Re-evaluation Decision RVD2018-20

Metiram and Its Associated End-use Products

Final Decision

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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.

Metiram is a protectant, contact fungicide with multi-site mode of action used in agriculture on a number of food crops. Three products containing metiram are currently registered in Canada under the authority of the *Pest Control Products Act*, including one technical grade active ingredient and two commercial class end-use products. Currently registered products containing metiram are listed in Appendix I.

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

This re-evaluation decision was consulted on as Proposed Re-evaluation Decision PRVD2014-03, *Metiram*.[2] The 90-day consultation period ended on 18 September 2014. The PMRA received comments and new data/information 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 PRVD2014-03. Appendix II of this document summarizes the comments received and provides the PMRA's response.

Regulatory Decision for Metiram

The PMRA has completed the re-evaluation of metiram. Under the authority of the *Pest Control Products Act*, the PMRA has found the continued registration of products containing metiram acceptable for foliar application to potatoes. An evaluation of available scientific information found that the foliar application of metiram 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 metiram 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 metiram in Canada:

- Cancel all Canadian uses for metiram with the exception of foliar application to potatoes.
- Permit a maximum of 3 applications per year on potatoes, at a maximum application rate of 1.40 kg a.i./ha with 7-day application intervals, and a 14-day pre-harvest interval using aerial or ground spray only.

To protect mixer/loader/applicators:

- Engineering controls: Closed mixing and loading (water soluble packaging), and a respirator with an open cab for groundboom application or closed cab application.
- Additional layer of personal protective equipment: Coveralls over a long-sleeved shirt, and long pants, and chemical-resistant gloves.

To protect postapplication workers:

- Restricted-entry intervals (REI): Depending on the activity, lengthened REIs are required.

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

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

Metiram does not present unacceptable risk to human health when used according to the revised conditions of registration, which include 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 metiram in Canada

- Spray buffer zones to protect non-target habitats from pesticide spray drift.
- 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 metiram to aquatic organisms; birds; small, mammals; certain beneficial insects; and terrestrial plants.

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.

Other Information

Any person may file a notice of objection[3] regarding this decision on metiram 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 of Metiram

The initial toxicological assessment for metiram was provided in PRVD2014-03. Comments and data were received from the registrant regarding a range of issues including reproduction and developmental toxicity, neurotoxicity, and genotoxicity. Data addressing deficiencies noted in PRVD2014-03, including an acute neurotoxicity study, a two-generation reproduction study with a comparative thyroid assay (adult vs. young), along with an acceptable bridging rationale for the use of the ethylene thiourea (ETU) extended one-generation reproduction toxicity study (EOGRTS) in rats. This is in lieu of a reproductive toxicity study for metiram, as well as a rabbit developmental toxicity study using ETU, were submitted (see Appendix IV). Comments were also provided on registrant efforts to address data gaps identified by the PMRA. Overall, there were some changes to the toxicology reference values from those outlined in PRVD2014-03. As a result of the new data submitted to address deficiencies identified in PRVD2014-03, the previously applied database uncertainty factor was removed. Revised reference values are provided in Appendix V, Tables 1a and 1b. Detailed responses to the comments received are provided in Appendix II.

1.2 Dietary Exposure and Risk Assessment

The initial dietary risk assessment for the re-evaluation of metiram was presented in the Proposed Re-evaluation Decision (PRVD2014-03). Dietary risks of concern were identified from exposure to metiram and cancer risks of concern were identified from exposure to ETU, a degradate of metiram and other ethylenebisdithiocarbamate (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 PMRA, additional data that may help refine the risk assessments were identified in PRVD2014-03.

Comments and data received from the Mancozeb Task Force (MTF) through the consultation on the Proposed Re-evaluation Decision for mancozeb (PRVD2013-01) were also considered relevant to the metiram and ETU assessment. The Canadian Horticultural Council and other stakeholders provided information regarding the importance of metiram. Comments related to the dietary exposure assessment and the PMRA responses are summarized in Appendix II.

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 PRVD2014-03. 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) Updated percent crop treated estimates and percent domestic/import food supply information were used in conjunction with chemical-specific processing factors and metiram-to-ETU conversion factors to adjust the available residue data.

3) 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.

4) The dietary exposure and health risk assessments for metiram 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 continued 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 the Canadian Horticultural Council. Of these, only the foliar use of metiram on potatoes resulted in no occupational risks of concern. Therefore, the dietary exposure and risk assessments for metiram and ETU were revised to reflect the potato use only. As such, only food derived from potatoes were included (for example, uncooked potato, cooked potato, chips and potato flour).

As metiram is not expected to occur in drinking water, chronic and acute risk assessments were conducted to assess exposure to metiram through consumption of food only. A cancer risk assessment was not conducted for metiram 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 metiram through food (potato use only) are not of concern.
- Metiram is not expected to occur in drinking water due to its rapid degradation and low water solubility. Therefore, non-cancer risks from exposure to metiram 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 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 PRVD2014-03, chemical-specific enforcement methods for the EBDC fungicides, including

metiram, are not currently available. Therefore, the PMRA had proposed to revise the residue definition for metiram to residues of "metiram expressed as carbon disulphide (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, PMRA is considering revising the residue definition for the DMDTCs to carbon disulphide. 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, PMRA has sufficient data to propose an MRL for metiram expressed as carbon disulphide 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 (CFIA). 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 metiram 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. 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 risk assessment (see Appendix VII). However, the overall risk conclusions remained consistent with those presented in PRVD2014-03. Based on the updated dietary risk assessment (see section 1.2), and the determination in PRVD2014-03 that the occupational risks associated with the potato foliar use were not of concern, the updates to the occupational exposure and risk assessments for metiram outlined below reflect the potato foliar use only.

