*	NOEC = 8.0	8.0	Potato/lentils/wheat (1688)	324	**41**	Yes
					Potato (1688 × 10, 7d)	1729	**216**	Yes
Freshwater alga	Acute	Green algae *(Selenastrum capricornitum)*	120-h EC_{50} = 63	31.5	Potato/lentils/wheat (1688)	49	**1.6**	Yes
					Potato (1688 × 10, 7d)	259	**8.2**	Yes
Freshwater aquatic community	Chronic	rotifer *Brachionus leydigi*	EC_{20} = 4.5	4.5	Potato/lentils/wheat (1688)	49	**11**	Yes
					Potato (1688 × 10, 7d)	259	**58**	Yes
Plant	No data available							
Invertebrate	Acute	Mysid shrimp *(Mysidopsis bahia)*	96-h LC_{50} = 21.9	11.0	Potato/lentils/wheat (1688)	49	**4.5**	Yes
					Potato (1688 × 10, 7d)	259	**24**	Yes
Fish	Acute	Sheepshead minnow *(Cypronodon variegates)*	96-h LC_{50} = 2300	230	Potato/lentils/wheat (1688)	49	0.2	No
					Potato (1688 × 10, 7d)	259	**1.1**	Yes
plant	No data available							

1- Endpoints used in the acute exposure risk assessment (RA) are derived by dividing the EC50, LC50 from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of ten (10) for fish and amphibians.
2 - The assessment of potential risk from drift was assessed for the lowest single and highest cumulative application rates specific to aerial application (potato/lentils/wheat and potato, respectively).
3 - Risk quotients shown in bold exceed the level of concern (RQ > 1).

Table 19 Runoff Risk Assessment for Mancozeb on Non-target Aquatic Organisms Using Runoff Values as Predicted by PRZM-EXAMS Model

Organism	Exposure	Species	Endpoint reported (µg a.i./L)	Endpoint for RA[1] (µg a.i./L)	EEC[2] (µg a.i./L)	RQ[3]	LOC exceeded
Freshwater Invertebrate	Acute	*Daphnia magna*	48-hLC_{50} = 580	290	261	0.9	No
	Chronic	*Daphnia magna*	21-d NOEC = 5.9	5.9	225	**38**	Yes
Freshwater fish	Acute	*Onchorhynchus mykiss*	96 –h LC_{50} = 210	21	251	**12**	Yes
	Chronic	*Pimephales promelas*	28-d ELS NOEC = 4.65	4.65	225	**48**	Yes
Amphibian	Acute	*Rana pipiens*	96 –h LC_{50} = 200	20	1126	**56**	Yes
	Chronic	*Bufo americanus*	NOEC = 8.0	8.0	808	**101**	Yes
Freshwater alga	Acute	Green algae *(Selenastrum capricornitum)*	120-h EC_{50} = 63	31.5	251	**8.0**	Yes
Freshwater aquatic community	Chronic	rotifier *Brachionus leydigi*	EC_{20} = 4.5	4.5	120	**26**	Yes
Plant	No data available						
Marine/estuarine invertebrate	Acute	Mysid shrimp *(Mysidopsis bahia)*	96-h LC_{50} = 21.9	11.0	251	23	Yes
Marine/estuarine fish	Acute	Sheepshead minnow *(Cypronodon variegates)*	96-h LC_{50} = 2300	230	251	1.1	Yes
Plant	No data available						

1- Endpoints used in the acute exposure risk assessment (RA) are derived by dividing the EC_{50}, LC_{50} from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of ten (10) for fish and amphibians.
2 - EEC based on a 15 cm water body depth for amphibians and a 80 cm water depth for all other aquatic organisms.
3 - Risk quotients shown in bold exceed the level of concern (RQ > 1).

Table 20 Summary of Screening Level Risk Assessment of ETU to Aquatic Organisms

Organism	Exposure	Species	Endpoint value (mg a.i./L)	Endpoint for RA[1] (mg a.i./L)	EEC[2] (mg a.i./L)	RQ[3]
Freshwater species						
Invertebrate	Acute	*Daphnia magna*	48-hLC$_{50}$ = 26.9	13.5	2.2	0.16
	Chronic		21-d NOEC = 2.0	2.0	2.2	**1.10**
Amphibian	Acute	Surrogate fish *(Onkorynchus mykiss)*	96-h LC$_{50}$ = 502	50.2	11.6	0.23
	Chronic	*Xenopus laevis*	90-d NOEC = 1.0 (thyroid changes)	1.0	11.6	**11.60**
Fish	Acute	Rainbow trout *Onkorynchus mykiss*	96-h LC$_{50}$ = 502	50.2	2.2	0.04
	Chronic	No data available				
Freshwater algae	Acute	Green Algae (*Pseudokirchneriella subcapitata*)	72-h EC$_{50}$ = 23.0	11.5	2.2	0.19
Vascular plant	Over-spray acute	Duckweed (*Lemna. gibba*)	7-d EC$_{50}$ = 960	480	2.2	0.00
Marine species						
Invertebrate	Acute	Mysid (*Americamysis bahia*)	96-h LC$_{50}$ = 9.2	4.6	2.2	0.48
	Chronic	No data available				
	Acute	Eastern oyster (*Crassostrea virginica*)	96-h LC$_{50}$ = 110	55	2.2	0.04
	Chronic	No data available				
Fish	Acute	sheepshead minnow (*Cyprinodon variegatus*)	96-h LC$_{50}$ = 900	90	2.2	0.02
	Chronic	No data available				
Marine algae	Acute	No data available				

1 - Endpoints used in the acute exposure risk assessment (RA) are derived by dividing the EC$_{50}$ or LC$_{50}$ from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of ten (10) for fish and amphibians.
2 – EECs are based on the highest cumulative application rate for mancozeb (and all the EBDCs) for use on apples (4800 g a.i./ha × 6 at 7 day intervals) in a 15 cm water body depth for amphibians and a 80 cm water depth for all other aquatic organisms .
3 - Risk quotients shown in bold exceed the level of concern (RQ > 1).

