Re-evaluation Decision RVD2018-21

Mancozeb and Its Associated End-use Products

Final Decision

(publié aussi en français)

21 June 2018

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6607 D
Ottawa, Ontario K1A 0K9

Internet: canada.ca/pesticides
hc.pmra.publications-arla.sc@canada.ca
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
hc.pmra.info-arla.sc@canada.ca

Canada

ISSN: 1925-1017 (print)
1925-1025 (online)

Catalogue number: H113-28/2018-21E (print version)
H113-28/2018-21E-PDF (PDF version)

Table of Contents

Re-evaluation Decision

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

Mancozeb is a broad spectrum contact fungicide with multi-site mode of action used in agriculture on a wide variety of food and feed crops. Mancozeb is also registered for use on ornamentals, oilseed and fiber crops, as well as in forests and woodlots. Thirty-eight products containing mancozeb are currently registered in Canada under the authority of the *Pest Control Products Act*, including 5 technical grade active ingredients, 32 commercial class end-use products and 1 manufacturing concentrate. Currently registered products containing mancozeb are listed in Appendix I.

This document presents the re-evaluation decision[1] for mancozeb. All products containing mancozeb that are registered in Canada are subject to this re-evaluation decision.

This re-evaluation decision was consulted on as Proposed Re-evaluation Decision PRVD2013-01, *Mancozeb*.[2] The consultation period was extended to 109 days and ended on 15 November 2013. The PMRA received comments relating to the health, value and environmental risk assessments. These comments and new data/information resulted in revisions to some parts of the risk assessments (see the Science Evaluation Update) and subsequent changes to the proposed regulatory decision as described in PRVD2013-01. Appendix II of this document summarizes the comments received and provides the PMRA's response.

Regulatory Decision for Mancozeb

The PMRA has completed the re-evaluation of mancozeb. Under the authority of the *Pest Control Products Act*, the PMRA has found the continued registration of products containing mancozeb acceptable for foliar application to potatoes. An evaluation of available scientific information found that foliar application of mancozeb to potatoes meets current standards for protection of human health and the environment, when used according to the conditions of registration which include required amendments to label directions. All other uses of mancozeb are being cancelled due to unacceptable risks to human health and will be removed from the labels. Label amendments, as summarized below and listed in Appendix III, are required for all end-use products.

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

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

Risk Mitigation Measures

Registered pesticide product labels include specific instructions for use. Directions include risk reduction measures to protect human health and the environment. These directions must be followed by law. The key risk-reduction measures required are summarized below. Refer to Appendix III for details.

Human Health

To protect the general population, the following risk-reduction measures are required for continued registration of mancozeb in Canada:

- Cancel all Canadian uses of mancozeb with the exception of foliar application on potatoes.
- Permit a maximum of 10 applications per year on potatoes at a maximum application rate of 1.69 kg a.i./ha with 7-day application intervals and a 1-day pre-harvest interval using aerial or ground spray only.

To protect mixer/loader/applicators:

- Engineering controls: Closed mixing and loading for wettable powder products (water soluble packaging). Closed-cab groundboom tractor or respirator for custom applicators applying dry flowable formulations.
- Personal protective equipment (PPE): Respirator when mixing/loading dry flowable products.

To reduce potential exposure to ethylene thiourea (ETU) from use of multiple ethylene bisdithiocarbamate (EBDC) pesticides:

- Limit applications of both mancozeb and metiram on potatoes during the same growing season.

Mancozeb does not present unacceptable risk to human health when used according to the revised conditions of registration, which include additional mitigation measures and label amendments. Label amendments are required for all end-use products and are listed in Appendix III.

Environment

To protect the environment, the following risk-reduction measures are required for continued registration of mancozeb in Canada:

- Spray buffer zones to protect non-target habitats from pesticide spray drift.
- Limiting aerial application to once per season.
- Standard runoff reduction statement on product labels.
- Hazard statements on product labels warning of the potential to contaminate groundwater through leaching.

- Warnings on product labels regarding toxicity of mancozeb to aquatic organisms; birds; small, wild mammals; and certain beneficial insects.

Next Steps

To comply with this decision, the required mitigation measures and removal of all but the potato foliar use must be implemented on all product labels sold by registrants no later than 24 months after the publication date of this decision document.

For the products being cancelled as a result of this re-evaluation (not registered for foliar application to potatoes), the last date of sale of the affected commercial products by the registrants and retail is 12 months and 24 months, respectively, following the publication date of this document. The registration of these products will expire 36 months following the publication date of this document.

Other Information

Any person may file a notice of objection[3] regarding this decision on mancozeb within 60 days from the date of publication of this Re-evaluation Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides and Pest Management portion of Canada.ca (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service.

[3] As per subsection 35(1) of the *Pest Control Products Act.*

Science Evaluation Update

1.0 Revised Health Risk Assessment

1.1 Toxicology Assessment for Mancozeb

The initial toxicological assessment for mancozeb was provided in PRVD2013-01, *Mancozeb*. Comments and data were received from the registrant regarding a range of issues including the significance of retinopathy in rats, the use of a developmental inhalation toxicity study, and interpretation of available genotoxicity studies. Data addressing deficiencies noted in PRVD2013-01, including developmental neurotoxicity and immunotoxicity for mancozeb and its metabolite ethylene thiourea (ETU) were submitted (Appendix IV). Some of the toxicology reference values outlined in PRVD2013-01 were revised based on evaluation of newly submitted data and as a result of comments received. Revised reference values are provided in Appendix V Table 1a and 1b. Detailed responses to the comments are provided in Appendix II.

1.2 Dietary Exposure and Risk Assessment

The initial dietary risk assessment for the re-evaluation of mancozeb was presented in the Proposed Re-evaluation Decision (PRVD2013-01). While no dietary risks of concern were identified from exposure to mancozeb, cancer risks of concern were identified from exposure to ethylene thiourea (ETU), a degradate of mancozeb and other ethylene bisdithiocarbamate (EBDC) fungicides, through food and drinking water. In addition, there were limitations in the available residue chemistry data used to estimate residues of ETU in both food and drinking water. To further refine the dietary exposure estimates and to address uncertainties in the residue chemistry data available to the PMRA, additional data that may help refine the risk assessments were identified in PRVD2013-01.

In response to PRVD2013-01, comments relevant to the dietary exposure were received primarily from the Mancozeb Task Force (MTF) on behalf of Dow AgroSciences Canada Inc. and United Phosphorus, Inc., the Canadian registrants of mancozeb. Various other stakeholders such as the Canadian Horticultural Council, other grower groups and provincial agricultural/food departments provided information regarding the importance of mancozeb. Comments related to the dietary exposure assessment and the PMRA responses are summarized in Appendix II. In addition, new data were submitted by the MTF (see References).

As a result of comments and new data received during the consultation process, revisions were made to the dietary exposure and health risk assessment outlined in PRVD2013-01. These revisions included the following changes:

1) Updated toxicology reference values were used. It should be noted, however, that although non-cancer reference values were revised, the cancer potency factor (q_1*) for ETU did not change.

2) The uses no longer supported by the registrants and those being cancelled due to occupational risks of concern, which could not be mitigated further, were not included. These uses were seed treatment for barley, corn, flax, oat and wheat; potato seed-piece treatment; grapes; greenhouse-grown tomatoes, and orchard crops, including apples and pears.

3) Updated percent crop treated estimates and percent domestic/import food supply information were used in conjunction with chemical-specific processing factors and mancozeb-to-ETU conversion factors to adjust the available residue data.

4) A revised drinking water estimated environmental concentration (EEC) derived from the 2002–2003 EBDC/ETU Task Force United States national drinking water monitoring survey was used in the ETU cancer assessment.

5) The dietary exposure and health risk assessments for mancozeb and ETU were conducted using the latest version of the Dietary Exposure Evaluation Model – Food Commodity Intake Database™ (DEEM-FCID™; Version 4.02, 05-10-c) program, which incorporates food consumption data from the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) dietary survey for the years 2005–2010 available through Centers for Disease Control and Prevention's National Center for Health Statistics.

Despite these changes, there continues to be cancer risks of concern from exposure to ETU through food (see Appendix VI, Table 1).

Since dietary cancer risks from exposure to ETU through food continued to be of concern, further refinements were considered for key uses identified by various Canadian stakeholders. Of these, only the foliar use of mancozeb on potatoes resulted in no occupational risks of concern. Therefore, the dietary exposure and risk assessments for mancozeb and ETU were revised to reflect the potato use only. As such, only potatoes and foods derived from potatoes were included (for example, cooked potato, chips and potato flour).

As mancozeb is not expected to occur in drinking water, chronic and acute risk assessments were conducted to assess exposure to mancozeb through consumption of food only. A cancer risk assessment was not conducted for mancozeb as it was considered to be addressed by the cancer risk assessment of ETU. For ETU, cancer, chronic and acute risk assessments included food and drinking water. The updated results indicate that:

- Non-cancer risks from exposure to mancozeb through food (potato use only) are not of concern.
- Mancozeb is not expected to occur in drinking water due to its rapid degradation and low water solubility. Therefore, non-cancer risks from exposure to mancozeb through drinking water are not of concern.
- Non-cancer and cancer risks from exposure to ETU through food (potato use only) and drinking water are not of concern.

The detailed results are presented in Appendix VI, Tables 2–5.

Maximum Residue Limits (MRLs)
Currently, Canadian MRLs for ethylene bisdithiocarbamate (EBDC) fungicides, including mancozeb and metiram, are specified for a number of commodities on the basis of a residue definition expressed as manganese and zinc ethylenebis (dithiocarbamate) (polymeric). Other crops with registered uses, including potatoes, are regulated under the general MRL (GMRL) of 0.1 ppm. As noted in PRVD2013-01, chemical-specific enforcement methods for the EBDC fungicides, including mancozeb, are not currently available. Therefore, the PMRA had proposed to revise the residue definition for mancozeb to residues of "mancozeb expressed as carbon disulfide (CS_2)." Another class of fungicides called the dimethyldithio-carbamates (DMDTCs), including ferbam, thiram and ziram, are currently registered in Canada and are also being re-evaluated. Similar to the EBDCs, the PMRA is considering revising the residue definition for the DMDTCs to carbon disulfide. The residue definition and MRLs for the EBDCs and DMDTCs will be considered as a whole when the re-evaluations of the DMDTCs are close to completion. Currently, the PMRA has sufficient data to propose an MRL for mancozeb expressed as carbon disulfide on potatoes based on field trial data for potato (foliar application). Any changes to the MRLs will be consulted on through a Proposed Maximum Residue Limit (PMRL) document.

There are no specific MRLs established for ETU under the *Pest Control Products Act*. However, ETU is regulated as a contaminant in foods from all sources under Division 15 of the *Food and Drug Regulations*. ETU is in Part 1 of the List of Contaminants and Other Adulterating Substances in Foods, which stipulates that no amount of ETU is considered acceptable in foods, with some exceptions when included in Part 2 of the List. In Part 2 of the List, a Maximum Level of 0.05 ppm is specified for ETU in fruits, vegetables and cereals. As noted above, the dietary cancer risk from ETU (from all current uses and imports, with the exception of potatoes) is of concern; imports are a major source of exposure which would normally require risk-based MRLs to mitigate dietary exposure to Canadians. However, the current Maximum Level of 0.05 ppm is close to the upper bound limit of quantification (LOQ) of 0.04 ppm of the enforcement methods used by the Canadian Food Inspection Agency. Therefore, with the current regulations for ETU as a contaminant in foods, the establishment of a health risk-based MRL for ETU from pesticide sources under the *Pest Control Products Act* would not be required. In addition, no further mitigation for ETU, beyond cancelling all uses of mancozeb other than foliar application on potatoes, is required.

1.3 Occupational and Non-Occupational Risk Assessment

The scenarios and crops considered for occupational exposure have not changed from the previous assessment (other than those no longer supported by the registrant in response to PRVD2013-01). The occupational exposure and risk assessment was updated to incorporate the revised toxicology assessment, additional use information, and to reflect current evaluation standards. Comments were received and considered in the updated health risk assessment (see Appendix VII). However, the overall risk conclusions remained consistent with those presented in PRVD2013-01. Based on the updated dietary risk assessment (see section 1.2), and the determination in PRVD2013-01 that the occupational risks associated with the potato foliar use were not of concern, the updates to the occupational exposure and risk assessments for mancozeb outlined below reflect the potato foliar use only.

1.3.1 Applicator Exposure Risk Estimates

For the potato foliar use, the calculated margins of exposure (MOE) for mixer, loader, and applicator exposure exceeded the target MOEs for both mancozeb and ETU and there are no cancer risks of concern from ETU. Therefore, this use is not of concern, provided engineering controls (e.g., wettable powders in water soluble packaging, closed cab application for custom applicators) and additional PPE (e.g., respirators when mixing/loading dry flowable formulations) are employed. The occupational risk conclusions for this use are consistent with those presented in PRVD2013-01.

1.3.2 Postapplication Exposure Risk Estimates

For the potato foliar use, the calculated MOEs exceeded the target MOEs for both mancozeb and ETU and there are no cancer risks of concern from ETU with a restricted-entry interval (REI) of 12 hours. Therefore, this use is not of concern.

1.3.3 Bystander Spray Drift Inhalation Risk Estimates

Based on the previously published PRVD2013-01, there are no risks of concern for bystanders.

1.4 Aggregate Exposure and Risk Assessment

In PRVD2013-01, the aggregate risk assessment considered exposure to mancozeb from food and drinking water only. Although there are no residential uses for mancozeb, potential non-occupational exposures could occur from pick-your-own facilities or to bystanders from spray drift. These exposures were not included in the previous aggregate risk assessment since cancer risks of concern were already identified from exposure to ETU through food and drinking water.

The current dietary risk assessment has been revised to include only the potato use and drinking water exposure. With this mitigation, the dietary cancer risks from exposure to ETU are not of concern. Therefore, an aggregate assessment for non-occupational and dietary exposures can be conducted. With cancellation of the orchard uses, the only relevant sources of exposure are dietary and bystander inhalation. Exposure to bystanders from drift was very low compared to dietary exposure and would not significantly contribute to aggregate risk. Therefore, aggregate risk is not of concern when the required mitigation measures are implemented.

1.5 Cumulative Assessment

A cumulative risk assessment for the pesticidal uses of the EBDCs based on the common metabolite, ETU, is required. The risk characterization for ETU showed the thyroid effects to be a more sensitive endpoint than peripheral neuropathy in 90-day studies for both mancozeb and metiram. This is consistent with other regulatory authorities, such as the USEPA.

Exposure to ETU in food and drinking water may occur from the use of mancozeb or any other EBDC fungicide. 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 also occur from non-pesticidal sources of ETU. These sources are regulated under the *Canadian Environmental Protection Act* (1999).

The dietary exposure to residues of ETU in food and drinking water resulting from the foliar application of mancozeb to potatoes is not of concern. This assessment also considers residues of metiram on potatoes, since market basket survey data, which do not distinguish the source of the ETU, were used to estimate dietary exposure. Similarly, for the drinking water exposure estimates, which were based on a water monitoring study, ETU residues could be from both mancozeb and metiram uses. Hence, the dietary assessment for ETU represents a cumulative risk assessment since it includes ETU exposure from all sources, and compares that to the ETU toxicology reference values.

2.0 Revised Environmental Risk Assessment

During the consultation period of PRVD2013-01, the registrant proposed to modify the foliar use pattern on potato. The existing application rates on product labels for potato range from 1.69 to 1.8 kg a.i./ha at a maximum of 10 applications per season using either ground or aerial equipment. Under the revised use pattern, foliar use on potato is restricted to 1.69 kg a.i./ha with up to 10 applications via ground equipment; aerial application is limited to a single application.

The environmental risk assessment has been updated to reflect the revised use pattern as well as additional information and comments received during the consultation period. Updates include:

1) Recalculation of aquatic DT_{50} values for the mancozeb complex to be used to estimate exposure concentrations for the aquatic risk assessment.
2) The use of arthropod residue study data to estimate a dissipation half-life for mancozeb on insects for use in the bird and mammal risk assessment; the dissipation half-life was used to estimate exposure of insectivorous birds and mammals to mancozeb.
3) Recalculation of spray buffer zones for the protection of aquatic habitats.

In the initial environmental risk assessment conducted for PRVD 2013-01, mancozeb was shown to pose a potential risk of concern to beneficial arthropods, birds, small wild mammals and aquatic organisms. This risk assessment was based on foliar application rates that were much higher than those registered for potato. The current revised environmental risk assessment (based on the revised use pattern for potato) shows that mancozeb remains a potential risk of concern to beneficial arthropods, birds, small wild mammals and aquatic organisms, however, the risk exceedances for these organisms are relatively low.

The revised environmental risk assessment considered the maximum of 10 foliar applications of mancozeb to potato per season at a minimum interval of 7 days between applications. Based on typical use information, the number of applications to potato in a season varies across Canada ranging from two (Alberta) to a maximum of eight (Maritimes); these differences are likely due to differences in disease pressure. The number of applications may be further reduced by using other fungicides in rotation with mancozeb, a resistance management strategy that is recommended on all product labels. As a result, the revised environmental risk assessment for mancozeb using the revised use pattern for potato is considered to be conservative. The potential risks identified can be addressed with the implementation of additional mitigation measures and precautionary label statements. A general summary of the mancozeb and ETU environmental assessment follows.

2.1 Updates to the Environmental Risk Assessment

When mancozeb is released into the environment it decomposes rapidly via hydrolysis into mancozeb complex, which consists of variable/low molecular weight polymeric chains (polymer fragments), monomeric species, intermediate species, transformation products and other unidentified materials. In the terrestrial environment, mancozeb complex is non-persistent and binds strongly to soils, therefore, mancozeb parent and mancozeb complex are not expected to leach into groundwater.

ETU is a transformation product formed from mancozeb and other EBDC (ethylene bisdithiocarbamate) pesticide such as, metiram and nabam. However, nabam is registered in Canada for industrial uses only. ETU forms via chemical reactions in water, through action of light and by microbial action after the application of mancozeb to the environment. ETU undergoes rapid breakdown in soil, through microbial action, but the rate depends on the soil moisture levels and could be slightly to moderately persistent in soil. ETU generally does not bind strongly to soils and has high to very high mobility in soil, indicating it could reach surface water and groundwater. Canadian water monitoring data have confirmed ETU detections in surface water but not in groundwater.

In the aquatic environment, mancozeb complex formed after the rapid hydrolysis of mancozeb parent is slightly persistent under aerobic conditions. Anaerobic aquatic conditions appear to be conducive for slowing down mancozeb parent transformation. Therefore, mancozeb complex is expected to persist longer under anaerobic conditions. ETU is slightly persistent in the aquatic environment under aerobic conditions and moderately persistent to persistent under anaerobic conditions. Mancozeb residues are not expected in the air because of its low volatility and it has a low potential for bioaccumulation in biota. ETU may partition into air as indicated by its high vapour pressure, however, if it reaches air, it is unlikely to be persistent ($T_{1/2}$ ranges from <2 hours to 9 days). ETU has a low potential for bioaccumulation in biota.

Mancozeb may pose a risk to beneficial arthropods, birds, small wild mammals, and to aquatic organisms. ETU may also pose a risk to small wild mammals. The risk to beneficial predatory arthropods from mancozeb triggers a requirement for precautionary label statements.

Chronic risks were identified for birds and mammals that may potentially ingest mancozeb residues on food items; this risk is anticipated to be low and the reduction of the potato application rate will further reduce the risk to birds and mammals.

In order to minimize the potential exposure of aquatic organisms to mancozeb, a spray buffer zone is required between the sprayer and downwind sensitive habitats. The width of these spray buffer zones will be specified on the product label. Aquatic organisms will be at negligible risk due to the formation of ETU from the use of mancozeb.

Spray buffer zones will not mitigate runoff. To reduce the potential for runoff 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.