1.3.1 Applicator Exposure Risk Estimates

For the potato foliar use, calculated margins of exposure (MOE) for mixer, loader, and applicator exposure exceed the target MOE, and are not of concern for both metiram and ETU, and there are no cancer risks of concern from ETU. Therefore, this use is not of concern, provided additional PPE (coveralls over a long-sleeved shirt, and long pants, and chemical-resistant gloves, respirator for open cab application or closed cab application), and engineering controls

(water dispersible granules in water soluble packaging) are employed. The occupational risk conclusions for this use are consistent with those presented in PRVD2014-03.

1.3.2 Postapplication Exposure Risk Estimates

For the potato foliar use, the calculated MOEs exceeded the target MOEs for both metiram and ETU and there are no cancer risks of concern from ETU with a Restricted-entry interval (REI) of 30 days for hand-set irrigation, 5 days for roguing, and 12 hours for all other activities.

1.3.3 Bystander Spray Drift Inhalation Risk Estimates

Based on the previously published PRVD2014-03, there are no risks of concern for bystanders

1.4 Aggregate Exposure and Risk Assessment

In PRVD2014-03, the aggregate risk assessment considered exposure to metiram from food and drinking water only. Although there are no residential uses for metiram, 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 identified from dietary exposures of 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 United States Environmental Protection Agency.

Exposure to ETU in food and drinking water may occur from the use of metiram or any other EBDC fungicide. Presently, mancozeb 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 metiram to potatoes is not of concern. This assessment also considers residues of mancozeb 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

The environmental risk assessment was conducted on exposure to "metiram complex," which is produced in the environment as a result of the application of the active ingredient metiram. Metiram complex includes the transformation product ethylenethiourea (ETU), which is a common transformation product of the EBDC (ethylenebisdithiocarbamate) pesticide such as, mancozeb and nabam. However, nabam is registered in Canada for industrial uses only. The amount of ETU produced in the environment from the use of metiram is expected to be small compared to other uses. Additional information on the environmental risks of ETU can be found in the assessment of mancozeb (PRVD2013-01).

During the consultation period of PRVD2014-03, the registrant proposed to modify the foliar use pattern on potato, reducing the application rate (from 1800 g a.i./ha to 1400 g a.i./ha) and number of applications per season (from 10 down to 3), with a 7-day application interval. The registrant also submitted studies in response to data gaps identified in PRVD2014-03. The studies included metiram degradation studies (foliar, arthropod and aerobic aquatic) and environmental toxicology studies (predatory mites, freshwater/marine invertebrates and fish). Following review, updated endpoints were incorporated into an updated environmental risk assessment (see Appendix VIII).

The environmental risk assessment has been updated to reflect the revised use pattern for potato and incorporate the submitted study data. Updates include revised risk assessments for terrestrial plants and marine/estuarine organisms, freshwater invertebrates as well as the use of foliar and arthropod residue data to estimate exposure to birds and mammals that may feed on contaminated insects and plants.

2.1 Updates to the Environmental Risk Assessment

When metiram is released into the environment, it can enter soil and surface water where it is expected to break down quickly to form metiram complex. Metiram complex is not expected to build-up in the soil and be carried over into the next growing season.

In aerobic aquatic environments, metiram complex is expected to have slight to moderate persistence. Metiram complex residues are not volatile and are not expected to be found in the air or be subject to long range transport. Metiram complex is not expected to bioaccumulate in organisms.

Metiram complex does not pose risks of concern to earthworms and bees. When used at the proposed application rates on potato without any risk reduction measures, metiram complex may cause adverse effects on plants, certain beneficial insects, birds, mammals, aquatic organisms and amphibians. Mitigation measures in the form of spray buffer zones and hazard statements are

required to reduce exposure to non-target organisms. When used according to the revised label directions, metiram complex is not expected to pose risks of concern to the environment.

The revisions to the environmental risk assessment resulted in reduced environmental risk (lower risk quotients) as compared to those presented in PRVD2014-03. Some potential risks were still identified for aquatic organisms (freshwater and marine), birds and mammals (using foliar and arthropod dissipation half-life provided by the registrant and incorporated into the review), predatory mites, and terrestrial vascular plants; however, the exceedances of the Level of Concern (LOC) were small and can be addressed with the implementation of additional mitigation measures. Mitigation in the form of spray buffer zones (up to 5 m for field sprayers and 450 m for aerial applications) are required to protect terrestrial, amphibian, freshwater and marine habitats. Product labels will require instructions on reducing runoff, hazard statement warning of the potential to contaminate ground water through leaching and warnings regarding the toxicity of the product to aquatic organisms, birds, small wild mammals, certain beneficial insects and terrestrial plants.