Table 21 Refined Risk Assessment of ETU to Freshwater Aquatic Organisms

Organism	Exposure	Species	Endpoint value (mg a.i./L)	EEC[1] (mg a.i./L)	RQ[2]
Freshwater species					
Invertebrate	Chronic	*Daphnia magna*	2.0	0.8	0.4
Amphibian	Chronic thyroid (90 d)	*Xenopus laevis*	1	4.3*	4.3
	Chronic Forelimb (90 d)		10	4.3**	0.43

* Histological changes to the thyroid, but effect on survival of amphibians is unknown
**Developmental effects in forelegs are expected to affect survival of amphibians
1 - EECs are based on the highest cumulative application rate for mancozeb (and all the EBDCs) for use on apples (4800 g a.i./ha × 6 at 7 day intervals) in a 15 cm water body depth for amphibians and a 80 cm water depth for all other aquatic organisms.
2 - Risk quotients shown in bold exceed the level of concern (RQ>1).

Appendix X Water Monitoring and Modelling for Use in Drinking – Water Risk Assessment

Water Monitoring Data

EBDC fungicides are very short-lived in the environment and are not expected to persist in surface waters or reach groundwater because they hydrolyze rapidly into their complexes. The complex comprises of a suite of chemical species including ETU, a common transformation product of all the EBDCs. ETU is highly water soluble and may reach both surface and groundwater in the right conditions. Therefore, the monitoring data for ETU and EBDC complexes will be used in the assessment of exposure concentrations in water for all EBDCs.

A search for Canadian water monitoring data on EBDC fungicides such as metiram, mancozeb, nabam and their common degradate ETU was undertaken. The Federal Provincial and Territorial representatives from all of the provinces and territories in Canada were contacted, requesting water monitoring data for EBDC fungicides. In addition, requests were submitted to Environment Canada, the Department of Fisheries and Oceans and the drinking water sub-committee through Health Canada. A response was received by most provinces and territories indicating that either monitoring data were not available or the available data were submitted.

The search resulted in a number of datasets in which either the individual parent compounds, EBDC (dithiocarbamates) or ETU were included in the analyte list. There were recorded detections of ETU and EBDCs. In some cases, the parent compounds were detected, but a high level of uncertainty and loss of sensitivity in the analytical methods made the results questionable.

US databases were searched for detections of all the EBDCs and ETU. No data were available from the United States Geological Survey National Water Quality Assessment program (NAWQA), for either groundwater or surface water, nor from the Six Year Review of National Drinking Water Regulations, as part of the United States National Contaminant Occurrence Database (NCOD). However, in 2001-2003, the EBDC/ETU Task Force conducted a targeted monitoring study in seven states chosen to represent the high historic EBDC use areas in the US.

A summary of the findings is presented in Table 2.

Table 1 Summary of Available Monitoring Studies and Data

Data Source	Location	EBDC tested	Min detection or detection limit (µg/L)	# of samples tested	# of samples with detections	%Detection Frequency	Absolute Maximum concentration (µg/L)
PMRA# 1345897	Maritimes surface and groundwater (Prince Edward Island) 1999	Mancozeb	N/A	N/A	N/A	N/A	6.9; 20
	2000	Mancozeb	N/A	N/A	N/A	N/A	1.40
PMRA# 1726638	PEI (municipal, institutional & private water supply) 2006	EBDC complexes	N/A	124	N/A	8-43	34-53
PMRA# 1726642	2007	EBDC complexes	N/A	N/A	10	10-50	16-60
PMRA# 1346006	Canada/PEI Water Management Agreement 1987	Mancozeb	25	21	4	19	32
PMRA# 1737520	PEI (groundwater)	Metiram & Mancozeb	100	101	N/D	N/D	N/D
PMRA# 1311124	Alberta (surface water)	Metiram & Mancozeb	10	20	N/D	N/D	N/D
PMRA# 1307578	Quebec (Déversant du Lac stream) close to Apple orchard 1995	ETU	N/A	N/A	N/A	12	1.1
	1996	ETU	1	N/A	N/A	N/A	2.3
PMRA# 1311119, 1311120	Quebec (private water wells located in potato growing areas) 2000-2001	ETU	N/A	51	N/D	N/D	N/D
USEPA RED for metiram, 2005	EBDC/ETU Task Force targeted monitoring study in seven USA states of high historic EBDC use 2001-2003	ETU (in public drinking water well in Lee County, Florida)	N/A	N/A	N/A	N/A	0.21
		ETU (in private water well in Apple growing area of New York)	N/A	N/A	N/A	N/A	0.57

N/D = Not detected
N/A = Not available

Modelling results

Table 2 Level 1 and Level 2 Estimated Environmental Concentrations of ETU in Potential Drinking Water Sources

Modelling Level	Groundwater EEC (µg a.i./L)		Surface Water EEC (µg a.i./L)			
			Reservoir		Dugout	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]	Daily[3]	Yearly[4]
Level 1	0.36	0.35	75	8.6	74	19
Level 2	N/A[5]	N/A	16	2.9	27	7.2

1 90th percentile of daily average concentrations
2 90th percentile of yearly average concentrations
3 90th percentile of yearly peak concentrations
4 90th percentile of yearly average concentrations
5 Not applicable

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Toxicology

A. Studies/Information Submitted by Registrant (Unpublished)

Mancozeb

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Mancozeb

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