3.0 Incident Reports

As of 16 October 2017, there were seven human (including three serious), one domestic animal, and one human and domestic animal incident reported to the PMRA. This encompasses the two human and one animal incident reports noted in PRVD2013-01. There are currently no environmental incident reports involving mancozeb in Canada.

In the human incidents, exposure often occurred via the respiratory or ocular routes. Three of the human incidents were considered to be possibly associated with the pesticide exposure; reported symptoms included eye or respiratory irritation and vomiting. The remaining incident reports, including the three serious human incidents, did not contain sufficient information to determine an association to the pesticide exposure or were unrelated to the exposure. Overall, given the presence of multiple active ingredients and lack of exposure information in the serious human incidents, as well as the relatively minor nature of symptoms seen in the minor or moderate cases, no additional mitigation measures are recommended as a result of these incidents.

Domestic animal incidents involved dogs that experienced seizures, but exposure involved multiple active ingredients and the reports did not contain sufficient information to determine whether the observed effects were associated with the reported exposure. Based on the presence of multiple active ingredients and lack of exposure information in the incidents, no additional mitigation measures are required as a result of these reports.

List of Abbreviations

abs	absolute
atm	atmosphere
ADI	acceptable daily intake
AGD	anno-genital distance
a.i.	active ingredient
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ASR	acoustic startles response
ARfD	acute reference dose
BCF	bioconcentration factor
bw	bodyweight
bwg	bodyweight gain
CAF	composite assessment factor
Ctrl	control
d	day(s)
DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EEC	estimated environmental exposure concentration
ETU	Ethylenethiourea
EOGRTS	Extended one generation reproduction toxicity study
F1	first generation
F2	second generation
fc	food consumption
FIR	food ingestion rate
g	gram(s)
GD	gestation day
ha	Hectare
hr(s)	hour(s)
HC_5	hazardous concentration to 5% of the species
IUPAC	International Union of Pure and Applied Chemistry
Ig M	Immunoglobulin M
IQ	Intelligence quotient
K_{ow}	octanol water partition coefficient
K_d	adsorption quotient
K_{OC}	adsorption quotient normalized to organic carbon
K_{OW}	octanol-water partition coefficient
kg	kilogram(s)
kg a.i./ha	kilograms active ingredient per hectare
L	litre(s)
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LD	lactation day

LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOQ	limit of quantification
LOEC	lowest observed effect concentration
LOEL	lowest observed effect level
LR_{50}	lethal rate 50%
m	metre(s)
mg	milligram(s)
mg/L	milligrams per litre
MOE	margin of exposure
MTC	maximum tolerated concentration
MTD	Maximum tolerated dose
MTF	Mancozeb Task Force
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NOEC	no observed effect concentration
NOAEEC	no observed adverse ecological effect concentration
OC	organic carbon content
OM	organic matter content
p*K*a	dissociation constant
P	parental generation
PC	positive control
PMRA	Pest Management Regulatory Agency
PND	postnatal day
ppb	parts per billion
ppm	parts per million
PTU	Propylenethiouracil
q_1*	cancer potency factor
REI	restricted-entry interval
rel	relative
ss	statistically significant
SD	Sprague Dawley
SRBC	sheep red blood cells
$T_{1/2}$	half-life
T_4	thyroxin
TSH	thyroid stimulating hormone
TSMP	toxic substances management policy
USEPA	United States Environmental Protection Agency
UV	ultraviolet
µg	microgram
µL	microlitre
µm	micrometre
w	week(s)
vs.	versus
wt	weight

Appendix I Products Containing Mancozeb that are Registered in Canada[1] as of 6 February 2018

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
31266	Technical	Agria S.A.	FORTUNA MANCOZEB TECHNICAL FUNGICIDE	Solid	Mancozeb 92.3%;
31267	Commercial		FORTUNA MANCOZEB 80 WP FUNGICIDE	Wettable Powder	Mancozeb 80%;
31478	Manufacturing Concentrate		FORTUNA 80 WP MUC FUNGICIDE	Wettable Powder	Mancozeb 80%;
31858	Commercial		FORTUNA 75 WDG FUNGICIDE	Dry Flowable	Mancozeb 75.0%;
28159	Commercial	Bayer Cropscience Inc.	GENESIS MZ POTATO SEED-PIECE TREATMENT	Dust Or Powder	Mancozeb 6.0%; Imidacloprid 1.25%;
28160	Commercial		GENESIS XT POTATO SEED-PIECE TREATMENT	Dust Or Powder	Thiophanate-Methyl 3.0%; Mancozeb 6.0%; Imidacloprid 1.25%;
8556	Commercial	DOW Agrosciences Canada Inc.	DITHANE M-45 FUNGICIDE	Wettable Powder	Mancozeb 80%;
10186	Commercial		DITHANE M-45 8% DUST POTATO SEED PIECE FUNGICIDE	Dust Or Powder	Mancozeb 8%;
20552	Commercial		DITHANE F-45 FUNGICIDE	Solution	Mancozeb 37.0%;
20553	Commercial		DITHANE RAINSHIELD FUNGICIDE	Wettable Granules	Mancozeb 75.0%;
20734	Technical		DITHANE TECHNICAL FUNGICIDE	Wettable Powder	Mancozeb 83.2%;
23655	Commercial		DITHANE 80 FUNGICIDE	Wettable Powder	Mancozeb 80%;
27616	Commercial		DITHANE M-45 SEED PROTECTANT FUNGICIDE	Wettable Powder	Mancozeb 80%;
29221	Commercial		DITHANE DG 75 FUNGICIDE	Dry Flowable	Mancozeb 75.0%;
29377	Commercial	Engage Agro Corporation	SOLAN MZ POTATO ST FUNGICIDE	Dust Or Powder	Mancozeb 16%;
29378	Commercial		TUBERSEAL MZ POTATO ST FUNGICIDE	Dust Or Powder	Mancozeb 16%;
31181	Commercial		AGROSOLAN LIQUID FUNGICIDE	Solution	Mancozeb 37%;
17042	Commercial		TUBERSEAL POTATO SEED PIECE DUST	Dust Or Powder	Mancozeb 16.0%;
31280	Technical	FMC Corporation	FMC MANCOZEB TECHNICAL FUNGICIDE	Solid	Mancozeb 87.2%;
31281	Commercial		KINGPIN 75 WDG FUNGICIDE	Wettable Granules	Mancozeb 75%;
26842	Commercial	Gowan Company LLC	GAVEL DF FUNGICIDE	Dry Flowable	Zoxamide 8.3%; Mancozeb 66.7%;
24734.01	Commercial	Loveland Products Canada Inc.	PSPT 16%	Dust Or Powder	Mancozeb 16%;

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
26157	Commercial	Norac Concepts Inc.	MANCOPLUS POTATO SEED PIECE TREATMENT	Dust Or Powder	Mancozeb 16%;
26158	Commercial		CONDOR MZ POTATO SEED PIECE TREATMENT	Dust Or Powder	Mancozeb 16%;
25379	Commercial	Syngenta Canada Inc.	RIDOMIL GOLD MZ 68WP FUNGICIDE	Wettable Powder	Metalaxyl-M And S-Isomer 4%; Mancozeb 64%;
25419	Commercial		RIDOMIL GOLD MZ 68WP WATER SOLUBLE BAG FUNGICIDE	Wettable Powder	Metalaxyl-M And S-Isomer 4%; Mancozeb 64%;
27965	Commercial		MAXIM MZ PSP	Dust Or Powder	Mancozeb 5.7%; Fludioxonil 0.5%;
28893	Commercial		RIDOMIL GOLD MZ 68WG FUNGICIDE	Wettable Granules	Metalaxyl-M And S-Isomer 4.00%; Mancozeb 64.0%;
10526	Commercial	United Phosphorus Inc.	MANZATE 200 WP FUNGICIDE	Wettable Powder	Mancozeb 80%;
19788	Technical		MANCOZEB TECHNICAL FUNGICIDE	Solid	Mancozeb 93%;
21057	Commercial		MANZATE DF FUNGICIDE	Dry Flowable	Mancozeb 75.0%;
25166	Technical		PENNCOZEB TECHNICAL FUNGICIDE	Dust Or Powder	Mancozeb 87%;
25396	Commercial		PENNCOZEB 80WP FUNGICIDE	Wettable Powder	Mancozeb 80%;
25397	Commercial		PENNCOZEB 75DF FUNGICIDE	Wettable Granules	Mancozeb 75%;
28217	Commercial		MANZATE PRO-STICK FUNGICIDE	Wettable Granules	Mancozeb 75%;
30241	Commercial		PENNCOZEB 75DF RAINCOAT FUNGICIDE	Wettable Granules	Mancozeb 75%;
32271	Commercial		ELIXIR FUNGICIDE	Wettable Granules	Chlorothalonil 12.5%; Mancozeb 62.5%;
24734	Commercial	Wilbur Ellis Company LLC	POTATO ST16	Dust Or Powder	Mancozeb 16%;

1 Excluding discontinued products or products with a submission for discontinuation as of 6 February 2018 based upon the PMRA's Electronic Pesticide Regulatory System (e-PRS) database.

Appendix II Comments and Responses

In response to the consultation document PRVD2013-01, *Mancozeb*, comments related to the health risk and environmental assessment, as well as on the value of mancozeb were received primarily from the Mancozeb Task Force (MTF) on behalf of Dow AgroSciences Canada Inc. and United Phosphorus, Inc., the Canadian registrants of mancozeb. Various other stakeholders such as the Canadian Horticultural Council, other grower groups and provincial agricultural/food departments provided information regarding the importance of mancozeb.

The comments received and the PMRA responses are summarized in this Appendix.

1.0 Comments and Responses Related to the Toxicology

As a result of new information, and in consideration of the comments submitted following publication of PRVD2013-01, the PMRA has updated the toxicology assessment. The evaluation of new studies and information is reflected in Appendix IV, Table 1a and 1b. Updates to Toxicology Reference Values for risk assessment are reflected in Appendix V, Table 1a and 1b.

1.1 Comment concerning the significance of mild bilateral retinopathy in the rat chronic/oncogenicity study

The MTF suggested that the observed bilateral retinal degeneration was not significant at dose levels ≤ 125 ppm, that a study NOAEL of 125 ppm (4.8 mg/kg bw/day) was appropriate, and that treatment related effects were limited to the high-dose group (750 ppm). Further, the available epidemiology studies (Kamel et al. (2000), Kirrane et al., (2005), were thought to have deficiencies, and did not support a relationship between mancozeb exposure and human retinal degeneration.

PMRA Response:
An increased incidence of mild bilateral retinopathy was evident in the high-mid-dose females, and in both males and females in the high-dose group in the chronic rat study (Stadler, 1990; PMRA #1135743). The incidence in these groups was statistically significant using the Fisher's exact test.

Available historical control data reported the incidence of retinopathy in control males and females from long-term feeding studies (1984–1989). However, only one chronic study (1987) falls within an acceptable time-frame for comparison with the mancozeb study (Stadler, 1990).

A new statistical analysis conducted by the commenter comparing the historical control values (one study) with the 4.8 mg/kg/day dose group (female high-mid dose) from the mancozeb study did not demonstrate a statistically significant difference (Fisher's exact test). Also, the trend statistics (Yates's Chi-Square pairwise tests and Cochran-Armitage linear trend tests) comparing the concurrent control and historical control with the low- and mid-dose values of the study in question, was "not significant".

However, the trend test was performed after excluding the highest dose data from analysis. Since there was no valid rationale to exclude the high dose values from linear trend test, the statistical analysis remains questionable. Thus, the historical control data and the new statistical analysis submitted do not fully support the claim that bilateral retinal degeneration is only increased at dose levels more than 4.8 mg/kg/day in females.

With respect to the referenced epidemiology studies, limitations of the study included the use of prevalent cases and self-reported exposure and disease information. In general, however, the reported limitations do not exclude a relationship between fungicide exposure and human retinopathy. Specific compounds of interest included maneb/mancozeb and ziram. Since these chemicals share the same "organic" part of their formulation and these epidemiology studies correlate with the animal data, they were taken into consideration in the PMRA's risk assessment of mancozeb.

There is no convincing evidence upon which to revise the PMRA's interpretation of the retinopathy findings in this study.

1.2 Comment concerning the dog study selected to establish the ADI

The MTF suggested that a second available 1-year dog dietary study better characterized the mancozeb dose-response curve than the study selected by the PMRA as the point of departure for the ADI, and thus, for a variety of reasons, should be used instead to derive the ADI.

PMRA Response:
In PRVD2013-01, the ADI for mancozeb was based on consideration of all treatment related effects noted in both of the available 1-year dog studies. In the study selected to establish the ADI, 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 was supported by the NOAEL of 1.75 mg/kg bw/day in the second 1 year dog study.

As noted by the MTF, the dose spacing in the selected study was wide, making determination of the real NOAEL less accurate. For this reason, both 1-year dog studies were considered together as they used different and overlapping doses. Although the commenter suggests that the use of gelatin capsules as a means to deliver mancozeb to the dogs compromises the study, their use provides a more accurate dose compared to dietary exposure, especially considering the high variability in food concentration and consumption noted in the second dog study.

In addition, the NOAEL selected from the 1-year dog study was supported by the ETU dietary 1-year dog study (PMRA #1619162). The ETU 1-year dog study NOAEL of 0.18 mg/kg bw/day, equals 2.4 mg/kg bw/day when converted to mancozeb equivalents which is consistent with the NOAEL of 2.3 mg/kg bw/day established in the 1-year mancozeb dog study selected for risk assessment.

In the absence of any further information, the NOAEL selected to derive the ADI remains unchanged.

1.3 Comment concerning the adequacy of the Bindali and Kaliwal (2002) study for regulatory use

The adequacy of the published study by Bindali and Kaliwal (2002) (PMRA #1852272) was questioned by the MTF due to major deficiencies in study design and data interpretation. In addition, the MTF noted that the toxicological findings by Bindali and Kaliwal (2002) were not supported by the guideline two-generation reproductive toxicity study (Solomon et al., 1988).

PMRA Response:
Following assessment of new toxicology studies and in consideration of the submitted comments, the studies selected for risk assessment were reconsidered. A point of departure (POD) from the mancozeb rat developmental neurotoxicity study (PMRA #2047261) was selected for the ARfD (Females 13–49 years of age) and the occupational short- and intermediate-term dermal exposure scenarios, rather than from the study by Bindali and Kaliwal (2002). This change is reflected in the revised Toxicology Reference Values identified in Appendix V, Table 1a.

1.4 Comment concerning the interpretation of the inhalation developmental toxicity study

The MTF stated that increased resorptions in the inhalation developmental toxicity study, as noted by the PMRA, occurred only at doses that exceeded the maximum tolerated concentration (MTC). Further, there was uncertainty that the neurological signs (hind limb weakness) at 55 mg/m^3 were due to a direct effect on the nervous system, given that the large decrease in body weight and body weight gain during gestation (11% and 40%, respectively) at the highest concentration indicated that MTC was exceeded. The MTF suggested that the appropriate maternal and fetal NOEL and MTC is 17 mg/m^3 [5.27 mg/kg bw/day].

PMRA Response:
With respect to the observed slight increase in “average percent resorbed [fetuses] per litter” at 55 mg/m^3, it is not possible to determine whether the effect is secondary to maternal toxicity or is the result of direct toxicity in the foetus. The maternal effects at this dose were mild in nature, although body weight and body weight gain were decreased by 11% and 40%, respectively. The maternal effects at this dose were not considered significant enough to clearly suggest that the resorptions were an effect secondary to maternal toxicity. Higher doses (110, 890 and 1890/500 mg/m^3) caused increasing maternal mortality and lead to total litter resorption in all dams of the 890 mg/m^3 group and in all but three dams in the 1890/500 mg/m^3 group. In this context, the slightly increased “average percent resorbed per litter” at 55 mg/m^3 was considered by the PMRA to be a dose and treatment related effect. Resorptions were noted in other developmental toxicity studies in this database. This effect on fetal viability is considered by the PMRA to be a serious effect, and was discussed in the *Pest Control Products Act* hazard characterization section of PRVD2013-01.

With respect to the neurotoxicity effects, the incidence and severity of the neurological signs (hind limb weakness) increased with dose in this study. Although the effect is mild at 55 mg/m^3, the PMRA considers that it may be an early indicator of peripheral neuropathy. This interpretation is supported by the fact that this effect, and other evidence of neurotoxicity, was noted in other developmental and neurotoxicity studies in the toxicology database.

Therefore, the outcome of the study evaluation with respect to foetal resorptions and neurological signs seen at the LOAEL of 55 mg/m^3 remains unchanged.

1.5 Comment concerning the adequacy of the inhalation developmental toxicity study chosen for use in risk assessment for inhalation scenarios

The MTF noted that the study chosen by the PMRA for risk assessment (Lu and Kennedy, 1986; PMRA #852277) used a whole body exposure technique. As this technique results in a systemic exposure higher than calculated, it was felt that an available 90-day inhalation study (PMRA #1220614), which used a nose-only technique, was more appropriate.

PMRA Response:
PMRA concurs with the fact that a "whole body" exposure technique used in the Lu and Kennedy (1986; PMRA #1852277) study could result in a higher overall systemic exposure than reported in the study. In addition, the PMRA agrees that the 90-day inhalation study (nose only) (PMRA #1220614) is a relevant study for inhalation exposure risk assessment for short- and intermediate-term scenarios. It should be noted that 90-day nose-only inhalation studies also included an oral exposure component that resulted in a higher than calculated systemic exposure. However, the inhalation developmental toxicity study was chosen for the short- and intermediate-term inhalation risk assessment because the 90-day inhalation study did not assess effects of concern, namely, the serious effect of resorptions noted in the inhalation developmental toxicity study (Lu and Kennedy, 1986). In addition, resorptions were noted in other rat and rabbit studies, as discussed in PRVD2013-01, Section 3.1.1 *Pest Control Products Act* hazard characterization. Therefore, the study selection for short- and intermediate-term inhalation risk assessment remains unchanged.

For the 90-day inhalation study, the commenter performed a recalculation of the respirable dose. The recalculated respirable dose was 21 mg/kg bw/day, in contrast to the respirable dose of 9.4 mg/kg bw/day used by the PMRA. In the 90-day inhalation study, the study authors reported a MMAD of 3.8–4.2 µm with a mean respirable fraction of 42–46%. In a guideline inhalation toxicity study, the acceptable range for the MMAD is 1–3 µm and particles in this range are considered respirable to the lung alveoli. The method used by the commenter to determine respirable dose included components of the dose which deposited in the nasal airways, tracheal/bronchial airways, and alveolar region of the rat, using the rationale that all of this material eventually contributes to total dose through absorption through the lungs or orally for material cleared from the lungs. This method of calculating respirable dose is not used by, or considered acceptable to, the PMRA. The NOAEL of 9.4 mg/kg bw/d (respirable) established by the PMRA in the 90-day rat inhalation study is comparable to the NOAEL of 5.27 mg/kg bw/day from the rat inhalation developmental toxicity study.

1.6 Comment concerning the appropriate NOAEL for the acute neurotoxicity study

The MTF noted that the appropriate NOAEL for the acute neurotoxicity study (PMRA #1571642) was 500 mg/kg bw/day, a dose the PMRA identified as a LOAEL.

PMRA Response:
The PMRA did not set a specific NOAEL for neurotoxicity, rather, a study NOAEL incorporating all treatment related effects was set. With respect to setting an ARfD reference value, all studies available were examined for acute toxicological effects.

With respect to the acute neurotoxicity study, the total session motor activity data showed decreased total motor activity compared to the control group on the day of treatment, although a dose response was not clear as there was significant variability in the data. The decrease affected all male and female treated groups. There was histopathology of nerve tissue noted at the high-dose group in the study that was similar to lesions seen in the 90-day neurotoxicity study. Mild systemic toxicity at 500 mg/kg bw included perineal staining, decreased body weight, and decreased rectal temperature.