3.0 Incident Reports

As of 30 January 2018, the PMRA had received one moderate environment incident involving metiram. Damage via drift was reported to grape crops after several active ingredients including metiram were applied to a neighboring corn field. Visible injury, curling leaves and pale veins, were noted.

The United States Ecological Incident Information System (EIIS) was also searched for environmental incidents. As of 30 January 2018, there was one incident in the EIIS database. Mortality was reported in an unknown aquatic species as a result of a metiram product runoff from potato fields. The incident was assigned a causality level of unlikely.

As of 30 January 2018, the PMRA had received one human incident involving metiram. In this incident, the individual reported having skin contact with a product containing metiram on one occasion and, since then, started developing symptoms of swollen eye, erythema and rash every time they applied the product. The active metiram and the reported product are potential skin sensitizers. The label of the reported product does not contain the hazard signal words “POTENTIAL SKIN SENSITIZER” as required on the primary display panel, although, a statement is present on the secondary panel of the label. As such, the label will be amended as noted in Appendix III. No other risk mitigation measures are required as a result of the incident.

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 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
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
rel	relative
ss	statistically significant
SD	Sprague Dawley
SRBC	sheep red blood cells
TGAI	technical grade active ingredient
$T_{1/2}$	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
w	week(s)
vs.	versus
wt	weight

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

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
20084	Technical	BASF Canada Inc.	TECHNICAL METIRAM (POLYRAM)	Solid	Metiram 89%
20087	Commercial		POLYRAM DF WATER DISPERSIBLE GRANULAR FUNGICIDE	Wettable Granules	Metiram 80%
30395	Commercial		CABRIO PLUS	Wettable Granules	Pyraclostrobin 5.00%; Metiram 55%

[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 PRVD2014-03, *Metiram,* comments and data related to the health risk assessment and value of metiram were received. In addition, information received from the Mancozeb Task Force (MTF) and the Canadian Horticultural Council through consultation on PRVD2013-01 (Mancozeb) was also considered relevant to the metiram and ETU assessments.

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

1.0 Comments and Responses Related to Toxicology

As a result of new information, and in consideration of the comments submitted following publication of PRVD2014-03, the PMRA has updated the toxicology assessments. The evaluation of new studies and information is reflected in Appendix IV, Tables 1a and 1b. Updates to Toxicology Reference Values for risk assessment are reflected in Appendix V, Tables 1a and 1b.

1.1 Comment concerning the metiram toxicology database deficiencies noted by the PMRA in PRVD2014-03

Additional data was submitted by the registrant to address the developmental neurotoxicity, identified by the PMRA in PRVD2014-03, through assessment of the thyroid-related parameters in the submitted enhanced reproductive toxicity study, and Extended One Generation Reproductive Toxicity Study (EOGRTS) conducted with ETU, which assessed neurotoxicity endpoints in pups. Additionally, a newly conducted rabbit developmental toxicity study on ETU, in place of a rabbit developmental toxicity study with metiram, was submitted.

The registrant requested the PMRA to revisit the Toxicology Reference Value selection, and associated uncertainty factors, in consideration of the data submitted to address developmental toxicity concerns identified in PRVD2014-03.

PMRA Response:
The PMRA considered the additional information in the context of the previously available toxicology database. The hazard assessment described in PRVD2014-03 was updated to incorporate the new information, Appendix IV, Tables 1a and 1b. The new studies submitted (acute neurotoxicity study, 2 generation reproduction study with a comparative (adult vs. young) thyroid assay, along with an acceptable bridging rationale for the use of the ETU EOGRT study in rats (in lieu of a new metiram rat reproduction study) and the ETU rabbit developmental toxicity study, were considered sufficient to address the toxicological data gaps identified in PRVD2014-03. As a consequence, the toxicology reference values and associated uncertainty factors chosen for risk assessment were updated (Appendix V, Tables 1a and 1b).

1.2 Comment concerning the amount of ETU formed after administration of metiram

The registrant suggested that the risk assessment could be refined by using a metiram specific conversion to ETU rate rather than the average conversion rate for the pesticides in the EBDC chemical class which produce ETU.

PMRA Response:
For the purpose of risk assessment, the PMRA, in agreement with the United States Environmental Protection Agency (USEPA), is using an in vivo metabolic conversion of parent EBDC pesticide to ETU of 7.5% on a weight basis [USEPA 1989]. This value represents an average value for all EBDC pesticides (mancozeb, metiram, maneb, zineb, nabam). Maneb and zineb are not currently registered in Canada.
The total ETU exposure for treated animals using metiram-specific conversion rates is approximately 6.5% (4% from the metabolic conversion + 2.5% from metiram degradation in the feed). This does not result in a significant difference compared to the conversion rate of 7.5% identified above.

Additionally, from an enforcement and residue perspective, it is not possible to determine the source of the ETU, since all the EBDC pesticides contain ETU as a contaminant, as a degradate and from metabolism. ETU also has non-pesticidal uses, such as a vulcanization accelerator, in electroplating baths, in dyes, synthetic resins, and pharmaceuticals and as a scavenger in waste water treatment, making it impossible to identify the source of residues in some matrices.

1.3 Comments concerning the neurotoxic potential of metiram

In PRVD2014-03, the PMRA noted some evidence of potential neurotoxicity in short-term oral studies. Concern for potential neurotoxicity in the young, either directly or indirectly through effects on thyroid hormones, formed the basis for identification of the requirement of a developmental neurotoxicity study to address these concerns. The registrant requested that PMRA reconsider the neurotoxic potential of metiram based on the additional submitted neurotoxicity and developmental neurotoxicity data for both metiram and ETU. Specifically, the commenter requested a reconsideration of decreased myelination in sciatic, sural, and tibial nerves.

PMRA Response:
Following a reconsideration of the 90-day dietary toxicity study in rats, including the neurotoxicological addendum (PMRA #1589559), the PMRA agrees that the myelinated axon area for sciatic, sural, and tibial nerves was not statistically significantly decreased in the high dose females compared to control animals. However, the decrease in the areas for the myelinated axons of sciatic, sural and tibial nerves is still considered to be a treatment related effect. Evidence of neurotoxicity was also seen in another metiram rat 90-day dietary toxicity study (PMRA #1589582), as indicated by muscle atrophy associated with proliferation of sarcomlemmal nuclei, and hindlimb paralysis at a higher dose. Similar findings were noted in the supplemental chronic toxicity study in rats (PMRA #1230454, 1230456); increased incidence and severity of muscular atrophy, along with decreased T_4, increased T_3.

With respect to subchronic neurotoxicity potential of metiram, including potential neurotoxicity associated with ETU, results from the EOGRT study (PMRA #2313478), the metiram 2-generation reproduction toxicity study (PMRA #2458356) are considered sufficient to support a neurotoxicity NOAEL at 31 mg/kg bw/day metiram, corresponding to a dose level of 2 mg/kg bw day ETU based on metabolic bioconversion.

The evaluation of new information and reconsideration of previously submitted data did not alter the toxicology assessment outlined in PRVD2014-03. The Toxicology Reference Values selected for risk assessment are protective of concerns related to neurotoxicity.

1.4 Comment concerning the quality of the rabbit developmental toxicity study

The registrant requested that PMRA reconsider its characterization of the metiram rabbit developmental toxicity study as supplemental.

PMRA Response:
The rabbit developmental toxicity study (PMRA #1589585, 1589586) was considered supplemental as it lacked documentation of a detailed examination of the fetal heads according to OECD guideline for a developmental toxicity study. As a result, characterization of the study as supplemental remains unchanged.

1.5 Comment concerning the epidemiological link to neurotoxicity for maneb

The link to epidemiological findings made with maneb and mancozeb was considered inappropriate by the registrant, as unlike maneb and mancozeb, metiram does not contain manganese.

PMRA Response:
PMRA agrees with the comment and has revised the statement.

1.6 Comment concerning the PMRA's assessment of the genotoxic potential of ETU

The registrant requested that the characterization of the genotoxic potential of ETU be revisited.

PMRA Response:
There are about 100 ETU genotoxicity studies available in the toxicology database. In 1988, the World Health Organization 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 abberations). 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 PRVD2014-03: ETU has weak genotoxic potential (USEPA Reregistration Decision2005). A q_1* approach for cancer risk assessment was presented in PRVD2014-03. 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".

1.7 Comments concerning PMRA's assessment of the carcinogenic potential of metiram

The registrant requested that the PMRA revisit its hazard and risk assessment approach to characterizing the carcinogenic risk associated with exposure to metiram for both the thyroid and liver tumours noted in experimental animals. The use of a quantitative approach (q_1*) based on the liver tumours in mice was not considered to be the most biologically relevant tool for chronic risk assessment and the thyroid tumours observed in rats were not felt to be relevant to humans.

PMRA Response:
No additional toxicology data was submitted to support the position outlined in the comment. ETU is currently classified by the USEPA as a B2 carcinogen, with a q_1* = 0.0601 (mg/kg bw/day). The low-dose extrapolation for human risk assessment is based on liver tumours in female mice. Mode of action data (MOA) was not submitted for either the liver or thyroid tumours to support a reconsideration of their relevancy to humans or to allow the use of a threshold approach for risk assessment.

The PMRA concurs with the USEPA assessment and considers ETU to be the residue of concern for the cancer assessment of all EBDC fungicides. This position was recently confirmed in the USEPA Scoping Document in Support of Registration Review (1 June 2015). These tumours occurred at comparable or lower doses than the thyroid and pituitary tumours. Although the comment contained a rationale to dismiss the relevance of the liver tumours, this rationale was considered insufficient in the absence of supporting MOA data presented in the IPCS framework for assessment of such data. Thus, the PMRA approach for assessing the carcinogenic risk associated with ETU and Metiram remains unchanged.

1.8 Comment concerning the teratogenic effects of ETU

While acknowledging that ETU is considered to be a developmental toxicant, the human relevance of developmental findings in rats was challenged by the registrant, based on the lack of such findings in mice, hamsters, rabbits and guinea pigs, and in consideration of potential rat-specific metabolism of ETU.

PMRA Response:
There is a steep dose-response with regard to developmental toxicity of ETU in rat. Developmental toxicity occurs in rabbits as well, but at higher doses than in rats. Although there are differences in the metabolism, storage and timing of action for thyroid hormone between mammalian species, there no information available indicating that humans would be less sensitive than the rat to the developmental effects of ETU. Zoeller and Crofton, (2005) concluded that humans and rats may be similarly sensitive to PTU, a close structural analog of ETU, and its effects on thyroid hormone synthesis, with rats exhibiting effects on hormone levels after shorter exposures than in humans, though the ultimate effect may be the same.