In a gavage dose-range finding developmental neurotoxicity (DNT) study, and in a full DNT study (Axelstad et al., 2011), female rats exposed to mancozeb at much lower doses (150–350 mg/kg bw/day) experienced hind limb paralysis within a few days of dosing, although the raw and summary data were not available for examination.

In consideration of the available information, the study LOAEL of 500 mg/kg bw/day based on decreased motor activity remains unchanged.

1.7 Comment concerning the applied database uncertainty factor

The MTF requested that the threefold database uncertainty factor applied in PRVD2013-01 be removed based on studies submitted (mancozeb developmental neurotoxicity, mancozeb immunotoxicity, ETU extended one-generation reproductive toxicity study ("EOGRTS"), and ETU immunotoxicity study) following publication of PRVD2013-01.

PMRA Response:
Since the data requirements outlined in PRVD2013-01 were satisfied through submission of the requested information, the previously applied threefold database uncertainty factor was removed. This change is reflected in the revised Toxicology Reference Values (Appendix V, Table 1a and 1b).

1.8 Comment concerning the assessment of ETU's genotoxicity

The MTF suggested that the PMRA revise its assessment of the genotoxicity of ETU to be consistent with other international regulators, such as the Joint FAO/WHO Meeting on Pesticide Residues and the EU, who consider ETU not genotoxic in mammalian systems.

PMRA Response:
There are about 100 ETU genotoxicity studies available in the toxicology database. In 1988, the WHO concluded that ETU itself is generally not mutagenic, especially in mammalian test systems. However, a more recent and extensive review by Dearfield (1994) reported that ETU has a weak genotoxic potential (gene mutation and structural chromosomal aberrations).

This was contradicted by Elia (1995), who suggested that the thyroid tumours in rats and liver tumours in mice were induced by a non-genotoxic, or threshold, mechanism. While the thyroid tumours appear to have a threshold mechanism of action, no such mechanism has been developed for the mouse liver tumours.

The PMRA concurs with the USEPA assessment, as noted in PRVD2013-01: ETU has weak genotoxic potential (USEPA RED 2005). A q_1* approach for cancer risk assessment was presented in PRVD2013-01. This position was recently confirmed in the USEPA Scoping Document in Support of Registration Review (1 June 2015): "ETU is classified as a probable human carcinogen (B2), based on female mouse liver tumours observed in the ETU carcinogenicity study in mice. The ETU cancer potency factor (q_1*) of 0.0601 $(mg/kg/day)^{-1}$ is used to quantitate risk".

2.0 Comments and Responses Related to Dietary Exposure

2.1 Error Correction for the Dietary Monograph

a) Mancozeb was first registered in the United States in 1962, not in 1948. Zineb was registered in 1948.

b) Plant Metabolism: EDI (ethylene di-isothiocyanate) should be changed to EBIS (ethylene bisisothiocyanate).

c) Plant Metabolism: The PMRA indicated that the residue of toxicological concern, ETU, has been found in all the matrices. However, of the plant metabolism studies in potatoes, soybean, sugar beet, tomato and wheat, ETU was only found in the ^{14}C metabolism study on potatoes.

d) All of the processing studies and residue studies were submitted by the MTF, not the EBDC/ETU Task Force.

e) The statements regarding vulcanizer accelerators apply to ETU and not to EBDCs.

PMRA Response (a) to (e)
The PMRA has made these corrections.

f) PMRA #1749197 is listed as an apple processing study. In the list of references, this study is listed as a potato processing study.

PMRA Response
PMRA #1749197 is a potato processing study. The PMRA has made this correction.

g) The current residue definition for mancozeb should be stated as zinc ethylenebis (dithiocarbamate), which is the chemical name of zineb.

PMRA Response:
The PMRA acknowledges that the residue definition for mancozeb per se should be stated as zinc ethylenebis (dithiocarbamate). However, the current residue definition for all EBDCs in all commodities is expressed as manganese and zinc ethylenebis (dithiocarbamate) (polymeric). As noted in section 1.2 of the Science Evaluation Update.

2.2 Comment concerning the use pattern

The registrants noted that they will cancel the uses on greenhouse-grown tomatoes, alfalfa grown for seed, and the cereal seed treatments (barley, corn, flax and oats) and reduce the use patterns for apples, carrots, celery, cucurbits, grapes, onions, pears and field-grown tomatoes. The refined application rates include aerial and ground spray for potatoes at 10 × 1.688 kg a.i./ha with 7-day application intervals (the current label rate is 1.8 kg a.i./ha; no maximum number of applications)

PMRA Response:
Given that certain uses were no longer supported by the registrant, these were not included in the revised dietary assessment, as they are no longer supported and would be removed from the label. For the remaining uses, the changes in the use pattern proposed by the registrants did not result in major changes to the residues used for the dietary exposure assessment, since crop field trials reflecting the reduced use pattern are not available. Therefore, the available market basket survey data were used for cucumber, onion, potato and tomato. For all other crops, residues from the existing crop field trials were used. In addition, a revised EEC value derived from the 2002–2003 EBDC/ETU Task Force US national drinking water monitoring survey was used for the drinking water in the ETU cancer risk assessment. Despite these changes, dietary cancer risks of concern remained (see Appendix VI, Table 1). The dietary assessment was refined further by including only potatoes (potato food forms listed in DEEM-FCID) and drinking water. All other commodities were set at zero ppm. This assessment resulted in a dietary cancer risk of 0.98×10^{-6}, thus, only the potato foliar use is acceptable.

2.3 Comment concerning key uses

Comments were received from many stakeholders, including various grower organizations, that mancozeb is a key component of disease management in many crops, the most important ones being potatoes, apples, pears, grapes and greenhouse-grown tomatoes.

PMRA Response:
As noted in the Science Evaluation Update Section of this document, dietary cancer risks from exposure to ETU through food alone continued to be of concern even when uses identified for cancellation by the registrants were removed from the dietary assessment. Therefore, further refinements were considered for certain key uses (potatoes, apples, pears, grapes and greenhouse-grown tomato seedlings), as identified by various stakeholders. However, all these uses had occupational risks of concern, which could not be refined further, with the exception of foliar use on potatoes. Therefore, the dietary exposure and risk assessments were revised to reflect the potato use only, and, as a result, no cancer risks of concern were identified for ETU.

Hence, the foliar use of mancozeb on potatoes will be maintained in Canada, with the registrant's revised use pattern of a maximum of 10 applications per year at a rate of 1.69 kg a.i./ha with 7-day application intervals.

More information concerning the value of these uses is presented in section 5.0 below.

2.4 Comment concerning the maximum residue limits

Although the American tolerances were previously based on zineb, the tolerances currently listed are based on carbon disulfide (CS_2). Mancozeb tolerances have been recently established for almonds, almond hulls, atemoya, broccoli, cabbage, canistel, cherimoya, cucurbit crop group, custard apple, ginseng, head lettuce, leaf lettuce, peppers, sapodilla, mamey sapote, white sapote, star apple, sugar apple, tangerines (import tolerance only), and walnuts. The American tolerances have been revised to reflect the current listings in 40 CFR 180.176. The current tolerance expression is: "residues of mancozeb (a coordination product of zinc ion and maneb (manganese ethylene bisdithiocarbamate)), including its metabolites and degradates. 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". The MTF supports the PMRA's proposal to express MRLs as mg CS_2/kg to harmonize with the United States, Codex, and the European Union.

PMRA Response:
As noted in section 1.2 of the Science Evaluation Update, the PMRA will revise the residue definition for mancozeb to residues of "mancozeb expressed as carbon disulfide (CS_2)". Another class of fungicides called the dimethyldithio-carbamates (DMDTCs), including ferbam, thiram and ziram, are currently registered in Canada and are also being re-evaluated. Similar to the EBDCs, the PMRA is considering revising the residue definition for the DMDTCs to carbon disulfide. The residue definition and MRLs for the EBDCs and DMDTCs will be considered as whole when the re-evaluations of the DMDTCs are close to completion. Any changes to the MRLs will be published in a Proposed Maximum Residue Limit (PMRL) document for consultation.

2.5 Comment concerning the residue analysis

For EBDCs, it is important to avoid latex gloves during the sampling procedures because latex gloves are treated with thiram, another carbon disulfide generator. Thus, artificial residues of EBDCs can be found if latex gloves are used. The MTF will add that there is some conversion of EBDCs to ETU during the residue analysis. As described in the Fourth Quarter Interim report of the market basket survey, ETU 8-01, October 1, 1990, 0.22% to 8.5% of the EBDC can be converted to ETU during residue analysis. Therefore, the ETU residue reported can be an over-estimate.

PMRA Response
While the PMRA recognizes that some conversion of EBDC to ETU may occur during residue analysis, it is difficult to determine with certainty how much residues of ETU are converted from EBDC during analysis and how much residues are derived from the agricultural use of EBDCs.

2.6 Comment concerning the livestock, poultry, egg and milk residue data

For dairy cattle, the MTF agrees that no residues would be found in edible tissues of livestock due to the feeding and grazing restriction and because of the metabolism study results. For that reason, the percent of crop treated for foods derived from animals, including meats and milk, should be zero for Canada in the dietary assessment.

For Poultry and Eggs, the MTF agrees that no residues would be found in edible tissues of hen due to the feeding and grazing restriction and because of the metabolism study results. For that reason, the percent of crop treated for foods derived from poultry, including meat and eggs, should be zero for Canada in the dietary assessment.

PMRA Response:
As stated in PRVD2013-01, it is expected that no secondary residues would be found in edible tissues of livestock and hen, thus, animal commodities were not included in the revised dietary exposure and risk assessments for mancozeb. The revised assessment included food commodities derived from the use of mancozeb on potatoes only. In addition to the feeding and grazing restriction, potatoes do not represent a significant feed item.

2.7 Comment concerning the crop field trials

a) PMRA stated that **alfalfa** residue trials would be required for the progeny seed harvested from mancozeb-treated seed. For regulatory reasons, the mancozeb registrants will cancel the alfalfa seed treatment use thus this requirement will not apply.

   PMRA Response:
   Since the mancozeb registrants will cancel the alfalfa seed treatment use, the data requirement for the alfalfa residue trials is no longer required.

b) For **wheat**, the American labels had a 26 day PHI until the mid-1990's. The use pattern on the current American labels is: "*Do not apply after Feekes*" growth stage 10.5 (typically 35–45 days), but no less than 26 days. The USEPA has accepted the study *Mancozeb and ETU Residues in Wheat* (PMRA#1748968) as fulfilling the residue guideline requirement.

   PMRA Response:
   The following statement was in the dietary monograph: "*No mancozeb or ETU residues (PMRA#1748968) were found in the wheat grain samples obtained 36 days after the final mancozeb application. However, the US PHI (CDN PHI of 40 days) is 26 days and the current US label directions recommend that no application is to be made within 26 days of harvest.*" Since the PMRA is removing all food uses from the Canadian labels due to risks of concern, except the foliar application of mancozeb on potatoes, the PHI in the crop field trials for wheat was not considered further.

c) Mancozeb is not registered for use on **carrots** in the US. The revocation of the use in the United States described in the EBDC Position Document (PD 4) was and is final. Carrots have not been on the American labels since 1992. For some reason USEPA has not cancelled the carrot tolerance, but there is no American registration.

PMRA Response:
The PMRA acknowledges this input and notes that this information was taken into consideration during the process of further refining the dietary risk assessment by setting residues in carrots imported from the United States at zero ppm. However, the dietary assessments had no cancer risks of concern only when all food uses were removed, except potatoes.

d) Mancozeb does not have any registrations for use on **celery** in the United States. The revocation of the use in the United States described in the EBDC Position Document (PD 4) was and is final. Celery has not been on the American labels since 1992. For some reason USEPA has not cancelled the celery tolerance, but there is no American registration. Although the registrants submitted data to support a reinstatement, that request was withdrawn by the registrants prior to any action from the USEPA. There is no interest in reinstating the celery use at this time or in the foreseeable future. No regional or time-limited tolerance was established.

PMRA Response:
The PMRA acknowledges this input and notes that this information was taken into consideration during the process of further refining the dietary risk assessment by setting residues in celery imported from the United States at zero ppm. However, the dietary assessments had no cancer risks of concern only when all food uses were removed, except potatoes.

e) PMRA indicated that acceptable field **corn** grain data (PMRA #1748970) was received from the EBDC/ETU TF. The MTF noted that that the report was submitted by the MTF. In addition all residue studies in Section 6.7.1 “Supervised residue trial study (DACO 7.4.1)” of the dietary monograph were submitted by the MTF.

PMRA Response:
As noted in response to Comment 2.1(d), the PMRA acknowledges the above and that all residue studies mentioned in Section 6.7.1 “Supervised residue trial study (DACO 7.4.1)” of the dietary monograph were submitted by the MTF.

f) PMRA indicated that mancozeb is registered for application on **cotton** in the United States. The MTF noted that the use of the foliar application on cotton was cancelled years ago. The only remaining use is the seed treatment of cotton.

PMRA Response:
The PMRA acknowledges this input; however, the dietary assessments had no cancer risks of concern only when all food uses were removed, except potatoes.

g) The USEPA has established a **cucurbit crop group** tolerance of 2 ppm based on carbon disulfide equivalents.

PMRA Response:
While discrepancies in the proposed American Tolerances for **cucumber**, **melon** and **summer squash** were noted in the dietary monograph, the PMRA acknowledges that the USEPA has established a cucurbit crop group tolerance of 2 ppm based on carbon disulfide equivalents.

h) PMRA indicated in the dietary monograph that the petitioner should provide mancozeb residue trial data in order to set an appropriate MRL in/on **ginseng**. The MTF noted that mancozeb is now also registered for use on ginseng in the United States with a tolerance of 1.2 ppm based on carbon disulfide equivalents and that residue data are included with their comments.

PMRA Response:
As noted in the Science Evaluation Update section of this document, dietary cancer risks from exposure to ETU through food alone continued to be of concern when uses identified for cancellation by the registrants were removed from the dietary assessment. Further refinements were considered; however, the dietary assessments had no cancer risks of concern only when all food uses were removed, except potatoes. Therefore, notwithstanding the crop residue data submitted for ginseng by the MTF, ginseng will be removed from mancozeb product labels.

i) While not all of the residues represented Canadian regions, there were many cases where the residue trials were generated in the Northern United States under conditions such as climate and geography similar to that of Canada.

PMRA Response:
The PMRA acknowledges this input and notes that residues from the available field trial data were used in the initial dietary assessments for the crops for which market basket survey data were not available.

j) PMRA indicated that residue decline studies on file for apple, grape, oat, potato, sugar beet and summer squash were conducted in the United States and might not be representative of the Canadian use conditions. The MTF noted that many of the studies represented Canadian use conditions and submitted, with their comments, residue decline studies on sweet corn, onion, summer squash, winter squash, papaya, pear, field corn, cranberries, cucumber, grape and celery.

PMRA Response:
The PMRA acknowledges receipt of the studies submitted by the MTF. As noted in the Science Evaluation Update Section of this document, the dietary assessments had no cancer risks of concern only when all food uses were removed, except potatoes. Since these crops will be removed from Canadian labels, the residue decline studies will not be considered further at this time.

2.8 Comment concerning processed food/feed

a) While there was variability in some of the processing studies, the variability is not as great as stated by PMRA. The apple example is not typical. As mancozeb residues are reduced during washing, the washing factor of 2.4 found in one of the studies is an unexplained anomaly.

PMRA Response:
While the PMRA acknowledges that the apple example may not be typical, it has been determined that the orchard uses, including apple, have occupational health risks of concern. As a result, the PMRA will cancel the use of mancozeb on apples.

b) PMRA stated that they followed the OECD recommendations for the Dietary Exposure Assessment. However, the OECD guidelines were not entirely followed.

PMRA Response:
The extent of variability of processing factors when multiple processing studies were conducted on a crop prompted the PMRA to use the resulting maximum processing factor, instead of using the median value recommended by OECD guidelines, in the dietary assessment presented in PRVD2013-01. This approach was used by the PMRA in an effort to avoid underestimating residue and to ensure human health protection. Nevertheless, since apple and grape had occupational health risks, they will be removed from Canadian labels.

c) Mancozeb is reduced through typical industrial/commercial/consumer practices. This has been demonstrated in studies on apple, grape juice, carrots and celery measuring the effects of commercial processing on field-treated commodities.

PMRA Response:
Although the PMRA noted that residues concentrate in some processed fractions (for example, potatoes processed to flakes and flour), it recognized that the processing studies indicate that mancozeb and more generally the EBDC residues in food commodities are reduced through typical industrial, commercial and consumer practices such as washing and peeling. The PMRA had used processing factors to the extent possible in the initial dietary assessment. For the current assessment, as noted in the Science Evaluation Update Section of this document, the dietary assessments had no cancer risks of concern only when all food uses were removed, except potatoes. Therefore, the PMRA will maintain only the use of mancozeb on potatoes while all other food uses will be removed from mancozeb product labels.

d) The potato processing study titled *Determination of the Magnitude of the Residue Due to Mancozeb and ETU in Potato Processed Fractions* (PMRA #1749197) was accepted by USEPA and no additional potato processing studies are required at this time.

PMRA Response:
The PMRA acknowledges this input and notes that no additional potato processing studies are required at this time.

e) In the dietary monograph, PMRA mentioned a requirement for cotton seed processing studies. However, the foliar application of mancozeb to **cotton** was cancelled.

PMRA Response:
Since the foliar application of mancozeb to **cotton** was cancelled in the United States, the PMRA agrees that requirements for cottonseed processing studies, referred to in the dietary monograph, are no longer applicable.

2.9 Comment concerning the conversion of mancozeb to ETU during processing

PMRA's dietary assessment over-states the conversion of mancozeb to ETU during cooking. The MTF submitted additional information.

PMRA Response:
While the equation used by the PMRA to estimate the conversion of mancozeb to ETU during cooking may overestimate the ETU residues, the PMRA wanted to ensure that residues would not be underestimated. For the determination of total ETU, the PMRA considered the sum of the ETU present in the respective raw agricultural commodity and the potential ETU transformed in vivo in the human body from the ingested mancozeb residue according to the following formula:

$$ETU_{tot} = (ETU_{RAC} * F_{ETU}) + (Mancozeb_{RAC} * F_{invivo} * F_{Mancozeb}) + (Mancozeb_{RAC} * F_{EBDC-ETU} * F_{Mancozeb})$$

Where,
The transformation factor $F_{in\ vivo}$ = 7.5% w/w.
F_{ETU} = processing factor of ETU to ETU in the transformation process.
$F_{Mancozeb}$ = processing factor of mancozeb in the transformation process.
$F_{EBDC\text{-}ETU}$ = processing factor of mancozeb (EBDC) to ETU in the transformation process.
$Mancozeb_{RAC}$ = concentration of mancozeb in the raw agricultural commodity.
ETU_{RAC} = concentration of ETU in the raw agricultural commodity.

The PMRA acknowledges the information provided by the MTF regarding the conversion of mancozeb to ETU during cooking for spinach, carrots, potatoes, tomatoes and cereals. However, as noted in the Science Evaluation Update Section of this document, the dietary assessments had no cancer risks of concern only when all food uses were removed, except potatoes. Therefore, the PMRA will maintain only the use of mancozeb on potatoes while all other food uses will be removed from Canadian labels.

2.10 Comment concerning the market basket survey

The market basket survey was conducted from 1989–1990, before there was a restriction on the number of applications, when there was a shorter pre-harvest interval for many crops, and when the application rates were higher for many crops. Therefore, the market basket survey data for many crops, especially potatoes, is representative of current Canadian use patterns. For potatoes, the use pattern in the US at the time of the market basket survey was a maximum of 1.6 lb a.i./acre (1.8 kg a.i./ha) with unlimited number of applications and a 0 day pre-harvest interval. The current Canadian use pattern has a comparable application rate and a one day pre-harvest interval.