The data from the EOGRT study confirmed a clear relationship between the thyroid hormone disruption at relatively low doses and neurotoxic and reproductive effects in rats. In addition, there are many animal and human studies in the published scientific literature that have shown a clear correlation between the transient maternal hypothyroidism during gestation and lactation, and neurotoxicity and reproductive effects in the offspring. The human relevance of the rat

developmental toxicity following exposure to metiram and ETU cannot be excluded. The PMRA's hazard conclusions with respect to the developmental effects remain unchanged.

1.9 Comment concerning the magnitude of the *Pest Control Products Act* and database uncertainty factors

The registrant stated that the *Pest Control Products Act* factor (PCPA factor) should be reduced to 1-fold. In support this position, the commenter submitted additional data to support the reduction of the 10-fold database uncertainty factor applied by the PMRA.

PMRA Response:
Following assessment of the newly submitted data, and consideration of submitted comments, the uncertainty factors applied to selected endpoints were reassessed along with the selection of endpoints for risk assessment. The revised toxicology reference values and associated uncertainty and PCPA factors chosen for risk assessment are noted in Appendix V, Tables 1a and 1b.

2.0 Comments and Responses Related to Dietary Exposure

2.1 Comment concerning the selective food commodities

Based on the statement that the grape commodities are driving the risk assessment, the Quebec Horticultural Council indicated that the commodity: grapes - wine; should not be taken into consideration in the risk assessment for children and pregnant women subpopulations.

PMRA Response:
The Canadian Food Intake Database used in the risk assessment estimation, takes into consideration the food consumption differences based on age and gender. The commodity: grapes – wine, was identified as a risk driving commodity for the general population sub-group.

2.2 Submitted food residue data study

In response to the consultation document PRVD2014-03, the PMRA received a food residue data study, a food residue summary, a rotational crop study, and a rotational crop summary from the registrant.

PMRA Response:
The data was reviewed by PMRA and the assessment is provided below.

<u>Food residue data:</u>

The registrant provided a table and a summary of field trial data conducted at several locations in the European Union (EU) on grapes, processed grapes, apples, potatoes and tomatoes. These studies were conducted at the new proposed application rate which would give the PMRA an indication of the residue value that can be expected with the new proposed application rate. The registrant considers that the data would be representative of Canada because it represents a wide distribution of geographic area in the EU (that is, both Northern and Southern EU) including several sites with conditions similar to Canada. However, the locations were not similar geographically and

climatically to Canadian agricultural zones and the results could not be translated from the EU geographical areas where the studies were performed to Canada. Furthermore, some of the analytical procedures were performed beyond the validated period of frozen storage stability. As such, the residue data provided is not considered acceptable to be used in the dietary risk assessment.

Rotational crops data:

The data was reviewed and found to be acceptable. The study and the summary of the study presented the total radioactive residues found in lettuce, white radish and spring wheat replanted in the metiram treated soil after 30 days, 121 days, and 365 days from the application. Since metiram is not soluble in water, it cannot be taken up by crops as such, and was, consequently, not detected by the residue analyses. Uptake of metiram by crops implies the decomposition of the metiram complex and formation of soluble degradation products in soil. The soil metabolites of metiram were taken up and transformed in the rotational crops primarily into sugars (glucose, fructose and sucrose), which were, without exception, the most abundant components in all matrices. In the present study, neither ETU, nor any other known degradation product of metiram was found. Therefore, replanting with other crops in areas treated with metiram can be done at the next growing season.

3.0 Comments and Responses Related to the Dietary Exposure Assessment of ETU provided by the Mancozeb Task Force (MTF)

Comments and data received from the Mancozeb Task Force (MTF) through the consultation on PRVD2013-01 (mancozeb) were also considered relevant to the metiram and ETU assessment.

3.1 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 ethylenebisdithiocarbamate)), 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 PMRA’s proposal to express MRLs as mg CS_2/kg to harmonize with the US, Codex, and the European Union.

PMRA Response:
As noted in Section 1.2 of this document, as well as in PRVD2013-01 and PRVD2014-03, PMRA will revise the residue definition for mancozeb and metiram to residues of the parent compound “expressed as carbon disulphide (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, 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.

3.2 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, 1 October 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 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.

3.3 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, no secondary residues would be expected in edible tissues of livestock and hen. As such, 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. These same conclusions apply to metiram.

3.4 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 PMRA to estimate the conversion of mancozeb and metiram to ETU during cooking may overestimate the ETU residues, it is necessary to ensure that residues would not be underestimated. For the determination of total ETU, 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.
$F_{EBDC-ETU}$ = 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 Update Evaluation Section of this document, the dietary assessments had no cancer risks of concern only when all food uses were removed, except potatoes. Therefore, PMRA will maintain only the use of metiram on potatoes while all other food uses will be removed from Canadian labels.

3.5 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 United States 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:
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 × 1.688 kg a.i./ha with 7-day application intervals and a one day pre-harvest interval or metiram on potatoes at 3 × 1.4 kg a.i./ha with 7-day application intervals and a 14-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.