PMRA Response:
Based on the above comment, the PMRA agrees that the use of the United States market basket survey may be representative of the current Canadian use pattern, and may also address the MTF proposed refined use pattern in Canada for the foliar application of mancozeb on potatoes at 10 × 1.69 kg a.i./ha with 7 day application intervals and a one day pre-harvest interval. Nevertheless, uncertainty in the residue estimates derived from the 1989–1990 remains, as eating habits and food availability are likely to have changed since the survey was conducted.

2.11 Comment concerning the percent crop treated

Regarding the percent crop treated data for countries other than Canada and the United States, PMRA conservatively assigned 100% crop treated (%CT) for imported commodities. It is highly improbable that all imported crops are treated with mancozeb. Therefore, the dietary contribution of mancozeb and ETU residues from imported crops are most likely over-estimated. It would take a considerable amount of time and resources to determine the actual %CT for the imported crops. Thus, the MTF is not providing any refinements for imports. The MTF wishes to point out that 100% CT for the non-US imported crops is highly conservative, except in the case for bananas, papayas, and mangoes. It is highly unlikely that all other imports would have been treated with mancozeb.

PMRA Response:
While the PMRA recognizes that it is unlikely that all imported crops are treated with mancozeb, it is the policy of the PMRA to use a 100% estimate whenever percent crop treated information is not available. This is generally the case for imported commodities from non-American countries. Although this approach may overestimate residues from some imported crops, data are not available to use values that are lower than the default assumption of 100% crop treated.

2.12 Comment concerning the dietary exposure and risk assessments

a) PMRA conducted acute, chronic and cancer dietary risk assessments 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. The MTF revisions to the dietary risk assessment were conducted using the current DEEM-FCID Version 3.16, which uses 2003–2008 food consumption data from the United States Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What we Eat in America (NHANES/WWEIA).

   PMRA Response:
   The PMRA's revised acute, chronic and cancer dietary exposure and risk assessments were conducted using the latest version of the Dietary Exposure Evaluation Model – Food Commodity Intake Database™ (DEEM-FCID™; Version 4.02, 05-10-c) program which incorporates food consumption data from the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) dietary survey for the years 2005-2010 available through the Centers for Disease Control and Prevention's National Center for Health Statistics.

b) The MTF conducted cancer and chronic risk assessments for ETU in drinking water using the upper bound residue of 0.21 ppb from the United States drinking water survey. The assessed chronic exposure of ETU from drinking water was a maximum of 1.9% of the ADI for all relevant subpopulations, and is below the level of concern. Using a value of 0.21 ppb, the ETU theoretical cancer risk is 2.7×10^{-7} and is not of concern.

In the ETU acute drinking water exposure the estimated concentration of 9.2 ppb from apple applications was based on PRZM/EXAMS modeling. The acute assessment is for females aged 13 to 49 years of age and the estimate for ETU in drinking water was 7% of the ARfD and is not of concern.

PMRA Response:
Based on the targeted nature of the EBDC/ETU Task Force United States National Drinking Water Monitoring Survey, the PMRA used the maximum ETU residue value of 0.57 ppb to assess cancer risk from exposure to ETU through drinking water in the current assessment. Using a value of 0.57 ppb, the revised cancer risk from exposure to ETU through drinking water alone is 0.69×10^{-6} and is not of concern. As indicated in PRVD2013-01, acute and chronic risks from exposure to ETU through drinking water are not of concern.

c) The MTF provided comments regarding possible conservatisms in the dietary risk assessment and the acceptability of cancer risk. The MTF also referred to the USEPA's assessment of mancozeb and their policy for cancer risk assessment. Overall, the MTF considers the dietary exposure assessment conducted by PMRA to be conservative. The MTF conducted dietary risk assessments (food and drinking water) and provided the basis of their calculations. Their results indicated that the cancer risk from exposure to ETU from food is 1.85×10^{-6} and from food and drinking water is 2.12×10^{-6}. The MTF stated that statistically, these risks are comparable to 1×10^{-6} and are in the negligible risk range. Therefore, the risks meet Canada's standard that there is a reasonable certainty that "*no harm to human health, future generations or the environment will result from exposure to or use of the product, taking into account its conditions or proposed conditions of registration*." The MTF encouraged PMRA to follow the USEPA's conclusion that risks falling within the negligible range meet the standard that there is a reasonable certainty of no harm from the use of a pesticide. Such an approach is significantly and statistically defensible. With such an approach, the aggregate theoretical cancer risk from ETU is not of concern. Historically, USEPA has defined the risk of 1×10^{-6} as reflecting a range rather than a single specific number. There is no "bright line" in the cancer risk assessment because of the uncertainties in estimating the cancer potency factor (q_1*). USEPA has defined negligible risk to include risks up to 3×10^{-6}. USEPA's policy is reflected, for example, in a recent Final Rule establishing new tolerances for Mancozeb (*Federal Register Volume 78, Number 142, July 24, 2013, page 44454*). In this action, USEPA calculated a theoretical aggregate cancer risk of 3×10^{-6} for ETU. In describing the risks, although the mancozeb risk assessment was considered highly refined, USEPA acknowledged the conservatism built into the risk estimates for the calculation of the cancer potency factor (q_1*) and the conservatism maintained in the exposure assessment. Accordingly, EPA has concluded the cancer risk for all existing mancozeb uses and the uses associated with the tolerances established in this action fall

within the range of 1×10^{-6} and are thus negligible. In summary, the negligible risk for the ETU theoretical cancer risks should be considered as a range up to 3×10^{-6}. Conservatism is maintained in the exposure for the mancozeb risks described in the mancozeb PRVD because for example:

- field trial residues were used for many crops;
- PMRA assigned 100% crop treated for non-United States imported crops, while it is unlikely that 100% of many crops would have been treated with mancozeb;
- the processing factors do not take into account all of the operations involved between the field and grocery store, for example the effects of packaging and hydrocooling seen in carrot and celery studies that reduced residues significantly might be seen in other crops as well.

PMRA Response:
In PRVD2013-01, the dietary risk assessment was conducted based on currently registered uses of mancozeb. Cancer risks from food only and drinking water only were 4.3×10^{-6} and 3.7×10^{-6}, respectively. Before considering refinements to the food assessment, the PMRA first revisited the drinking water EEC for ETU. The EEC was revised from 2.9 ppb to 0.57 ppb, based on the 2002–2003 EBDC/ETU Task Force United States national drinking water monitoring survey. This refined EEC is based on Canadian relevant ecozone water monitoring data and is the peak detection from the dataset. The vast majority of the data from the EBDC/ETU Task Force United States survey is from California and Florida, which are ecozones that are not equivalent to any regions in Canada and are not considered to be suitable for use in a Canadian risk assessment. The MTF used a value of 0.21 ppb in their cancer risk assessment, which is from a sample taken in Florida. The PMRA limited data consideration to samples taken from states that are considered to be equivalent in terms of ecozones to Canadian conditions (Maine, Michigan, Minnesota and New York). The MTF excluded the 0.57 ppb value (from a sample taken in New York), classifying it as an outlier. On review of the dataset, the PMRA concluded that the 0.57 ppb value is not an outlier and therefore considered it in the assessment. The use of a peak water monitoring detection for a chronic risk assessment is a conservative approach. Using the 0.57 ppb value as the EEC in the drinking water assessment puts the cancer risk at 0.69×10^{-6}, which is not of concern. The choice of EEC to be used in the risk assessment (0.57 ppb chosen by the PMRA or 0.21 ppb chosen by the MTF) does not change the conclusion, which is that there is no risk of concern. The PMRA concedes that there is a great deal of conservatism in the assessment given the use of the peak detection value, but as the conclusion is that risks are not of concern, additional refinement is not needed. ×

In terms of the risk assessment for food alone, as presented in PRVD2013-01, this was considered a refined assessment since it was based on residues from the market basket survey, and incorporated percent crop treated data and percent domestic/import food supply information. The PMRA agrees that some inputs in the initial dietary assessment may overestimate ETU residues, including the use of crop field trial data for commodities not included in the market basket survey, and the assumption of 100% crop treated for imported commodities from non-American countries. Generally, the use of chemical-specific processing factors and conversion factors is considered a refinement. In the case

of mancozeb and ETU, these data were highly variable and therefore, were used in a manner not to underestimate potential residues. Nonetheless, the use of these chemical-specific factors still represents a significant refinement in the exposure assessments. Therefore, on balance, the PMRA considers the dietary exposure assessment to be refined. The PMRA also considers the dietary assessment to be uncertain due to the age of the market basket survey data.

Since data were not available to further refine or address some of the uncertainties identified in the initial assessment for food alone, consideration was given to removing uses of mancozeb. Some uses had occupational risks of concerns, which had been proposed for cancellation in PRVD2013-01. These uses included seed treatment for barley, corn, flax, oat wheat and potato seed-pieces; application on orchard crops including apples and pears; and application on grapes and greenhouse tomatoes. During the consultation period, the registrants expressed intent to cancel uses on greenhouse-grown tomatoes, alfalfa grown for seed, and the cereal seed treatments (barley, corn, flax and oats) and reduced the use patterns for apples, carrots, celery, cucurbits, grapes, onions, pears and field-grown tomatoes.

Despite these mitigations, the overall occupational risk conclusions did not change for potato seed piece treatment, apples, pears and grapes. When the domestic uses identified for cancellation by the registrant and/or due to occupational risks of concern were removed from the dietary risk assessment, the ETU cancer risk from food and drinking water was 3.9×10^{-6}.

In terms of acceptability of cancer risks, as noted in the PMRA Science Policy Notice SPN2000-01, A Decision Framework for the Risk Assessment and Risk Management in the Pest Management Regulatory Agency, this is a risk management decision that cannot rely exclusively on a numerical standard, but needs to take into consideration all the factors that influence risk. When the majority of inputs in the cancer risk assessment are conservative or are overestimates, cancer risks above the threshold of 1×10^{-6} (that is, one in a million) may be considered acceptable. For ETU, however, as noted above, the PMRA considers the dietary assessment to be refined overall with some uncertainties. As such, the cancer risk of 3.9×10^{-6} was considered unacceptable, and further refinements were pursued.

For this stage of refinement, the PMRA removed all crops from the dietary assessment, except those crops deemed key by various stakeholders such as the Canadian Horticulture Council, other grower groups and provincial agricultural/food departments. These crops were potatoes, apples, pears, grapes and greenhouse tomatoes. Since all these crops had occupational risks of concern, with the exception of foliar application on potatoes, the final dietary risk assessment included only potato food forms and drinking water. All other commodities, including imports, were set at zero ppm. This final dietary assessment resulted in a cancer risk of 0.98×10^{-6} (or 1×10^{-6} when rounded), which was considered acceptable.

3.0 Comments and Responses Related to Occupational Exposure

3.1 Comment concerning the potato seed piece treatment mitigation

Registrants, through the MTF, indicated that they supported any mitigation measures required to maintain registration. However, growers stated that the interim mitigation measures identified in the PRVD were not feasible and provided use data to support this position.

PMRA Response:
The occupational risk assessment was updated to incorporate the revised toxicological reference doses; however, this did not change the risk conclusions for potato seed piece treatment. The level of mitigation required to address the occupational risks of concern for the potato seed piece treatment use is not considered to be agronomically feasible. However, there are no risks of concern from the foliar use on potato.

3.2 Comment concerning the planting treated vegetable seed

Vegetable growers with small acreages may not be able to comply with the statement “Do not plant treated seed by hand.” These growers often start their seeds as plugs in a polyhouse. These would be planted by hand. If vegetable seeds come treated with mancozeb, the package should specify that the seeds have been treated and list the name of the pesticide(s).

PMRA Response:
Mancozeb is not registered for treatment of vegetable seeds in Canada, nor for imported treated vegetable seeds.

3.3 Comment concerning the availability of exposure data

One commenter stated that the re-evaluation of mancozeb appears to have been conducted without adequate data to review, specifically for the potato seed piece treatments.

PMRA Response:
In order to assess potential risks of pesticide use to the health of Canadians, the PMRA must be able to estimate their potential exposure to pesticides and any pesticide transformation products that might be of toxicological concern. The main determinates in the exposure assessment are the properties of the pesticide and the characteristics of the exposed population. The combined information from exposure factors and pesticide specific data allows for the estimation of the magnitude, frequency, and duration of pesticide exposure to the population. Default exposure factors are used in combination with pesticide specific data to estimate exposure to the population. The PMRA requested chemical-specific data from the registrant to refine the exposure assessment, including the potato seed piece treatment use. No data were received to revise the occupational assessment of this use. However, there was extensive stakeholder engagement during the consultation period including on this aspect.

3.4 Comment concerning the consideration of risk mitigation measures and refined use information

Risk mitigation measures and use pattern information such as reducing the number of applications, limiting the area treated per day, increased PPE and engineering controls were provided by the registrants and grower groups.

PMRA Response:
The updated occupational risk assessment for mancozeb involved detailed analyses of chemical-specific use information but still resulted in risks of concern for some uses, even when considering all possible refinements and mitigation. The impact of additional PPE and engineering controls was assessed, as were refined application rates, number of applications, area treated per day, and limiting the amount of active ingredient handled per day.

The use information provided from a variety of stakeholders confirmed the use-pattern related assumptions and inputs that were used in the risk assessment. Risks of concern were identified even with lower numbers of applications at the lowest rates. Despite the proposed refinements and mitigation measures that were factored into the assessment, the overall risk conclusions remained consistent with those presented in PRVD2013-01. Continued registration of mancozeb on potato seed pieces, apples, pears, and grapes cannot be supported based on occupational exposure concerns. When both the dietary and occupational risk assessments were considered, only the potato foliar use was found to be acceptable for continued registration of mancozeb.

3.5 Comment concerning the postapplication personal protective equipment (PPE)

Postapplication PPE was proposed to greatly decrease exposure during postapplication activities to the point where continued registration is expected. The proposed restricted-entry intervals (REIs) were not considered to be feasible and it was suggested that postapplication PPE could decrease the REIs to the point where they would become agronomically feasible.

PMRA Response:
Studies that are used currently to estimate postapplication worker exposure are based on workers wearing long-sleeved shirts, long pants, socks and footwear. It is also understood that many postapplication workers may wear gloves for their own personal comfort or for food safety purposes (to reduce food contamination). However, there are no reliable data to indicate the degree of protection gloves may provide to postapplication workers, or conversely, the extent that gloves may enhance exposure under certain conditions.

Before the PMRA can estimate risk for workers wearing gloves or other PPE, worker exposure studies comparable to those currently used by the PMRA are required. Studies that are currently used are discussed further in the *Regulatory Proposal PRO2014-14 Updated Agricultural Transfer Coefficients for Assessing Occupational Postapplication Exposure to Pesticides*. Most, if not all, studies conducted by the Agricultural Re-entry Task Force (ARTF), submitted by registrants, or available in the scientific literature and used to determine the transfer coefficients used in the PMRA's occupational risk assessments did not include personal protective equipment. Gloves may be worn, but they function as dosimeters to measure hand exposure, rather than for the purpose of reducing exposure as a result of protection from the glove.

Some available studies suggest that exposure actually increases when wearing gloves (Brouwer, 2000; Boman et al., 2005; Garrigou et al., 2011; Graves et al., 1995; Keifer, 2000; Rawson et al., 2005).

In addition to the lack of scientific studies to estimate postapplication exposures while using specific PPE, the feasibility of postapplication workers wearing PPE must also be considered. As such, compliance, enforcement, training, regulatory jurisdiction, labeling, and communication are all aspects that need to be in place.

The PMRA is actively exploring these issues, including the feasibility of obtaining postapplication exposure studies for workers wearing certain PPE, for the purpose of estimating risk under these types of conditions.

3.6 Comment concerning the transfer coefficients for minor use crops

It was noted in PRVD2013-01 that PMRA used transfer coefficients for sweet potato as a surrogate to estimate exposure for ginseng. The Ontario Ministry of Agriculture and Food and Ministry of Rural Affairs (OMAF and MRA) indicated they would be willing to discuss with PMRA as to whether sweet potatoes is an appropriate surrogate for ginseng in the risk assessment.

PMRA Response:
The PMRA welcomes ongoing dialogue with OMAF and MRA on developing appropriate exposure factors for minor use crops.

3.7 Comment concerning the postapplication exposure in orchards

Growers commented that postapplication exposure is expected to be much lower in modern orchard structures.

PMRA Response:
The PMRA acknowledges that modern orchard structures will have different exposure profiles from standard plantings. Where possible, these differences are considered in the postapplication assessment, but before the PMRA can estimate risk for workers in high density orchards, worker exposure studies comparable to those currently used by the PMRA are required. In the case of mancozeb, no new chemical-specific data were available to revise the postapplication assessment for orchard activities. Studies that are currently used are discussed further in the *Regulatory Proposal PRO2014-14 Updated Agricultural Transfer Coefficients for Assessing Occupational Postapplication Exposure to Pesticides*.

The PMRA is currently exploring this issue, and the means to estimate worker risks in modern orchard settings. This includes the feasibility of obtaining chemical-specific postapplication exposure studies for workers in high density orchards, for the purpose of estimating risk under these conditions. Alternatively, transfer coefficients reflective of modern orchard structures could be developed from new worker exposure studies with concurrent dislodgeable foliar residue (DFR) data, should such studies become available.

3.8 Comment concerning the REI for orchard thinning

The proposed restricted entry intervals of 54–62 days for orchard thinning are not agronomically feasible. REIs of 2 to 3 weeks may be feasible.

PMRA Response:
The occupational risk assessment was updated to incorporate the revised toxicological endpoints; however, this did not change the risk conclusions for postapplication workers in orchards. The level of mitigation required to address the occupational risks of concern for the orchard postapplication workers is not considered to be agronomically feasible.

3.9 Comment concerning the dermal absorption

It was felt that the dermal absorption value used for ETU (45%) was too high based on the amount of transfer/absorption occurring in orchards along with the use of protective equipment. It was suggested that a dermal absorption value of 29% be used for ETU based on the fact that skin bound residues should not be included in the dermal absorption value since it was shown in the dermal absorption study that dermal absorption plateaus by day 2 and is completed by day 7.

PMRA Response:
The PMRA occupational postapplication exposure and risk assessment considered the risk from both mancozeb and ETU. In order to be considered acceptable, both the mancozeb and ETU risk assessments need to demonstrate risks are not of concern. In general, exposure from mancozeb was of primary concern in the occupational assessments, rather than ETU. In terms of the dermal absorption value for ETU, the scientific evidence available to the PMRA supports a value of 45%.

3.10 Comment concerning the dislodgeable foliar residue

There were concerns that decay of residues were not taken into consideration when determining postapplication exposure. It was suggested that there would be a dilution of ETU or mancozeb residues on the outer leaves as the acreage dosage is dispersed to cover all surfaces of leaves, twigs, and trunks.

PMRA Response:
When calculating dislodgeable foliar residues, daily dissipation (i.e., decay) of residues and initial residues are taken into consideration. Study data was submitted for mancozeb and ETU on several different crops. These data were used to calculate a chemical-specific initial deposited residue and daily dissipation rate for mancozeb and ETU for all crops.

3.11 Comment concerning the cancer risk estimates

There were concerns that the cancer risk calculated was unreasonably high. Suggestions to mitigate cancer exposure included decreasing the number of applications to six per year and addition of postapplication PPE along with consideration of modern orchard structure to virtually eliminate postapplication exposure.

PMRA Response:
The occupational risk assessment and mitigation measures considered exposures to both mancozeb and ETU. The cancer risk from ETU was not always the primary risk driver in the occupational assessment. For postapplication workers, the required REIs were determined from both the ETU and mancozeb assessments. As such, the suggested refinements to the cancer risk assessment would still not be sufficient to change the overall risk conclusions presented in PRVD2013-01 when occupational risks were identified as a result of exposure to mancozeb.

The occupational cancer risk assessment for ETU considered exposures to workers that may occur over the lifetime, and used typical rather than high-end exposure values, so as not to over-estimate exposure and risk.

3.12 Comment concerning the cancer risk estimates and multiple chemical exposures

Other commenters such as Earth Action stated that the calculated cancer risk was unreasonably low because individual exposure scenarios may exceed the estimates of 'high-end' exposure and that exposure due to multiple chemicals was not considered.

PMRA Response:
As noted above, cancer risk assessments consider the potential lifetime exposure to a carcinogen. The exposure estimates used are based on the typical or average daily levels, rather than a high-end point estimate, as this is more representative of the actual lifetime exposure for any individual. Cancer risk assessments for the potential exposures of both workers and the general population to ETU were conducted.

Aggregate and cumulative risk assessments were conducted and are presented in Sections 1.4 and 1.5 of the Science Evaluation Update Section. These evaluations took into account the additional information provided during the consultation period for PRVD2013-01, as well as the mitigation measures to protect human health.

With respect to multiple chemical exposures, cumulative assessment is aimed at identifying the human health risks associated with co-exposures to two or more pesticides that cause a common toxic effect(s) by the same, or essentially the same, sequence of major biochemical events (that is, a common mechanism of toxicity). Concurrent exposure routes (oral, dermal, inhalation) and pathways (for example, diet, drinking water, residential use) to pesticides that share a common mechanism of toxicity are assessed to determine the potential for cumulative effects, based on the likelihood that people may be exposed to more than one of these pesticides at the same time. Cumulative assessment is undertaken to explore the possibility of whether low-level exposures to specific multiple pesticides that cause a common toxic effect by a common mechanism, could lead to the same adverse health effect as would a higher level of exposure to any of the pesticides individually. Additional details on the PMRA cumulative risk assessment framework can be found in the Science Policy Note, SPN2018-02, *Cumulative Health Risk Assessment Framework.*

3.13 Comment concerning the bystander exposure to mancozeb

There were concerns that people in Prince Edward Island (PEI) would have a higher than average level of exposure due to pesticides lingering in the air in areas that are not near agricultural sites. The commenter stated that there are studies that show that pesticides remain in

the air at all times. There were also concerns regarding exposure in residential areas adjoining sprayed fields. There were concerns that ETU itself was not measured in the study used to determine bystander inhalation exposure.

There were also concerns that dietary exposure does not substitute for assessing inhalation exposure.

Concerns were raised regarding PPE being required for applicators, when bystanders and adjoining residential areas could be exposed at the same level and would not have protective equipment. There was a question regarding spray drifting into adjoining residential areas and how exposure in these areas would differ from postapplication worker exposure.

PMRA Response:
The PMRA considered all relevant routes and pathways of bystander exposure including dermal, inhalation, and dietary exposure to mancozeb.

In the case of mancozeb, reliable air monitoring data were available that measured air concentrations of mancozeb in areas bordering fields in PEI where pesticide application occurred. Peak air monitoring data, collected at the edge of a potato field during spraying, was used to determine inhalation exposure to bystanders. Using this information, the inhalation risk assessment did not show any risks of concern (i.e., the lifetime cancer risk for bystanders was well below 1×10^{-6}). Metabolic conversion data of mancozeb to ETU was used to determine ETU exposure from mancozeb. A lifetime cancer risk that is at or below 1×10^{-6} (one in a million) usually does not indicate a risk concern for the general population when exposure occurs through pesticide residues in the air, and to otherwise unintentionally exposed persons.

Dermal exposure to sprays that have drifted into residential areas are generally much lower than a worker treating fields or entering a treated field, as residues will be higher and activity will be more intense for application and postapplication workers. There are no risks of concern from the foliar use on potato.

4.0 Comments and Responses Related to the Environmental Assessment

4.1 Comment concerning the proposed advisory statements

The PMRA proposes to add warnings to the label indicating mancozeb is toxic to aquatic organisms, small wild animals, birds and beneficial organisms. Horses and farm animals graze in pastures around sprayed potato fields. They not only inhale mancozeb but they eat pasture grasses and drink water contaminated with spray drift. Pets, especially chained dogs, can be seen in yards next to fields with sprayers operating.

PMRA Response:
The mammalian risk assessment considers small mammals in the weight range of 15 to 1000 g; effects on much larger animals such as horses, livestock and pets, would be negligible. Although the mammalian risk assessment shows that mancozeb may pose a potential reproductive risk to small mammals, this risk is expected to be low based on the consideration of additional information. The chronic mammalian risk assessment was based on the most sensitive endpoint reported for reduced body weight in rat offspring (NOEL = 2.5 mg a.i./kg body

weight/day); in this study, the end-use product Penncozeb was used. Consideration was also given to the results of a technical grade active ingredient-based chronic reproductive study in which no effects were observed at the highest dietary test concentration (NOEL ≥69 mg a.i./kg body weight/day) in offspring of the same rat species and following the same testing protocol. The NOEL for reproduction in both studies was greater than the highest dietary concentration tested (NOEL >110 and >69 mg a.i./kg body weight/day). Based on the collective results from both studies, the risk to mammals is anticipated to be low. The reduction of the potato application rate will further reduce the risk to birds and mammals.

4.2 Comment concerning the proposed buffer zones

The PMRA proposes that no ground spraying of potatoes should take place in a buffer zone at least 25 metres wide when a freshwater body is less than 1 metre deep, and 5 metres for a freshwater body deeper than 1 metre. For saltwater, buffer zones are only 5 meters for depths less than 1 metre and 2 metres for depths greater than 1 metre. The shellfish industry is important to PEI and depends on clean water in estuaries, as do other living things in estuaries. All streams eventually flow into estuaries, often carrying a heavy burden of pesticides and nitrates from potato fields. Buffer zones need to be at least 25 metres in all cases, and realistically much wider to afford better protection.

PMRA Response:
There are two main ways that pesticides can enter water bodies 1) spray drift and 2) runoff from field of application. The PMRA's spray drift buffer zones for aquatic habitats are designed to protect all organisms in the body of water that may receive spray drift from the effects of mancozeb. These spray buffer zones are only required when the body of water is downwind of the site of application. The buffer zones are calculated based on the estimated concentration of the chemical in a water body following drift during application in relation to the toxicity endpoint. The spray buffer zone represents the distance at which drift is not expected to pose risks of concern to aquatic organisms.

To help reduce potential impacts from pesticide runoff, the PMRA requires runoff mitigation statements on product labels, including the recommendation of maintaining a vegetative filter strip between the treated area and the edge of the water body. In 2000, the Province of Prince Edward Island (PEI) introduced legislation which mandated vegetative filter strips for various land uses, including agricultural crops. The legislation required all agricultural fields that border water courses to maintain a 10-metre vegetated filter strip along the water edge. The minimum filter width was increased to 15 metres in a 2008 amendment to PEI's *Environmental Protection Act*. Fields with steeper slopes (i.e., >5%) within 50 meters of the upland boundary of the 10-metre filter and having no other mitigating management practices in place are required to have a 20-metre vegetative filter strip.

4.3 Comment concerning the following proposed label statement:

> "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."

This same warning is on other pesticide labels including Admire (imidacloprid) which has been used extensively on PEI potatoes for about 15 years. PEI's soil is sandy, the bedrock is fractured sandstone, the water table is generally shallow and PEI is 100% dependent on groundwater for drinking water. Government figures show virtually all PEI groundwater is contaminated by nitrates mainly from potato fields, so its clear chemicals percolate into the water table easily. Yet Admire is used without impunity. There is no expectation that this new warning will prevent mancozeb from being used in conditions not allowed by the label. A New Brunswick Department of Health study (Ecobichon et al. 1985) sampled 100 wells in a potato-growing area and found ETU in every well. ETU was found in some wells 6 months after the last application.

PMRA Response:
The information available to the PMRA indicates that mancozeb is mobile and has the potential to leach to groundwater. The PMRA recognizes groundwater as an important water source for many Canadians and as such, it is considered in the human health risk assessment. The label statement is added to the product label to inform users of the potential leaching concern. The PMRA conducts a national assessment and issues a product label that applies to the entire country. Individual provinces have their respective pesticide regulations and can impose additional restrictions to the use of pest control products. These concentrations are then used in health and environmental risk assessments and the acceptability of risks associated with the pesticide are evaluated. For mancozeb, Canadian water monitoring data shows that mancozeb does not reach levels in groundwater that would present a concern to human health.

4.4 Comment concerning manganese contamination

The PMRA says: The degree to which mancozeb application would contribute to drinking water manganese concentrations is not known. There is no indication the PMRA is requesting more information about manganese contamination from mancozeb. The risks associated with manganese in groundwater are largely unknown, however studies with Quebec children found manganese in drinking water is significantly associated with decreased IQ (Mergler *et al*. 2010).

PMRA Response:
The exposure to manganese from drinking water that would occur from mancozeb use was considered in PRVD2013-01 (see Section 3.4.2). 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 on health-based effects.

Median background concentrations of manganese in surface and groundwater are lower than guideline concentrations, with exceedances 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.

4.5 Comment concerning endocrine disruption

On endocrine disruption effects, the re-evaluation document states: 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 endocrine 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 Environmental Health News, Dr. Laura Vandenberg says: There truly are no safe doses for chemicals that act like hormones, because the endocrine system is designed to act at very low levels https://academic.oup.com/edrv/article/33/3/378/2354852. Mancozeb is listed as an endocrine disruptor by the European Union, Dr. Theo Colborn, and Charles Benbrook (Growing Doubt: A Primer on Pesticides Identified as Endocrine Disruptors and/or Reproductive Toxicants, National Campaign for Pesticide Policy Reform, 1996).

On thyroid effects, the re-evaluation document states: 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. Mancozeb is well studied for thyroid effects. The United States Environmental Protection Agency states: the thyroid is the target organ for mancozeb. Thyroid effects were observed in multiple studies across species. Thyroid toxicity was manifested as alterations in thyroid hormones, increased thyroid weight, and microscopic thyroid lesions (mainly thyroid follicular cell hyperplasia), and thyroid tumours. (Mancozeb Facts, 2005).

PMRA Response:
The PMRA is aware that mancozeb and ETU are listed as potential endocrine disrupters of concern (e.g., EPA 1997, EU 1996 – as cited in above comment). For chemicals exhibiting endocrine disrupting properties (e.g., disturbance of hypothalamic-pituitary gonadal, thyroid or adrenal axes, etc.), the environmental risk assessment considers any observed endocrine effect(s) that directly relate or result in a measurable, holistic effect endpoint (e.g., reproduction, growth development, behavioural) that would potentially cause harm at the community/population level and at environmentally relevant concentrations.

The environmental risk assessment for the potato use pattern shows that mancozeb may pose a potential reproductive risk to birds and mammals feeding on field and adjacent to fields where mancozeb has been applied. For birds, the chronic risk assessment was based on the most

sensitive endpoint reported for the bobwhite NOEL = 13.2 mg a.i./kg body weight/day where significant reductions in the percentage of 14-day old survivors of normal hatchlings and reductions in hatchling and 14-day old survivor bodyweights were observed. The risk assessment is highly conservative as it assumes that the dietary intake of birds comprises 100% of each type of food item (insect, grain, seed, fruit or plant). Although a reproductive risk is identified for birds, the risk quotient exceedances are of low magnitude and are considered unlikely to significantly affect the reproductive success of bird populations. For mammals, the chronic risk assessment was based on the most sensitive endpoint reported for reduced body weight in rat offspring (NOEL = 2.5 mg a.i./kg body weight/day); in this study, the end-use product Penncozeb was used. Consideration was also given to the results of a technical grade active ingredient based chronic reproductive study in which no effects were observed at the highest dietary test concentration (NOEL ≥69 mg a.i./kg body weight/day) in offspring of the same rat species and following the same testing protocol. The NOEL for reproduction in both rat studies was greater than the highest dietary concentration tested (NOEL >110 and >69 mg a.i./kg body weight/day). Based on the collective results from both studies, the risk to mammals is anticipated to be low. The reduction of the potato application rate will further reduce the risk to birds and mammals.

4.6 Comment concerning the proposed buffer zones for the use on potatoes

Currently, there are no required buffer zones stated on the Canadian or American labels for the foliar uses of mancozeb. As the PMRA is developing risk mitigation measures for the continued use of mancozeb as a foliar fungicide for potatoes, it is hoped that the proposed buffer zones for both the ground (field sprayer) and aerial application will be revisited. The proposed buffer zones may not be harmonized with provincial requirements: for example a 25m buffer zone is proposed for freshwater aquatic environments < lm in depth, while the provincial requirement for many foliar products including mancozeb in PEI is 15m. The buffer zones proposed in PRVD2013-01 far exceed buffer zones on other fungicides registered for use on potatoes in Canada (e.g. chlorothalonil = 15m for surface water bodies).

Additionally, the United States Environmental Protection Agency (USEPA) completed a re-evaluation of mancozeb in 2005 (USEPA, 2005) and did not require buffer zones be introduced. We urge the PMRA to develop buffer zones that protect aquatic habitats, while considering the history of use in Canada without aquatic environmental incidents, as well as the decision of the USEPA.

PMRA Response:
The PEI provincial requirement for a 15-metre buffer provides both spray drift mitigation and runoff mitigation. The buffer zones required by the PMRA are spray buffer zones, intended to protect aquatic habitats from the effects of spray drift at the time of application. The PMRA, like other pesticide regulatory agencies, considers adverse effects of spray drift in the evaluation of new or currently used pesticides. The mitigation measures adopted, however, are specific to each jurisdiction. The spray drift buffer zones determined for mancozeb during the re-evaluation were based on the PMRA's current risk assessment and mitigation policies and are expected to prevent adverse effects from spray drift occurring in habitats downwind at the time of application. Spray drift buffer zones are directly related to the degree of risk expected for the product's intended use pattern. For this reason, spray drift buffer zones are unique to each product and will not be the same for other similar fungicide products registered in Canada. Applicators can also consult the

PMRA's online buffer zone calculator to adjust the buffer zone distance on the product label according to the application equipment used and weather conditions at the time of use.

5.0 Comments and Responses Related to the Value Assessment

The PMRA received several comments from stakeholders regarding the value of the mancozeb uses in response to PRVD2013-01. The comments were considered for refinement of the risk assessments, mitigation measures and in the value assessment to identify crops with pest management concerns.

5.1 Comment concerning the importance of mancozeb for resistance management

BC Tree Fruits Cooperative Growers, Nova Scotia Fruit Growers' Association, Peak of the Market, Manitoba; BC Vegetable Marketing Commission, Ontario Sugar beet Growers' Association, Le Conseil québécois de l'horticulture, Scotian Gold Cooperative Limited, La Fédération des producteurs de pommes du Québec, Ontario Ministry of Agriculture, Food and Rural Affairs, BC Ministry of Agriculture, Ontario Fruit and Vegetable Growers Association, and the Canadian Horticultural Council commented that mancozeb is an effective, broad spectrum fungicide that has a very low risk of resistance due to its multi-site mode of action. It is an invaluable tool for resistance management and economical broad spectrum disease control. It is used as tank mix partner, in pre-mixes, and as rotational product for newer fungicides that are at high risk of resistance development.

PMRA Response:
The PMRA agrees that mancozeb is an important tool for disease control and resistance management. There are number of other active ingredients including some multi-site fungicides registered for most of the mancozeb crop-pest combinations being discontinued. Growers may use these fungicides in rotation or as a tank-mix partner with fungicides from different mode of action groups for disease control, and in alternation for resistance management in a disease management program.

5.2 Comment concerning the foliar use of mancozeb on potatoes

The PMRA received several comments from Peak of the Market, Manitoba; BC Vegetable Marketing Commission, Le Conseil québécois de l'horticulture, Ontario Ministry of Agriculture, Food and Rural Affairs, BC Ministry of Agriculture, Ontario Fruit and Vegetable Growers Association, and the Canadian Horticultural Council regarding the value of mancozeb to potato production. Mancozeb provides exceptional value in the management of fungal potato diseases particularly early and late blights and is critically important for resistance management.

Mancozeb when used in rotation or in combination with newer chemistries has a critical role in delaying or preventing the development of resistant pathogen populations. Potato producers in Canada compete in a North American marketplace and must remain competitive with the producers from the United States. Loss of mancozeb could have a devastating impact to the competitiveness of the Canadian industry. Mancozeb must remain available as a ground and aerial applications to Canadian potato growers.

PMRA Response:
In order to mitigate risks associated with the use of mancozeb, the PMRA considered a revised potato use pattern from the Mancozeb Task Force. In addition, the PMRA consulted extension specialists from different provinces regarding the use of mancozeb in current potato production practices. This information was used to refine the potential risks associated with the foliar use of mancozeb on potatoes, and as a result, foliar uses using ground and aerial application equipment were found to be acceptable for continued registration.

5.3 Comment concerning the use of mancozeb on apples

BC Tree Fruits Cooperative Growers, Nova Scotia Fruit Growers' Association, Perennia (Nova Scotia), La Fédération des producteurs de pommes de terre du Québec, Ontario Fruit and Vegetable Growers Association, Ontario Apple Growers, Le Conseil québécois de l'horticulture, Scotian Gold Cooperative Limited, The British Columbia Fruits Growers' Association, Ontario Ministry of Agriculture, Food and Rural Affairs, BC Ministry of Agriculture and the Canadian Horticultural Council commented that use of mancozeb is vital for controlling apple scab and for managing resistance. Phasing-out mancozeb will increase pressure on the use of single-site fungicides which will quickly become less effective as resistance builds. Some of the newer chemistry has already developed resistance to the scab pathogen. Many growers use mancozeb as a rotational product to slow down this resistance. Mancozeb is economical in pricing compared to other fungicides. If mancozeb is taken away, apple growing will become more difficult and expensive to the growers. Losing mancozeb from list of tools would be a struggle, and it would be much more expensive to control one of the larger problems facing apple growers.

PMRA Response:
The PMRA acknowledges the value of mancozeb for apple scab management in Canada. The PMRA received a revised use pattern for apples from the Mancozeb Task Force, in order to mitigate risks. The PMRA also consulted with grower groups and extension specialists from different provinces regarding current use information of mancozeb, and its role in apple production. This information was considered in refining the risk assessments. However, the risk concerns identified in PRVD2013-01 remain. As a result, the use of mancozeb on apples is being cancelled.

Currently, a number of alternative active ingredients from various mode of action groups including multi-site actives such as: captan, folpet, copper and sulfur, are registered to control apple scab. One of these alternatives, fluazinam, has a low risk of developing resistance to the apple scab pathogen, and is registered against a broad spectrum of apple diseases. For cedar apple rust and apple quince rust control, several active ingredients from different mode of action groups are registered. In general, apple growers have access to several different fungicides for both disease control and resistance management. The PMRA acknowledges that some of the newer, single-site mode of action fungicides are developing resistance to apple diseases, particularly to the apple scab pathogen.

5.4 Comment concerning the use of mancozeb on grapes

The PMRA received several comments from the Ontario Ministry of Agriculture, Food and Rural Affairs, Grape Growers of Ontario, British Columbia Ministry of Agriculture and Le Conseil québécois de l'horticulture regarding the value of mancozeb for use on grapes. Mancozeb

is an important tool for controlling downy mildew on grapes, a disease that can completely defoliate vines if left untreated, resulting in crop loss. If vines survive, they are more susceptible to cold injury. In addition, mancozeb is effective against black rot, an important disease of grape. Mancozeb is an effective and economical option for the management of foliar infections in grapes before the fruit susceptibility period (bloom through to 5 weeks post-bloom). It is also an important tool for resistance management due to its multi-site mode of action and broad spectrum disease control.

PMRA Response:
The PMRA consulted growers and extension specialists from different provinces regarding the use of mancozeb in current production practices of grapes. The PMRA also received revised use pattern information for grapes from the mancozeb Task Force. The PMRA also received revised use pattern information for grapes from the mancozeb registrant. This information was considered in refining the risk assessments. However, the risk concerns identified in PRVD2013-01 remain. As a result, the use of mancozeb on grapes is being cancelled.