3.6 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 PMRA recognizes that it is unlikely that all imported crops are treated with an EBDC fungicide, it is the policy of PMRA to use a 100% estimate whenever percent crop treated information is not available. This is generally the case for imported commodities from non-US 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.

3.7 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 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, 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 PRVD2014-03, 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, USEPA 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-US 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 PRVD2014-03, the dietary risk assessments were conducted based on currently registered uses of metiram. Cancer risks from food only and drinking water only were 9×10^{-6} and 3.7×10^{-6}, respectively. Before considering refinements to the food assessment, 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 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 and PRVD2014-03, 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. 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-US countries. Generally, the use of chemical-specific processing factors and conversion factors is considered a refinement. In the case of the EBDC fungicides 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, PMRA considers the dietary exposure assessment to be refined. PMRA also considers the dietary assessment to be uncertain due to the age of the market basket survey data.

PRVD2014-03 proposed the phase-out of metiram and all associated uses, due to human health risks which did not meet current standards. Dietary risks of concern were identified from exposure to metiram and cancer risks of concern were identified from exposure to ethylene thiourea (ETU), a degradate of metiram and other EBDC fungicides, through food and drinking water. As the revised drinking water estimate no longer presented cancer risks of concern, there was scope to consider a subset of the registered food commodities in an updated risk assessment. This was conducted in conjunction with the revised risk assessment for mancozeb, given the need to account for exposure to ETU from both mancozeb and metiram.

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 certain uses of mancozeb and metiram. Some uses of mancozeb had occupational risks of concern, which had been proposed for cancellation in PRVD2013-01, while all uses of metiram were proposed for cancellation in PRVD2014-03. For mancozeb, 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. 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 PMRA Science Policy Notice SPN2000-01, *A Decision Framework for the Risk Assessment and Risk Management in the Pest Management Regulatory Agency* (https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/cps-spc/alt_formats/pacrb-dgapcr/pdf/pubs/pest/pol-guide/spn/spn2000-01-eng.pdf), 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, 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, 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, grapes and 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.

4.0 Comments and Responses Related to Occupational Exposure

4.1 Comment concerning the exposure to grape and apple producers

Producers indicated their willingness to revise the use rates for grapes, to lengthen re-entry intervals and to explore other mitigation options for apples in order to reduce occupational exposure.

PMRA Response:
Even after taking into consideration a reduction in the application rate to 1.4 kg a.i./ha and a reduction in the maximum number of applications to 3 as proposed by the registrant, the mitigation measures required to reach the target MOE for postapplication workers are not considered to be agronomically feasible (i.e., REIs up to 100 days for grapes depending on the activity; REIs ranging up to 54 days for apples depending on the activity). Thus, continued registration of metiram on grapes and apples cannot be supported.

4.2 Comment concerning the differences in the mancozeb and metiram exposure assessments

The Canadian Horticultural Council requested that the PMRA outline the key differences between the metiram and mancozeb dietary risk assessments, and other aspects of the risk assessment that resulted in different outcomes for metiram than for mancozeb (PRVD 2014-03 and PRVD2013-01, respectively). In the case of both potatoes and carrots, the ground application of mancozeb was deemed acceptable for continued use, yet metiram was not.

PMRA Response:
In general, the occupational and postapplication exposure assessments for mancozeb and metiram are quite similar. Both assessments utilized unit exposure values from the Pesticide Handler Exposure Database, transfer coefficients as reported in the Science Advisory Council for Exposure Agricultural Transfer Coefficient (Revised 7 August 2000) (USEPA, 2000) and standard values for body weight, exposure duration, and number of years exposed.

The only difference in the two exposure assessments was the use of chemical-specific data for dermal absorption and dislodgeable foliar residues (DFR). For mancozeb, a dermal absorption value of 1% was used for risk assessment purposes; whereas, for metiram, a value of 7% was used. The dislodgeable foliar residue study used in the mancozeb postapplication risk assessment for potatoes and carrots was conducted in tomatoes and suggested that peak residues following up to 14 applications was 41.2% of the application rate, with a daily dissipation of 8.2%. The chemical-specific study that was used for metiram was based on apples and suggested a peak residue value of 10% of the application rate, with a daily dissipation of 2.3%. Since the study used in the metiram assessment was considered representative of a single application, multiple applications were modeled by assuming that residues were additive with successive applications. There was a degree of uncertainty in extrapolating data from this study to carrots and potatoes, as the application rate, foliage type, application equipment, and crop morphology may not be representative; however, despite these limitations, it was the only chemical-specific DFR study available for metiram and was considered to be the best available data at that time .

The use of differing dermal absorption values and DFR data as well as differences in toxicological endpoints, led to differing outcomes in the postapplication exposure assessment for carrots and potatoes for mancozeb and metiram. For metiram, the Restricted-entry intervals required to mitigate postapplication exposure (i.e., 32–133 days depending on the activity) were not considered to be agronomically feasible and cancellation of these uses was proposed in PRVD2014-03. The risk assessment has since been revised, as reported in this document.

4.3 Consideration of revised use pattern in the postapplication exposure assessment

The registrant proposed a new use pattern in all crops. For the products Polyram DF and Cabrio Plus the maximum rate of application metiram will be 1.4 kg a.i./ha. The new proposed number of applications will be 3 applications per year for all crops.