Currently, a number of other fungicide active ingredients are available to growers. Several multi-site fungicides including captan, folpet and copper are registered for downy mildew and black rot control. The PMRA acknowledges that some of the single-site mode of action fungicides have developed some level of resistance to the grape downy mildew pathogen.

5.5 Comment concerning the use of mancozeb on tomatoes

The PMRA received comments from the Ontario Ministry of Agriculture, Food and Rural Affairs regarding the importance of mancozeb for control of early blight and anthracnose on tomatoes. Mancozeb is an important tool in integrated pest management (IPM) strategies for the control of early blight and anthracnose in tomatoes.

PMRA Response:
The PMRA acknowledges the value of mancozeb for tomato disease control. However, due to occupational and dietary risk concerns, the PMRA is cancelling the use of mancozeb on tomatoes.

Currently, a number of other active ingredients, including multi-site fungicides, are registered for early blight and anthracnose control. Growers may use these fungicides for control of these diseases, and in rotation as part of their disease resistance management program.

5.6 Comment concerning the use of mancozeb on carrots

The PMRA received comments from the Ontario Ministry of Agriculture, Food and Rural Affairs regarding the importance of mancozeb for foliar leaf blight control on carrots. Mancozeb is commonly used as a protectant fungicide for management of Alternaria and Cercospora leaf blights. It is a broad spectrum product with lower risk of developing resistance. If the PMRA were to phase-out mancozeb, there would be a significant impact on carrot industry. Alternatives are currently available but they are from only a few chemical groups (i.e., mostly from Groups 7, 11), some of which have higher risks of developing resistance and/or are more costly.

PMRA Response:
The PMRA acknowledges the importance of mancozeb for Alternaria and Cercospora leaf blight management on carrots. However, due to occupational and dietary risk concerns, the PMRA is cancelling the use of mancozeb on carrots.

Currently, a number of other active ingredients including some of their pre-mix products and multi-site fungicides are currently registered for Alternaria leaf blight and Cercospora leaf blight control. Thus carrot growers have options to rotate these fungicides for Alternaria and Cercospora leaf blight control and for resistance management purposes.

5.7 Comment concerning the use of mancozeb on celery

The PMRA received comments from the Ontario Ministry of Agriculture, Food and Rural Affairs regarding the value of mancozeb for early and late blight control on celery. Mancozeb is a commonly used protectant fungicide for management of foliar early and late blights on celery. It is a broad spectrum fungicide with a low resistance risk. If the PMRA were to propose a phase-out of mancozeb, there would be a potentially significant impact on celery industry. Alternatives to mancozeb are from only a few chemical groups (i.e., mostly from Groups 7, 11), some of which have higher risks of developing resistance and/or are more costly.

PMRA Response:
The PMRA acknowledges the value of mancozeb for use on celery. The Agency also received revised use patterns for celery from the Mancozeb Task Force as a measure for risk mitigation. This information was considered in refining the risk assessments. However, the risk concerns identified in PRVD2013-01 remain. As a result, the use of mancozeb on celery is being cancelled.

Currently, several other active ingredients from different mode of action groups, including multi-site fungicides chlorothalonil, folpet and copper are currently registered for early and late blight control. Celery growers may use these fungicides for foliar blight control and in rotation as part of their resistance management programs.

5.8 Comment concerning the use of mancozeb on sugar beets

The PMRA received comments from the Ontario Sugar Beet Growers' Association regarding the value of mancozeb for the management of Cercospora leaf spot on sugar beets. Mancozeb is an important tool in the spray rotation used against Cercospora. The pesticide choice is very limited especially when it comes to avoid resistance build-up. If the sugar beet industry were to lose a chemical and no real new ones come along the pipeline that would be devastating for the industry.

PMRA Response:
The PMRA acknowledges the value of mancozeb for Cercospora disease management on sugar beets and its importance for resistance management. However, due to occupational and dietary risk concerns, the PMRA is cancelling the use of mancozeb on sugar beets.

Currently, several alternative active ingredients from different mode of action groups are registered for use on sugar beets. Growers may use these fungicides for Cercospora leaf spot control, and in rotation with other chemistries as part of their resistance management programs.

5.9 Comment concerning the use of mancozeb on ginseng

The PMRA received comments from the Ontario Ministry of Agriculture, Food and Rural Affairs regarding the value of mancozeb for controlling Alternaria leaf blight on ginseng. Mancozeb is an affordable, broad spectrum fungicide that serves as an important tool for the management of Alternaria leaf blight on ginseng. Typically, all the ginseng acreage on a farm is treated with mancozeb on the same day or possibly the next.

PMRA Response:
The PMRA acknowledges the value of mancozeb for management of Alternaria disease on ginseng. However, due to occupational and dietary risk concerns, the PMRA is cancelling the use of mancozeb on ginseng.

Currently, a number other active ingredients belonging to different mode of action groups, including the multi-site fungicide chlorothalonil, are currently registered for control of Alternaria leaf blight on ginseng. Growers may rotate these fungicides in Alternaria leaf blight management program.

5.10 Comment concerning the use of mancozeb on pears

The PMRA received comments from the British Columbia Ministry of Agriculture and Ontario Ministry of Agriculture, Food and Rural Affairs regarding the value of mancozeb for use on pears. Mancozeb is an effective, economical IPM tool that is used to manage pear scab in Ontario. There would be a significant impact on the Ontario pear industry if mancozeb is phased out.

PMRA Response:
Mancozeb is registered for the control of pear psylla. However, due to occupational and dietary risk concerns, the PMRA is cancelling the use of mancozeb on pears.

Currently, a number of other insecticide active ingredients are currently registered for pear psylla control.

5.11 Comment concerning the use of mancozeb on onions

The PMRA received comments from the Ontario Ministry of Agriculture, Food and Rural Affairs regarding the value of mancozeb for onion disease management. Mancozeb is a commonly used protectant fungicide for the management of Botrytis leaf blight and downy mildew in onions. It is used for the control of purple blotch disease and commonly used as an in-furrow treatment during planting or as a seed treatment for onion smut control.

Mancozeb is a broad spectrum, preventative product with low resistance risk. There are alternatives for management of these diseases, but they are from a limited number of chemical groups. There could be a potentially significant impact on the onion industry if mancozeb was no longer available as an IPM tool for the Ontario onion growers.

PMRA Response:
The PMRA acknowledges the value of mancozeb for use on onions. The Agency also received revised use patterns for onions from the Mancozeb Task Force. This information was considered during the risk refinement assessments This information was considered in refining the risk assessments. However, the risk concerns identified in PRVD2013-01 remain. As a result, the use of mancozeb on onions is being cancelled.

For the control of Botrytis leaf blight and downy mildew, a number of other active ingredients from different mode of action groups including two multi-site fungicides are registered. For purple blotch control, a number of other active ingredients from different mode of action groups are currently registered. Growers may rotate these fungicides for Botrytis leaf blight, downy mildew and purple blotch control and resistance management. To control onion smut, only a co-formulated product containing carbathiin and thiram is currently available for use as a seed treatment.

5.12 Comment concerning the use of mancozeb on head lettuce

The PMRA received comments from the Ontario Ministry of Agriculture, Food and Rural Affairs regarding the value of mancozeb for downy mildew management on head lettuce. Mancozeb is registered for use on head lettuce only in a co-formulation with metalaxyl-M and is used by growers as a rotational product for downy mildew control. For downy mildew control, other registered alternatives are from a limited number of chemical groups (i.e., mostly from Groups 33, 40) some of which have higher risks of developing resistance and/or are more costly. Rotational products for resistance management are of concern for this disease, even though some of the newer products show promise in terms of downy mildew management.

PMRA Response:
The PMRA acknowledges the importance of mancozeb in a co-formulated product with metalaxyl-M for this use. However, due to occupational and dietary risk concerns, the PMRA is cancelling the use of mancozeb on head lettuce.

Currently a number of other active ingredients from different mode of action groups are currently registered for downy mildew control on head lettuce. Some of them provide similar levels of control as mancozeb + metalaxyl-M. Growers may use these fungicides as a rotational chemistry for downy mildew control and resistance management.

5.13 Comment concerning the use of mancozeb on greenhouse tomatoes

The PMRA received comments from the Ontario Ministry of Agriculture, Food and Rural Affairs, British Columbia Ministry of Agriculture and the Canadian Horticultural Council regarding the use of mancozeb for greenhouse tomato production. There is limited use of mancozeb in greenhouse tomatoes in Ontario. If mancozeb is used, growers may use a maximum of two applications but the current PHI of 7 days severely restricts its use. If greenhouse tomato

growers were to lose mancozeb, this would leave only one registered alternative, which is Fontelis (penthiopyrad) for early blight control. In British Columbia, mancozeb is not commonly used in greenhouse tomato production and thus is not a critical use. However, it is a critical use for propagation of greenhouse tomato seedlings.

PMRA Response:
The PMRA acknowledges the importance of mancozeb for this use. However, due to occupational and dietary risk concerns, the PMRA is cancelling the use of mancozeb on greenhouse tomatoes.

Currently, four other active ingredients, polyoxin D, fluopyram, penthiopyrad and copper octanoate are registered for the control of greenhouse tomato early blight. Growers may use these fungicides for the management of early blight on greenhouse tomatoes including seedling propagation if needed.

5.14 Comment concerning the use of mancozeb on potato seed-piece treatment

Canadian Potato Council, Prince Edward Island Potato Board, Potatoes New Brunswick, Ontario Potato Board, Peak of the Market (Manitoba), Keystone Potato Producers' Association (Manitoba), BC Vegetable Marketing Commission (BC Potato & Vegetable Growers' Association and BC Certified Seed Growers' Association), Ontario Ministry of Agriculture, Food and Rural Affairs and BC Ministry of Agriculture and the Canadian Horticultural Council commented that the use of mancozeb as a potato seed piece treatment is critical for the management of seed-borne infections of Fusarium causing dry rot. Although seed borne late blight is not included on the labels, seed piece treatment with mancozeb provides additional control of early season late blight which spreads during seed cutting and handling. Mancozeb is the only broad spectrum seed piece treatment available and the loss of mancozeb would have a devastating effect to potato production. The importance of mancozeb as a seed piece treatment has increased due to concerns about resistance of *Fusarium spp*. to fludioxonil, thiabendazole and thiophanate-methyl and the limited number of actives that are registered for potato seed piece treatment. Mancozeb is commonly used in a premix with more resistant-prone chemistries like fludioxonil.

PMRA Response:
In addition to comments from different potato stakeholders, the PMRA also received revised use patterns proposed for potato piece seed treatment from the Mancozeb Task Force to mitigate risk concerns. This information was considered during the risk refinement assessments. This information was considered in refining the risk assessments. However, the risk concerns identified in PRVD2013-01 remain. As a result, the use of mancozeb for treating potato seed piece and seed potato in storage are being cancelled.

The PMRA acknowledges the importance of mancozeb as a seed piece treatment to manage Fusarium seed piece decay and control of Fusarium dry rot in seed potatoes in storage. The PMRA also acknowledges that a limited number of alternatives to mancozeb are registered, and that resistance in certain *Fusarium* populations has developed to some of these active ingredients, particularly fludioxonil.

Currently, a number of other active ingredients including co-formulated products containing penflufen and prothioconazole, and fludioxonil and difenoconazole from different mode of action groups are registered. The co-formulated product containing penflufen and prothioconazole is now the best option for potato seed piece treatment for the management of *Fusarium spp*. If fludioxonil alone or any co-formulated products containing fludioxonil is used for potato seed piece treatment, *Fusarium* resistance will have to be closely monitored.

Appendix III Label Amendments for End-use Products Containing Mancozeb

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

Uses cancelled:

Use instructions for crops which are no longer supported (all crops/uses except the foliar application to potatoes) must be removed from the label.

Primary Display Panel:

The following statement is required to be added to the primary display panel of all commercial products:

“FOR FOLIAR USE ON POTATOES ONLY.”

Directions for Use:

The following are required under the **DIRECTIONS FOR USE** section for all end-use products labels:

“A maximum of 10 applications per year on potatoes is allowed, using ground spray or aerial application, at a maximum application rate of 1.69 kg a.i./ha with 7-day application intervals and a 1-day pre-harvest interval, with no more than one aerial application.”

“The total seasonal application of mancozeb and metiram combined cannot exceed 10 applications per year with no more than 3 applications being metiram”

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

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

Buffer zones:

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

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

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:			
			Freshwater Habitat of Depths:		Estuarine/Marine Habitat of Depths:	
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m
Field sprayer	Potato		15	3	1	1
Aerial	Potato	Fixed wing	275	15	20	10
		Rotary wing	150	15	15	5

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

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

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 STORAGE section

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

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.

- This product demonstrates the properties and characteristics associated with chemicals detected in ground water. The use of **[product name]** in areas where soils are permeable, particularly where the water table is shallow, may result in ground water contamination.

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 non-target areas of human habitation or 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:

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.

Statements must be amended (or added) to include the following directions to the appropriate labels in order to mitigate the risk of exposure to mancozeb:

<u>For all formulations:</u>

“Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair. Gloves are not required during application within a closed cab or cockpit.”

<u>For dry flowable formulations (in addition to the required protective equipment above):</u>

“A respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides, or a NIOSH-approved canister approved for pesticides is required when mixing/loading.”

"When handling more than 350 kg a.i./day and applying by groundboom, use a closed-cab tractor that provides respiratory protection (such as dust/mist filtering system and/or vapour/gas purification system) OR if using an open-cab tractor, applicators must wear a respirator (with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides)."

Restricted-Entry Interval:

Statements must be amended (or added) to include the following directions to the appropriate labels in order to mitigate the risk of exposure to mancozeb:

"DO NOT enter or allow worker entry into treated areas during the restricted-entry interval (REI) of 12 hours."

Appendix IV Toxicology – Revised Assessment

Table 1a Summary of Additional Toxicity Studies for Mancozeb Submitted in Response to PRVD2013-01

Study Type/Animal/PMRA #	Study Results
Developmental Neurotoxicity Dietary study Dose-Range Finding SD rats PMRA #2047262	**Supplemental: Dose range finding study** **Maternal toxicity** **≥ 5 mg/kg bw/day:** ↓ body weight LD-17 and LD-21, low dose only, ↓ bwg , ↓ Fc LD17–21 **≥ 30 mg/kg bw/day:** ↓ bwg GD 6–20 , ↓ Fc GD 6–20 , ↓ T_4 LD 21, ↑ thyroid wt GD-20, ↑ minimal follicular cell hypertrophy, **60 mg/kg bw/day:** ↓ body weight GD 6–20, ↓ body weight LD 1, LD 17, LD 21, ↑TSH LD 21 No treatment related effects were observed on mortality, clinical signs, pregnancy rate, and reproductive parameters. **Developmental toxicity** **≥ 5 mg/kg bw/day:** ↓ bw PND 7–21 **≥ 30 mg/kg bw/day:** ↓ bwg PND 4–7 and 17–21
Developmental Neurotoxicity Dietary Study Main Study SD rats PMRA #2047261	**Maternal NOAEL = 15 mg/kg bw/day** **Developmental NOAEL = 15 mg/kg bw/day** **Maternal Toxicity** **30 mg/kg bw/day:** ↓ body weight gain on GD 6–9 and 6–12 and on GD 6–20, ↑ absolute and relative thyroid weight, ↑ incidence of thyroid follicular cell hypertrophy. No treatment-related effects were observed on mortality, clinical signs of toxicity, body weight, food consumption, FOB parameters, reproductive parameters, or gross lesions in the dams. **Developmental toxicity** **30 mg/kg bw/day:** ↓ bwg PND 1–4 (♂/♀); ↑ learning errors PND-22 (♂);↑ memory errors, PND-22 (♀). **No sensitivity of the young**
Developmental Neurotoxicity Gavage Study Dose-Range Finding Wistar rats (HanTac) PMRA #2849986 Axelstad et al., 2011	**Supplemental: Dose range finding study** All doses were halved on GD 12. ≥ 200/100 mg/kg bw/day: ↓ bw, ↑ signs of neurotoxicity (paralysis of the hind limbs within a few days of dosing start), 2 dams sacrificed on GD14. (No further signs of toxicity reported in the remaining dams after dose reduction) ≥ 350 mg/kg bw/day: ↓ bw, ↑ signs of neurotoxicity (paralysis of the hind limbs), all animals sacrificed (GD 14)
Developmental Neurotoxicity Gavage Study Main Study) Wistar rats (HanTac) PMRA #2849986 Axelstad et al., 2011	**Supplemental** **Maternal toxicity** **≥ 50 mg/kg bw/day:** ↓ bw gain (GD 7–21) and (GD 7–PND 1) ↓ T_4 level (GD 15) **150/100 mg/kg bw/day:** ↓ bw (PND 24), 2 dams sacrificed on GD 16 with mild hind leg paralysis, ↑ post implantation loss. **Dose was reduced to 100 mg/kg bw/day** Gestation length, litter size, neonatal deaths, gender distribution, were similar in the four groups

Study Type/Animal/PMRA #	Study Results
	Developmental toxicity **≥ 50 mg/kg bw/day:** ↓ trend in bw on PND 13, 24, and 31 **150/100 mg/kg bw/day:** ↓ bw PND 13 and 45 Levels of T_4 and thyroid weight were not affected in any dose group compared with controls on PND 16. Neonatal deaths, gender distribution, AGD, nipple retention, testosterone levels, reproductive organ weights, and histology on PND 16 were not affected by mancozeb. The adult offspring (3–7 months old) were tested in a battery of behavioral tests. None of the performed behavioral tests showed effects of mancozeb exposure, as neither activity levels in young or adult offspring, performance in the radial arm maze, or acoustic startle response were affected nor were any dose-dependent trends seen (data were not shown). **No sensitivity of the young**
Immunotoxicity 28-Day Dietary Study (SD) rats PMRA #2363852	**NOAEL = 16 mg/kg bw/day** **81 mg/kg bw/day:** ↓ bw, ↓ bwg, ↑ liver weights, ↑ thyroid weight. **SRBC antibody response was unaffected by treatment.**
Colosio et al, (1996; 2007) PMRA #1852265, 1852266	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.

Table 1b Summary of Additional Toxicity Studies for ETU Submitted in Response to PRVD2013-01

Study Type/Animal/PMRA #	Study Results
Gavage developmental toxicity study Main study (NZW)SPF rabbit PMRA #2039432	**Maternal NOAEL: 5 mg/kg bw/day** **Developmental NOAEL: 5 mg/kg bw/day** **Maternal toxicity** **≥5 mg/kg bw/day:** ↓bw , ↑abs. thyroid weight , ↑rel. thyroid weight **≥15 mg/kg bw/day:** ↓bwg (GD 7–29), ↓fc (GD 7–29), discolored/darkened thyroids, ↑early and late resorptions, ↑ post implantation loss **Developmental toxicity** **15 mg/kg bw/day:** ↓mean fetal weight, ↑ early resorptions, ↑ late resorptions, ↑ post implantation loss **50 mg/kg bw/day:** ↑ domed heads **No sensitivity of the young**
Dietary EOGRT Study Crl:CD(SD) rat PMRA #2055156	**Supplemental: Dose range finding study** **Constant dosing on mg/kg bw/day basis** **Toxicokinetic data collected on dams and pups** **≥2 mg/kg bw/day:** very slight-to-moderate follicular cell hypertrophy / hyperplasia; ↓ bw , ↓ bwg (dams gestation) (♀); ↓T_3 and T_4 levels, and ↑ TSH levels (♂) **10 mg/kg bw/day:** ↓ bwg premating (♂/♀); ↑ thyroid weights (♂); ↓ T_4 levels, and ↑ TSH levels (♀) Plasma samples from GD 20 dams, LD 4 dams and pups, LD 21 dams and pups, and adult males showed dose-proportional concentrations of ETU, indicating

Study Type/Animal/PMRA #	Study Results
	linear toxicokinetics at all dose levels in all age groups. There were no sex- or lactation-related differences in ETU kinetics. Plasma conc. of ETU in pups was ~22% of dam plasma conc. at LD 4, and ~65% of dam plasma conc. at LD 21. Thyroid effects with 12% decreases in bwg over the gestation period suggested that 10 mg/kg/day dose level was a sufficient high dose for EOGRTS.
Dietary) Extended One-generation Reproductive Toxicity Study (EOGRTS) Crl:CD(SD) rat PMRA #2313478	**Parental LOAEL = 0.2 mg/kg bw/day(♂)** **Parental NOAEL = 0.2 mg/kg bw/day(♀)** **Parental LOAEL = 2 mg/kg bw/day(♀)** **Constant dosing on mg/kg bw/day basis** **Parental toxicity** **≥ 0.2 mg/kg bw/day:** ↓ absolute and relative thyroid wt. (♂/♀); ↑ hypertrophy of individual cells in the pars distalis of the pituitary gland, ↑ diffuse thyroid follicular cell hypertrophy (♂); ↓ bwg premating and LD 1–4, ↓RBC count (marginal) (♀). **≥ 2 mg/kg bw/day:** ↓ absolute and relative thymus weights, ↑ diffuse follicular cell hypertrophy /hyperplasia of the thyroid gland, ↓ serum concentrations of T4 and ↑ in serum TSH levels; ↑creatinine, ↓ reticulocyte count, ↑total cholesterol. (♂); ↑reticulocyte count (♀). **10 mg/kg bw/day:** ↑ absolute and relative thyroid wt, ↑ hyperplasia of the thyroid gland: one case of adenoma and another one of nodular hyperplasia; ↓ bw premating: , ↓ bwg, ↓ fc , ↓ ALT, ↓ abs wt heart, kidneys, adrenal, and epididymides, ↑ hepatocyte vacuolization (fatty change) (♂); premating: ↓bw, ↓ fc, gestation:↓ bwg GD1–7, lactation: ↓ bw , ↓ fc,(LD 4–8), ↑ relative pituitary and liver weights, ↓ brain wt, ↑ relative uterine weight (♀). **Reproductive toxicity** No significant effect on any of the reproductive indices, including male and female mating, conception, fertility, and gestation indices, or percent post-implantation loss. No significant effect on time to mating or gestation length, or on mean estrous cycle length.
	Offspring: F1 Animals up to PND 21 **NOAEL= 0.2 mg/kg bw/day (thyroid toxicity)** **≥ 2 mg/kg bw/day:** ↓ in T_4 and ↑ TSH serum level PND 22, ↑very slight diffuse follicular cell hypertrophy of the thyroid gland; **10 mg/kg bw/day:** ↓ bw (by PND 14) and (by PND 21), ↓ in T_4 and ↑ TSH serum level PND 4, ↑ absolute and relative thyroid gland weights, very slight diffuse follicular cell hyperplasia, and slight hypertrophy of the thyroid gland; ↓absolute and relative thymus weights (♀). No effects on number of live pups born/litter, litter size or survival index on LD 1, 4, 7, 14, or 21. There were no treatment related effects in nipple retention and AGD in ♀/♂

Study Type/Animal/PMRA #	Study Results
	Cohorts 1A and 1B = Systemic/thyroid toxicity **LOAEL = 0.2 mg/kg bw/day (♂)** **NOAEL = 0.2 mg/kg bw/day (♀)** **≥ 0.2 mg/kg bw/day:** ↓ AST, ↓ ALT (♂/♀); ↑ TSH serum level ↓ thyroid weight both Cohorts, ↑ follicular cell hypertrophy of thyroid, ↑ hypertrophy pars distalis/ pituitary (♂). **≥ 2 mg/kg bw/day:** ↓ in T_4 serum, ↓abs and rel thymus both Cohorts; ↓ abs epididymides Cohort 1A/1B, ↑ follicular cell hyperplasia of thyroid (♂). **10 mg/kg bw/day:** ↓ bw/ bwg both Cohorts, ↑ cholesterol concentration, ↓reticulocyte count, ↓ abs and rel kidney; ↓brain wt Cohort 1A, ↑ relative liver wt Cohort 1A, ↓abs prostate, and epididymides Cohort 1A/1B, ↑ proportion of abnormal sperm, ↑ thymus atrophy (♂); ↑ ovarian follicle counts (small, growing, and total) (♀).
	Cohorts 1A and 1B – Reproduction **NOAEL = 2 mg/kg bw/day** **LOAEL = 10 mg/kg bw/day** 10% increase in the proportion of abnormal sperm compared to control animals (♂). Increased follicle count without a significant decrease in corpora lutea (♀).
	Cohort 2A and 2B - Developmental Neurotoxicity **NOAEL = 2 mg/kg bw/day** **≥ 2 mg/kg bw/day:** hypertrophy of pars distalis pituitary **(♂)** **10mg/kg bw/day:** ↓ overall brain size, ↓ habituation on ASR; ↓ brain weight, ↓ bw/bwg (PND 21-77), ↓fc, (♂). This neurotoxicity study was considered a screening level study
Gavage Developmental Neurotoxicity Study **Propylthiouracil (PTU)** Gavage GD 7 to postnatal day (PND) 17 Wistar rats PTU (0, 0.8, 1.6 or 2.4 mg/kg/day) from GD 7 to PND 17 Marta Axelstad at al., 2008 PMRA #2849973	**Supplemental** Study conducted to establish the relationship between transient hypothyroxinemia during development and long-lasting behavioural and functional changes. PTU-induced hypothyroxinemia influenced the developing rat brain in adult offspring. PTU exposure caused motor activity levels to decrease on PND 14, and to increase on PND 23 and in adulthood (two highest dose groups). In the adult offspring, learning and memory was impaired in the radial arm maze (two highest dose groups), and auditory function was impaired (highest dose group). These results were significantly correlated to reductions in T4 during development. This supports the hypothesis that decreased T4 may be a relevant predictor for long-lasting developmental neurotoxicity. **NOAEL (behavioural) = 0.8 mg/kg bw/day** **Maternal toxicity** **≥1.6 mg/kg bw/day:** ↓ T4 level (GD16), ↑ thyroid weight, ↑ thyroid marked hyperplasia. (♀)

Study Type/Animal/PMRA #	Study Results
	≥ 2.4 mg/kg bw/day: ↓bw gain (PND1–17) (♀) No effects on bw, gestation length, post-implantation loss, and litter size were observed **Developmental toxicity** **≥ 0.8 mg/kg bw/day:** ↓T_4 levels (PND-16), ↑ thyroid weight (PND 16 and 27), ↑incidence and severity histopathological changes in thyroid (PND16 and PND 64) **≥ 1.6 mg/kg bw/day:** ↑incidence and severity histopathological changes in thyroid (PND 27), ↑total motor activity on PND 64; ↓bw (PND 23–27), ↑ error in Radial arm maze (♂); ↓bwg (PND 23–27) (♀) **≥ 2.4 mg/kg bw/day:** ↓total motor activity on PND 14, and ↑ on PND 23, ↓bw (PND23–27), ↑ABR (auditory brain stem response) thresholds by 12–15dB, ↓ Cubic Distortion Products(CDP) at f2 = 4kHz by 12–13dB.
Assessment of developmental effects of hypothyroidism in rats from in utero and lactation exposure to anti-thyroid agents. PTU (0.39, 1.54 mg/kg bw) GD 10–20 and (0.67, 2.2 mg/kg bw/day) PND 1–20 Makoto Shibutani, Gye-Hyeong at al., 2009 (published) PMRA #2849980	The aim of this study was to clarify the developmental effects of hypothyroidism and to establish a detection system of resultant brain retardation. Pregnant rats were administered thyrotoxins, either PTU or methimazole. Pups were dosed until 11 weeks of age. PTU and methimazole caused clear hypothyroidism-linked effects in dams (increased relative thyroid weights and thyroid follicular cell hypertrophy). Growth retardation of the offspring lasted into adulthood with males more affected than females. At the end of the study, exposure to the thyrotoxins caused hypothyroidism-related thyroid follicular cell hypertrophy in the adult pups. In addition, mismigration of hippocampal CA1 pyramidal neurons, and a reduction in the area of corpus callosum and oligodendroglial cells in the cerebral deep cortex, reflecting impaired oligodendroglial development, was observed in adult pups.
Dietary Immunotoxicity Study Crl:CD(SD) rats PMRA #2363857	**NOAEL = not established** **LOAEL = 1 mg/kg bw/day** **≥ 1 mg/kg bw/day:** ↓T_4 serum level **≥ 4 mg/kg bw/day:** ↓ bw, ↓ bwg , ↓ fc, ↓ thymus weight **19 mg/kg bw/day:** ↓ spleen weight, ↑ thyroid weight, ↑ TSH serum level, moderate to severe follicular hypertrophy/hyperplasia in all males, minimal to slight centrilobular hepatocellular hypertrophy, diffuse fatty changes in liver There was no effect on the SRBC antibody response.

Appendix V Updates to Toxicology Reference Values for Risk Assessment

Table 1a Mancozeb: Revised Toxicology Reference Values

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
ARfD Females 13–49 years of age	Rat DNT Study	NOAEL = 15 mg/kg bw/day Neurotoxicity (learning and memory)	300
	ARfD Females 13-49 = 0.05 mg/kg bw		
ARfD General Population, excluding Females 13–49 years of age	Rat Acute Neurotoxicity	LOAEL 500 mg/kg bw/day Decreased motor activity	300
	ARfD General Pop = 1.7 mg/kg bw		
Chronic Dietary All Populations	1 Year Dog Toxicity Study	NOAEL = 2.3 mg/kg bw/day Liver and bodyweight gain, food consumption, thyroid hormone effects	100
	ADI = 0.023 mg/kg bw/day		
Short- and Intermediate-term Dermal[2]	**Occupational**		
	Rat DNT Study	NOAEL = 15 mg/kg bw/day Neurotoxicity (learning and memory)	300
Short- and Intermediate-term Inhalation[3]	**Bystander (Females 13-49 years of age)**		
	Rat Inhalation Developmental Toxicity Study	NOAEL = 5.27 mg/kg bw/day Bodyweight effects, resorptions, neurological effects	300
	Bystander (General Population, excluding Females 13-49 years of age)		
	Rat Inhalation Developmental Toxicity Study	NOAEL = 5.27 mg/kg bw/day Bodyweight effects	100*
	Occupational		
	Rat Inhalation Developmental Toxicity Study	NOAEL = 5.27 mg/kg bw/day Bodyweight effects, resorptions, neurological effects	300
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 PCPA 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.
*Resorptions and neurological effects in utero are not applicable to this population; therefore, the *Pest Control Products Act* is reduced to one-fold.

Table 1b ETU: Revised Toxicology Reference Values

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute Reference Dose, Females 13–49 years of age	Developmental rat	NOAEL = 5 mg/kg bw/day Malformations in the absence of maternal toxicity	1000
	ARfD Females 13-49 = 0.005 mg/kg bw		
Chronic Dietary	EOGRTS	LOAEL = 0.2 mg/kg bw/day hypertrophy of thyroid and pituitary in parental animals	300
	ADI = 0.0007 mg/kg bw/day		
Acute, Short-, and Intermediate-term Dermal[2] and Inhalation[3]	**Occupational**		
	Developmental rat	NOAEL = 5 mg/kg bw/day Malformations in the absence of maternal toxicity	1000
Short-term, All populations	**Aggregate**		
	EOGRTS	NOAEL = 0.2 mg/kg bw/day Thyroid effects in PND 21 offspring	100
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		

[1]CAF (Composite assessment factor) refers to the total of uncertainty and PCPA 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 45% 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.

Appendix VI Revised Dietary Exposure and Risk Estimates

Table 1 Summary of Dietary Cancer Risk from ETU

Exposure Scenario	Cancer Risk		Notes
	PRVD2013-01	Revised	
Drinking Water only	3.7×10^{-6} EEC[1] = 2.9 ppb	0.69×10^{-6} EEC[1] = 0.57 ppb	• The EEC[1] value of 0.57 ppb was derived from the 2002–2003 EBDC/ETU Task Force US national drinking water monitoring survey. ETU residues could be from both mancozeb and metiram uses.
Food only	4.3×10^{-6}	3.2×10^{-6}	• Domestic uses being cancelled due to occupational risks of concern, which could not be mitigated further, were not included in the dietary risk assessment. These uses were seed treatment for barley, corn, flax, oat and wheat; potato seed-piece treatment; orchard crops including apples and pears; grapes; and greenhouse tomatoes. • An EEC[1] value of 0.57 ppb was derived from the 2002–2003 EBDC/ETU Task Force US national drinking water monitoring survey. ETU residues could be from both mancozeb and metiram uses.
Food and Drinking Water	8×10^{-6}	3.9×10^{-6}	
Potato only[2]	N/A	0.28×10^{-6}	• Only domestic and imported potato commodities were included in the dietary risk assessment. Residues on all other foods were assumed to be zero. • An EEC[1] value of 0.57 ppb was derived from the 2002–2003 EBDC/ETU Task Force US national drinking water monitoring survey. ETU residues could be from both mancozeb and metiram uses.
Potato and Drinking Water[2]	N/A	0.98×10^{-6}	

N/A: Not applicable.
[1]EEC: estimated environmental concentration.
[2]The dietary exposure and risk estimates for this exposure scenario are presented in Table 5 of this Appendix.
Shaded cells indicate risks above the threshold of 1×10^{-6}, which are of concern.

Table 2 Summary of Dietary Acute and Chronic Exposure and Risk from Mancozeb

Population Subgroup	Potatoes only*			
	Acute (99.9th percentile)[1]		Chronic[2]	
	Exposure (mg/kg bw)	%ARfD	Exposure (mg/kg bw)	%ADI
General Population	N/A	N/A	0.000090	0.01
All Infants (<1 year old)	0.000002	0.0	0.000112	0.01
Children 1–2 years old	0.000005	0.0	0.000224	0.01
Children 3–5 years old	0.000004	0.0	0.000208	0.01
Children 6–12 years old	0.000003	0.0	0.000144	0.01
Males 13–19 years old	0.000002	0.0	0.000092	0.01
Males 20–49 years old	0.000002	0.0	0.000074	0.00
Adults 50–99 years old	0.000002	0.0	0.000075	0.00
Females 13–49 years old	0.000002	0.0	0.000069	0.14

N/A: Not applicable.

Population Subgroup	Potatoes only*			
	Acute (99.9th percentile)[1]		Chronic[2]	
	Exposure (mg/kg bw)	%ARfD	Exposure (mg/kg bw)	%ADI

[1]Acute Reference Dose (ARfD) of 0.05 mg/kg bw for females 13–49 years old and 1.7 mg/kg bw for all other populations (including children).
[2]Acceptable Daily Intake (ADI) of 0.023 mg/kg bw/day for all populations.

Table 3 Summary of Dietary Acute Exposure and Risk from ETU

Population Subgroup	Potatoes only*		Potatoes* and Drinking Water**	
	Exposure (mg/kg bw/day)	% ARD[1]	Exposure (mg/kg bw/day)	% ARD[1]
Females 13–49 years old	0.000236	4.7	0.001847	36.9

[1]Acute Reference Dose (ARfD) of 0.005 mg/kg bw for females 13–49 years old.

Table 4 Summary of Dietary Chronic Exposure and Risk from ETU

Population Subgroup	Potatoes only*		Potatoes* and Drinking Water**	
	Exposure (mg/kg bw/day)	%ADI[1]	Exposure (mg/kg bw/day)	%ADI[1]
General Population	0.000005	0.7	0.000016	2.3
All Infants (<1 year old)	0.000002	0.2	0.000045	6.4
Children 1–2 years old	0.000011	1.5	0.000026	3.8
Children 3–5 years old	0.000013	1.8	0.000026	3.7
Children 6–12 years old	0.000008	1.2	0.000018	2.5
Youth 13–19 years old	0.000005	0.7	0.000013	1.9
Adults 20–49 years old	0.000004	0.6	0.000016	2.2
Adults 50+ years old	0.000004	0.5	0.000015	2.1
Females 13–49 years old	0.000004	0.6	0.000015	2.2

[1]Acceptable Daily Intake (ADI) of 0.0007 mg/kg bw/day.

Table 5 Summary of Dietary Cancer Exposure and Risk from ETU

Population Subgroup	Potatoes only*		Potatoes* and Drinking Water**	
	Exposure (mg/kg bw/day)	Lifetime Risk	Exposure (mg/kg bw/day)	Lifetime Risk
General population	0.000005	0.29×10^{-6}	0.000016	0.98×10^{-6}

Potency factor (q_1*) of 0.0601 $(mg/kg\ bw/day)^{-1}$

* Only potato food forms listed in DEEM-FCID were included in the dietary assessment.

** Based on the targeted nature of the 2002–2003 EBDC/ETU Task Force United States national drinking water monitoring survey, the maximum value of 0.57 ppb was considered suitable for use as an estimate of the potential concentration of ETU residues in drinking water from the use of EBDC fungicides, and as such was used in the cancer risk assessment.

Appendix VII Revised Occupational Exposure and Risk Estimates

Table 1 Mancozeb Mixing/Loading and Applying Short- to Intermediate-Term Exposure and Risk Assessment

Use Site Category	Crop	Form	PPE[a]	Application Equipment	Application Rate[b] (kg a.i./ha)	Area Treated per Day[c]	Daily Exposure[d, e] (µg/kg bw/day)		Margin of Exposure[f, g] (MOE)	
							Dermal	Inhalation	Dermal	Inhalation
USC 14: Terrestrial Food Crops (High Acreage Field and Vegetable Crops) (also USC 13: Terrestrial Feed Crops (Potato and Wheat)	Potato	Dry flowable and Wettable granules	Single layer, CR gloves, Respirator	Aerial Mixer/loader	1.68	400	7.152	18.53	2100	280
			Single layer, CR gloves	Closed Cockpit Aerial Applicator			0.227	0.082	66000	64000
			Single layer, CR gloves, ML-Respirator	Open Cab Groundboom (farmer)		107	2.473	8.715	6100	600
				Closed Cab Groundboom (custom)		360	7.231	17.015	2100	310
		Wettable powder in water soluble packaging	Single layer, CR gloves	Aerial Mixer/loader	1.80	400	1.94	1.62	7700	3300
				Closed Cockpit Aerial Applicator			0.24	0.087	63000	60000
				Open Cab Groundboom (farmer)		107	1.132	4.478	13000	1200
				Open Cab Groundboom (custom)		360	3.808	15.066	3900	350
		Solution	Single layer, CR gloves	Open Cab Groundboom (farmer)	1.856	107	2.083	5.734	7200	920
				Open Cab Groundboom (custom)		360	7.007	19.293	2100	270

CR = chemical resistant; ML = mixer/loader; Form = formulation; PPE = personal protective equipment.
[a] Single layer = long pants, long sleeved shirt.
[b] Maximum listed label rate in kilograms of active ingredient per hectare (kg a.i./ha).
[c] Based on default assumptions.
[d] Where dermal exposure µg/kg bw/day = (unit exposure × area treated × application rate × 1% dermal absorption)/80 kg bw.
[e] Where inhalation exposure µg/kg bw/day = (unit exposure × area treated × application rate)/80 kg bw.
[f] Based on the short- to intermediate-term dermal NOAEL of 15 mg/kg bw/day from the oral modified reproductive toxicity study, target MOE of 300.
[g] 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 300. Shaded cells indicate MOEs that approach the target.