A Value assessment of the new proposed application rate shows that this application rate is of value to the grower.

PMRA Response:
The postapplication exposure assessment for metiram was updated taking into consideration the revised use pattern proposed by the registrant (maximum application rate of 1.4 kg a.i./ha and a maximum of 3 applications per year for all crops), updated transfer coefficients, and updated standard defaults for body weight and life expectancy. The mitigation measures required to reach the target MOE for postapplication workers, for apples and grapes was still not considered to be agronomically feasible, as the restricted-entry intervals required to mitigate postapplication exposure for some activities ranged from 21 to > 136 days. The lengthened restricted-entry intervals required to mitigate postapplication exposure for tomatoes, carrots, celery, asparagus, and sugar beets, may be agronomically feasible (ranged from 12 hours to 30 days depending on the activity). However, when both the dietary and occupational risk assessments were considered, only the potato foliar use was found to be acceptable for continued registration of metiram.

4.4 Comment concerning the dermal absorption

The registrant 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 metiram and ETU. In order to be considered acceptable, both the metiram and ETU risk assessments need to demonstrate risks are not of concern. In general, exposure from metiram 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%.

5.0 Comments and Responses Related to the Value Assessment

The PMRA received several comments from stakeholders regarding the value of the metiram uses in response to PRVD2014-03. The comments were considered for the refinement of the risk and mitigation measures and in the value assessment to identify crops with pest management concerns.

5.1 Comment concerning the value of metiram for resistance management.

The PMRA received several comments from the Ontario Apple Growers Association, Norfolk Fruit Growers Association, Ontario Ministry of Agriculture, Food and Rural Affairs, Le Conseil québécois de l’horticulture, Potato Growers of Alberta, Potatoes New Brurnswick, Peak of the Market, Manitoba; The Canadian Potato Council, Saskatchewan Seed Potato Growers association and the Canadian Horticultural Council regarding the importance of metiram for resistance management. Metiram is a multi-site inhibitor fungicide which has not been reported to be susceptible to the development of resistance in target pathogens after more than 30 years of use.

Given this important characteristic, metiram is a key component in a resistance management strategy when used in combination or rotation with single-site fungicides which are susceptible to resistance development.

Response
The PMRA agrees that metiram is important for resistance management in disease management programs. However, there are number of other active ingredients including some multi-site fungicides registered for most of the metiram crop-pest combinations that are being cancelled. Growers may use these fungicides in rotation with or in combination with newer chemistries from different mode of action groups for resistance management.

5.2 Comment concerning the foliar use of metiram on potatoes

The PMRA received several comments from the Ontario Ministry of Agriculture, Food and Rural Affairs, Le Conseil québécois de l'horticulture, Potato Growers of Alberta, Potatoes New Brurnswick, Peak of the Market, Manitoba; The Canadian Potato Council, Saskatchewan Seed Potato Growers association and Canadian Aerial Applicators Association and the Canadian Horticultural Council regarding the value of metiram to potato production in Canada. They indicated that metiram is essential and critical to Canadian potato production and that the registration of this active ingredient and associated end-use products for early and late blight control in potatoes must be maintained. When used in rotation or in tank mix with other fungicides, metiram contributes to the delay of the development of resistant pathogen populations.

PMRA Response:
To mitigate risks associated with the use of metiram, the PMRA considered a revised use pattern for potatoes from the metiram registrant. In addition, the PMRA consulted extension specialists from different provinces regarding the use of metiram in current potato production practices. This information was used to refine the potential risks associated with the foliar use of metiram 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 metiram on apples

The PMRA received several comments from the Ontario Apple Growers Association, Norfolk Fruit Growers Association, Ontario Ministry of Agriculture, Food and Rural Affairs, Le Conseil québécois de l'horticulture and the Canadian Horticultural Council regarding the value of metiram in apple production. They indicated that metiram is an important pest management tool for apple production. It is an effective and economical fungicide used to help manage apple scab, one of the most critically important diseases of apples. Metiram is also important in the management of apple rust which has been increasing in prevalence in Canada, and specifically in Ontario. There would be a significant impact on the apple industry if metiram was phased out. There are few if any multi-site fungicides available to producers to manage these diseases and reliance upon the newer, single-site fungicides have already led to documented resistance problems.

PMRA Response:
The PMRA acknowledges the value of metiram for apple scab and rust management in Ontario and across Canada. The PMRA received revised use patterns for apples from the metiram registrant as a measure for risk mitigation. The PMRA also consulted with extension specialists from different provinces regarding current use information of metiram, and its role in apple production. This information was considered in refining the risk assessments However, the risk concerns identified in PRVD2014-03 remains. As a result, the use of metiram on apples is being cancelled.

A number of alternative active ingredients from various fungicide mode of action groups including multi-site actives such as: captan, folpet, copper and sulfur, are available to control apple scab. One of the single-site mode of action alternative active ingredients, 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 alternatives from different mode of action groups are registered. In general, apple growers have access to several 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 metiram on grapes

The PMRA received comments from the Ontario Ministry of Agriculture and Food, and Rural Affairs and Le Conseil québécois de L'horticulture regarding the importance of metiram for management of black knot and downy mildew of grapes. Metiram is an important pest management tool for grape production. It is an effective and economical fungicide used to manage black knot and downy mildew of grapes. Metiram is one of very few multi-site fungicides that are effective against these diseases and is important for resistance management as a tank-mix partner or in rotation with other fungicides. The usual practice for vineyard sprays is to rely on protectant, multi-site, broad-spectrum products early in the growing season, before fruit have developed. Once fruit are present, the focus switches to the newer, site- specific products until fruit is no longer susceptible at 6 weeks post-bloom. If metiram is lost, vineyards will suffer from increased disease incidence and the risk of developing resistance in site-specific fungicides.