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

Use Site Category	Crop	Form	Application Equipment	Application Rate [a] (kg a.i./ha)	Area Treated per Day [b]	Daily Exposure (µg/kg bw/day)				Combined MOE [g]
						ETU Tank Mix [c, d]		Metabolic conversion from MCZ [e]	Total ETU [f]	
						Dermal	Inhalation			
USC 14: Terrestrial Food Crops (High Acreage Field and Vegetable Crops) (also USC 13: Terrestrial Feed Crops (Potato and Wheat)	Potato	Dry flowable and Wettable granules	Aerial Mixer/loader	1.68	400	0.322	0.019	1.926	2.267	2200
			Closed Cockpit Aerial Applicator			0.020	1.65×10^{-4}	0.023	0.044	110000
			Open Cab Groundboom (farmer)		107	0.137	0.013	0.839	0.989	5100
			Closed Cab Groundboom (custom)		360	0.363	0.017	1.818	2.199	2300
		Wettable powder in water soluble packaging	Aerial Mixer/loader	1.80	400	0.088	0.002	0.267	0.357	14000
			Closed Cockpit Aerial Applicator			0.022	1.74×10^{-4}	0.025	0.046	110000
			Open Cab Groundboom (farmer)		107	0.078	0.009	0.421	0.508	9800
			Open Cab Groundboom (custom)		360	0.264	0.029	1.416	1.708	2900
		Solution	Open Cab Groundboom (farmer)	1.856	107	0.122	0.010	0.586	0.718	7000
			Open Cab Groundboom (custom)		360	0.411	0.033	1.973	2.417	2100

Wearing PPE required for the mancozeb risk assessment. See Table 1 for details.
Form = formulation; ETU = ethylene thiourea; MCZ = mancozeb; MOE = margin of exposure; PPE = personal protective equipment
[a] Maximum listed label rate in kilograms of active ingredient per hectare (kg a.i./ha).
[b] Based on default assumptions.
[c] Where dermal exposure µg/kg bw/day = (unit exposure × area treated × application rate × tank mix conversion factor (0.1% for mixer/loader and 0.2% for applicator) × 45% dermal absorption)/80 kg bw.
[d] Where inhalation exposure µg/kg bw/day = (unit exposure × area treated × tank mix conversion factor (0.1% for mixer/loader and 0.2% for applicator) × application rate)/80 kg bw.
[e] Systemic exposure µg/kg bw/day = total exposure to mancozeb (as expressed in Table 1, dermal exposure + inhalation exposure) × metabolic conversion of mancozeb to ETU (7.5%).
[f] 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.
[g] 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 3 ETU Mixing/Loading and Applying Cancer Exposure and Risk Assessment

Use Site Category	Crop	Formulation	Application Equipment	Application Rate [a] (kg a.i./ha)	Area Treated per Day [b]	ETU Absorbed Daily Dose [c] (µg/kg bw/day)	Lifetime Average Daily Dose [d] (µg/kg bw/day)	Cancer Risk [e]
USC 14: Terrestrial Food Crops (High Acreage Field and Vegetable Crops) (also USC 13: Terrestrial Feed Crops (Potato)	Potato	Dry flowable and Wettable granules	Aerial Mixer/loader	1.68	318	2.197	0.093	6×10^{-6}
			Closed Cockpit Aerial Applicator			0.040	0.002	1×10^{-7}
			Open Cab Groundboom (farmer)		60	0.923	0.039	2×10^{-6}
			Closed Cab Groundboom (custom)		240	2.072	0.087	5×10^{-6}
		Wettable powder in water soluble packaging	Aerial Mixer/loader	1.80	318	0.338	0.014	9×10^{-7}
			Closed Cockpit Aerial Applicator			0.042	0.002	1×10^{-7}
			Open Cab Groundboom (farmer)		60	0.469	0.020	1×10^{-6}
			Open Cab Groundboom (custom)		240	1.611	0.068	4×10^{-6}
		Solution	Open Cab Groundboom (farmer)	1.86	60	0.660	0.028	2×10^{-6}
			Open Cab Groundboom (custom)		240	2.269	0.096	6×10^{-6}

Wearing PPE required for the mancozeb risk assessment. See Table 1 for details.
ETU = ethylene thiourea; PPE = personal protective equipment
[a] Maximum listed label rate in kilograms of active ingredient per hectare (kg a.i./ha).
[b] Based on default assumptions for cancer risk assessments.
[c] Represents total daily exposure to ETU expressed in µg/kg bw/day, as presented in Table 2 and adjusted for the lower area treated per day used for cancer risk assessments, when applicable.
[d] Lifetime Average Daily Dose (LADD), calculated using the following formula: Absorbed Daily Dose (mg/kg bw/day) × Treatment Frequency (30 days per year) × Working Duration (40 yrs) / 365 days/yrs × Life Expectancy (78 yrs)
[e] Calculated using the following formula: LADD (mg/kg bw/day) × q_1^* $(0.0601 \text{ mg/kg bw/day})^{-1}$.

Table 4 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/cm^2)	Peak Value[e] (%)	Half-life[f] (days)	Daily Dissipation[g] (%)	Correlation Coefficient (R^2)	Canadian Crops
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	Potatoes
				ETU	-0.079	0.06[i]	0.21	8.8	7.6	0.63	

MCZ = Mancozeb, ETU = ethylene thiourea; DFR = dislodgeable foliar residue.
[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 (In) 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 5 Mancozeb Short- to Intermediate-term Postapplication Risk Assessment and Restricted-Entry Interval

Crops	Rate[a] (kg a.i./ha)	Applications[b]		Activity	TC[c] (cm^2/hr)	DFR[d] (µg/cm^2)	Dermal Exposure[e] (µg/kg bw/day)	MOE[f] (Day 0)	REI[g] (days)
		Number	Interval						
USC 14: Terrestrial Food Crops (Field and Vegetable Crops)									
Potato	1.86	10	7–10	All activities	1750	7.64	13.37	1100	12 hrs

TC = Transfer coefficient; DFR = Dislodgeable foliar residues; REI = Restricted-Entry Interval; MOE = Margin of Exposure.
[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.
[c] Transfer coefficients are based on PMRA default values.
[d] Based on dislodgeable foliar residue data on day 0 using the minimum interval between applications.
[e] Dermal Exposure = DFR × TC × 8 hr × dermal absorption (1%)/80 kg.
[f] 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 15 mg/kg bw/day from the oral developmental neurotoxicity (DNT) study, target MOE of 300.
[g] 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 6 ETU Short- to Intermediate-term Postapplication Risk Assessment and Restricted-Entry Interval

Crop	Rate [a] (kg a.i./ha)	Number of Applications [b]	Activity	TC [c] (cm^2/hr)	MCZ REI [d]	MCZ Exposure [e] (µg/kg bw/day)	ETU Exposure (µg/kg bw/day)			MOE [i]	ETU REI [j]
							Dermal [f]	Metabolic Conversion from MCZ [g]	Total [h]		
USC 14: Terrestrial Food Crops											
Potato	1.86	10	All activities	1750	12 hrs	13.37	3.09	1.00	4.09	1200	12 hrs

TC = Transfer coefficient; DFR = Dislodgeable foliar residues; ETU = ethylene thiourea; MCZ = mancozeb; REI = Restricted-Entry Interval; MOE = Margin of Exposure.
[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.
[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 Table 5.
[e] Refers to mancozeb dermal exposure on the REI day, calculated as Dermal exposure = [MCZ DFR × TC × MCZ Dermal absorption (1%) × 8 hr] / 80 kg.
[f] Refers to ETU dermal exposure on the REI day, calculated as Dermal exposure = [ETU DFR × TC × ETU Dermal absorption (45%) × 8 hr] / 80 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] Restricted-entry interval refers to the day following application that ETU residues are less than the target DFR and calculated MOEs exceed the target of 1000.

Table 7 ETU Postapplication Cancer Exposure and Risk Assessment

	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 Lifetime Average Daily Dose[e] (µg/kg bw/day)	Cancer Risk[f]
USC 14: Terrestrial Food Crops								
Potato	1.86	10	All activities	1750	12 hrs	4.09	0.17	1×10^{-5}

TC = Transfer coefficient; DFR = Dislodgeable foliar residues; ETU = ethylene thiourea; REI = Restricted-Entry Interval; MOE = Margin of Exposure.
[a] Maximum listed label rates expressed in kilograms a.i./ha.
[b] Transfer coefficients are based on PMRA default values.
[c] REI day refers to the day following application that mancozeb and ETU exposure exceed the target MOE, as presented in Table 6.
[d] ETU Absorbed Daily Dose (ADD) expressed in µg/kg bw/day.
[e] ETU LADD (Lifetime Average Daily Dose, mg/kg/bw/day) calculated using the following formula:
LADD = Absorbed Daily Dose ETU (mg/kg bw/day) × Exposure Days (30 days/yr) × Working Duration (40 yrs/lifetime)
365 days/yrs × Life Expectancy (78 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)$^{-1}$.

Table 8 Mancozeb Inhalation Exposure Assessment and MOEs for Bystanders

Population	Air Concentration (µg/m^3) [a]	Inhalation Rate (m^3/hr)	Exposure Time (hrs/day)	Inhalation Exposure (µg/kg bw/day) [b]	MOE [c]
Adult	4.76	0.64	2.3	0.088	60000
Youth		0.63	1.9	0.100	53000
Children (1<2 yrs)		0.33	2.3	0.328	16000

MOE = margin of exposure

[a] Maximum concentrations from Garron et al., 2009.

[b] Where inhalation exposure = air concentration inhalation rate × exposure time/body weight

[c] Based on short-, intermediate-term NOAEL of 5.27 mg/kg bw/day with a target MOE of 300 for females 13–49 years of age and 100 for all other populations. Air concentration measurements for ETU were not available.However, since ETU is a contaminant and degradation product of mancozeb, air concentrations are expected to be low in comparison to mancozeb.

Table 9 ETU Inhalation Exposure Assessment and Cancer Risk for Bystanders

Population	MCZ Exposure [a] (µg/kg bw/day)	ETU Exposure [b] (µg/kg bw/day)	Exposure Days/Year	LADD [c] (µg/kg bw/day)	Total LADD (µg/kg bw/day)	Cancer Risk [d]
Adult	0.088	0.0066	10	1.45E-04	2.02×10^{-4}	1×10^{-8}
Youth	0.100	0.0075		1.32E-04		
Children (1<2 yrs)	0.328	0.0246		4.33E-05		

ETU = ethylene thiourea; MCZ = mancozeb; LADD = Lifetime average daily dose

[a] Based on mancozeb inhalation exposure calculated in Table 8.

[b] ETU Exposure calculated based on the metabolic conversion of mancozeb = MCZ exposure × 7.5%.

[c] LADD = ETU exposure × exposure frequency (10 days) × exposure duration (5 years for youth and children and 63 years for adults)/(365 days/year × Life expectancy (78 yrs))

[d] Cancer risk = LADD × q_1^* (0.0601 (mg/kg bw/day)$^{-1}$).

Table 10 ETU Aggregate Exposure Assessment, MOEs, and Cancer Risk for Bystanders

Population	ETU Exposure [a] (mg/kg bw/day)	ETU Chronic Dietary Exposure [b] (mg/kg bw/day)	Aggregate Exposure [c] (mg/kg bw/day)	MOE [d]	ETU LADD [e] (mg/kg bw/day)	Total ETU LADD [f] (mg/kg bw/day)	Cancer Risk [g]
Adult	6.57E-06	1.60E-05	2.26E-05	8900	2.02×10^{-7}	1.62×10^{-5}	1×10^{-6}
Youth	7.50E-06	1.30E-05	2.05E-05	9800			
Children (1<2 yrs)	2.46E-05	2.60E-05	5.06E-05	4000			

ETU = ethylene thiourea; MOE = margin of exposure; LADD = lifetime average daily dose

[a] ETU bystander exposure based on Table 9 converted to mg.

[b] ETU Chronic dietary exposure based on Appendix VI, Table 4.

[c] ETU Aggregate exposure = ETU exposure + ETU chronic dietary exposure

[d] Based on short-term aggregate NOAEL of 0.2 mg/kg bw/day with a target MOE of 100.

[e] ETU LADD based on Table 9.

[f] Total ETU LADD = ETU LADD + ETU Chronic dietary exposure for general population from Appendix VI, Table 4.

[g] Cancer risk = LADD × q_1^* $(0.0601\ (mg/kg\ bw/day)^{-1})$

References

Studies considered in the Updated Health Assessment

Toxicology

A. List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
2039432	2010, Ethylene thiourea (ETU): Developmental Toxicity Study in Rabbits. DACO:4.5.3
2055156	2011, Ethylene thiourea (ETU): Dietary reproduction probe study in Crl:CD(SD) rats. DACO:4.5.1, 4.5.14
2313478	2013, Ethylenethiourea (ETU): An F1 extended one generation reproductive toxicity study in Crl:CD(SD) RATS. DACO: 4.5.1,4.5.14
2363857	2012. Immunotoxicity study in male Wistar rats. Administration via the diet for 4 weeks. DACO: 4.3.8
2047262	2007, A dietary exposure and dose range-finding developmental neurotoxicity study of mancozeb in rats. DACO: 4.5.14
2047261	26 June 2008. An oral (dietary) developmental neurotoxicity study of mancozeb in rats. DACO: 4.5.14
2363852	2012, Mancozeb: assessment of immunotoxic potential using the sheep red blood cell assay after 28-day dietary exposure to male Crl:CD(SD) Rats. DACO: 4.3.8

B. Additional Information Considered

Published Information

PMRA Document Number	Reference
2849973	2008, Gavage DNT study of Propylthiouracil (PTU) in Wistar rats. Relationship between transient hypothyroxinemia during development and long-lasting behavioural and functional changes. Marta Axelstad. DACO:4.5.14
2849980	2009, Assessment of developmental effects of hypothyroidism in rats from in utero and lactation exposure to anti-thyroid agents. Makoto Shibutani, Gye-Hyeong. DACO: 4.5.2
2849986	2011, Developmental Neurotoxicity study in Wistar rats (HanTac), Axelstad. DACO: 4.5.14

Dietary

A. List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
2363861	1998, Analysis of Mancozeb and Ethylenethiourea by FDA Pesticide Analytical Manual Volume I, Protocols I through IV. DACO 7.2.1
2363866	2002, Validation of an Analytical Method for the Determination of Dithane® M-45 (as CS2) in grass, Sand and Poecilus cupreus by GC/MS. DACO 7.2.1
2363868	1986, Analytical Reports of Mancozeb and ETU Residues for Sweet Com Samples. DACO 7.4.2.
2363871	1986, Analytical Reports of Dithane and ETU Residues for Onion Samples. DACO 7.4.2.
2363877	1986, Analytical Reports of Dithane and ETU for Summer Squash Residue Samples. DACO 7.4.2.
2363881	1986, Analytical Reports of Dithane and ETU for Winter Squash Residue Samples. DACO 7.4.2.
2363883	1986, Analytical Reports of Mancozeb and ETU Residues for Papaya Samples. DACO 7.4.2.
2363886	1986, Analytical Reports of Dithane and ETU for Pear Residue Samples. DACO 7.4.2.
2363888	1987, Analytical Report of Mancozeb and ETU Residues in Pear Samples. DACO 7.4.2.
2363890	1986, Analytical Reports of Mancozeb and ETU Residues for Field Corn Samples. DACO 7.4.2.
2363895	1988, Analytical Report of Mancozeb and ETU in Cranberry Samples. DACO 7.4.2.
2363897	1986, Analytical Report of Mancozeb and ETU Residues in Cucumber Samples. DACO 7.4.2.
2363900	1988, Analytical Report of Dithane Fungicide and ETU Residues in Cucumber Samples. DACO 7.4.2.
2363902	1986, Analytical Reports of Mancozeb and ETU Residues for Grape Samples. DACO 7.4.2.
2363904	Analytical Reports of Dithane and ETU Residues for Celery Samples. DACO 7.4.2.
2363906	1998, Mancozeb: Magnitude of Residue on Ginseng. DACO 7.4.2.
2363910	2002, Residual Analysis of Grass Samples and Poecilus cupreus treated with Dithane® M-45. DACO 7.4.2.
2363912	1991, EBDC/ETU Consumer Practice Study Final Report. DACO 7.8.
2363916	2001, EBDC/ETU Task Force National Drinking Water Monitoring Survey. DACO 7.8.
2363931	2002, EBDC/ETU Task Force National Drinking Water Monitoring Survey - Interim Report #2 - Sampling Details and Analytical Results for October 27, 2001 through April 26, 2002. DACO 7.8.

2363949 2002, EBDC/ETU Task Force National Drinking Water Monitoring Survey - Interim Report #3 - Sampling Details and Analytical Results for April 27, 2002 through October 25, 2002. DACO 7.8.
2363956 2003, EBDC/ETU Task Force National Drinking Water Monitoring Survey - Final Report - Sampling Details and Analytical Results for May 4, 2002 through June 11, 2003. DACO 7.8.
2364293 2013, Comprehensive Data Summaries - Response of Mancozeb Task Force - on proposed re-evaluation decision for Mancozeb.

Occupational /Residential

A. List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
1335563	2006, GAUCHO 480 SC – Worker Exposure During On-farm and Commercial Seed Treatment of Cereals. DACO 5.4, 5.5
1885209	2010, Observational Study to Determine Dermal and Inhalation Exposure to Workers in a Commercial Seed Treatment Facilities: Mixing/Treating with a Liquid Pesticide Product and Equipment Clean-out. AHETF.
2313627	2013, Determination of Dermal and Inhalation Exposure to Operators During Loading and Sowing Seed Treated with Austral® Plus Net Using Conventional or Pneumatic Sowing Machines. AHETF. DACO 5.4, 5.5
2115788	2008, Data Submitted by the ARTF to Support Revision of Agricultural Transfer Coefficients.
2572744	2015, Agricultural Handler Exposure Scenario Monograph: Open Pour Mixing and Loading Dry Flowable Formulations. DACO 5.4, 5.5
2572745	2015, Agricultural Handler Exposure Scenario Monograph: Open Pour Mixing and Loading of Liquid Formulations. DACO 5.4, 5.5
2572743	2014, Agricultural Handler Exposure Scenario Monograph: Open Cab Airblast Application of Liquid Sprays. DACO 5.4, 5.5
2172938	2012, Agricultural Handler Exposure Scenario Monograph: Closed Cockpit Aerial Application of Liquid Sprays. DACO 5.4, 5.5
1913109	2009, Agricultural Handler Exposure Scenario Monograph: Open Cab Groundboom Application of Liquid Sprays. DACO 5.4, 5.5

B. Additional Information Considered

Published Information

PMRA Document Number	Reference
	Brouwer, D.H., de Vreede, S.A.F., Meuling.,W.J.A., van Hemmen, J.J. 2000. Determination of the efficiency for pesticide exposure reduction with protective clothing: a field study using biological monitoring. Chapter 5 In: Assessment of Occupational Exposure to Pesticides in Dutch Bulb Culture and Glasshouse Horticulture. Doctoral Thesis of D.H. Brouwer. pp.158-179.
	Boman, A., Estlander,T.,Wahlburg J.E., Maibach, H.I. 2005. Protective Gloves for Occupational Use Second edition. CRC Press LLC.
	Garrigou, A., Baldi I.,Le Frious P., Anselm R., Vallier M. 2011. Ergonomic contribution to chemical risks prevention: an ergotoxicologcial investigation of the effectiveness of coverall against plant pest risk in viticulture. 42: 321-330.
	Graves, CJ., Edwards, C., Marks R. 1995. The effects of protective occlusive gloves on stratum corneum barrier properties. Contact Derm 33: 183-187.
	Keifer, M.C., 2000. Effectiveness of Interventions in Reducing Pesticide Overexposure and Poisonings. American Journal of Preventive Medicine. 18 (4S); 80-89.
	Rawson, B.V., Cocker, J., Evans, P.G. Wheeler, J.P. and Akrill, P.M. 2005. Internal contamination of Gloves: routes and Consequences. Am. Occup. Hyg. 49 (6): 535-541.

Studies considered in the Updated Environmental Assessment

A. List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
2364293	2013, Comprehensive Data Summaries - Response of Mancozeb Task Force - on proposed re-evaluation decision for Mancozeb.