PMRA Response:
The PMRA consulted extension specialists from different provinces regarding the use of metiram in current production practices of grapes. The PMRA also received revised use pattern information for grapes from the metiram registrant. This information was considered in refining the risk assessments. However, the risk concerns identified in PRVD2014-03 remain. As a result, the use of metiram on grapes is being cancelled.

In terms of alternatives for grape diseases, a number of alternative active ingredients are available to growers. Several multi-site fungicides including captan, folpet and copper are registered for downy mildew control. For black rot control, a number of active ingredients from differing mode of action groups are registered, including the multi-site fungicides captan, folpet and copper. 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 metiram on tomatoes

The PMRA received comments from the Ontario Ministry of Agriculture, Food and Rural Affairs and Le Conseil québécois de L'horticulture regarding the importance of metiram for control of early and late blight on tomatoes. Metiram is an important pest management tool for tomato production. It is an effective and economical fungicide used to manage early blight and late blight of tomatoes. Metiram is one of very few multi-site fungicides that are effective against these diseases and is an important resistance management tool.

PMRA Response:
The PMRA acknowledges the value of metiram for tomato blight control. The PMRA received revised use patterns for tomatoes from the metiram registrant as a measure for risk mitigation. This information was considered in refining the risk assessments. However, the risk concerns identified in PRVD2014-03 remain. As a result, the use of metiram on tomatoes is being cancelled.

A number of other active ingredients, including multi-site fungicides, are registered for both early and late blight control. Growers may use these fungicides for tomato early and late blight control, and in rotation as part of their blight resistance management program.

5.6 Comment concerning the use of metiram on carrots and celery

The PMRA received comments from the Ontario Ministry of Agriculture, Food and Rural Affairs and Le Conseil québécois de L'horticulture regarding the use of metiram for foliar leaf blight control on carrots and celery. Metiram is currently not used very much in Ontario or Quebec for carrot and celery production. As such, the loss of metiram is expected to have minimal impact on the management of diseases in these crops in Ontario.

PMRA Response:
The PMRA also received revised use patterns for carrots and celery from the metiram registrant as a measure for risk mitigation. This information was considered in refining the risk assessments. However, the risk concerns identified in PRVD2014-03 remain. As a result, the use of metiram on carrots and celery are being cancelled.

For use on carrot, several other active ingredients from different mode of action groups, including the multi-site fungicide chlorothalonil, are registered for Alternaria leaf blight and Cercospora leaf blight control. For early and late blight control of celery, several other active ingredients from different mode of action groups, including the multi-site fungicides chlorothalonil, folpet and copper are currently registered. Carrot and celery growers may use these fungicides for foliar blight control and in rotation as part of their resistance management programs.

5.7 Comment concerning the use of metiram on sugar beets

The PMRA received comments from the Ontario Ministry of Agriculture, Food and Rural Affairs regarding the importance of metiram for management of Cercospora leaf spot on sugar beets. Metiram is an important pest management tool in Ontario sugarbeet production. It is an effective and economical fungicide used to manage Cercospora leaf spot of sugar beets. Metiram

is one of very few multi-site fungicides that are effective against this disease and is a critical resistance management tool. Resistance management is of critical concern to the sugar beet industry in North America as leaf spot disease has a well-documented history of resistance development. The loss of metiram could put the Ontario sugar beet industry in serious jeopardy and lead to the development of resistant strains which could impact the entire North American sugar beet sector.

PMRA Response:
The PMRA acknowledges the value of metiram for Cercospora disease management on sugar beets and its importance for resistance management. The PMRA also received revised use patterns for sugar beets from the metiram registrant as a measure for risk mitigation. This information was considered in refining the risk assessments. However, the risk concerns identified in PRVD2014-03 remain. As a result, the use of metiram on sugar beets is being cancelled.

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

5.8 Comment concerning the use of metiram on asparagus

The PMRA received comments from the Le Conseil québécois de L'horticulture regarding the use of metiram for rust management on asparagus. Although metiram is not used frequently in the production of asparagus in Quebec, some growers use this fungicide in rotation with other registered fungicides for rust management. Rust is an important disease that affects the foliage of asparagus. The disease affects the vigor of the asparagus, and that in turn causes a reduction in next year's harvest. Asparagus growers would like to keep this tool for better rust control and to prevent the development of resistance.

PMRA Response:
The PMRA received revised use patterns for asparagus from the metiram registrant, as a measure to mitigate risks. This information was considered in refining the risk assessments. However, the risk concerns identified in PRVD2014-03 remain. As a result, the use of metiram on asparagus is being cancelled.

Currently several other active ingredients from different mode of action groups, including the multi-site fungicide chlorothalonil, are registered for asparagus rust control. Growers may use these fungicides for rust control and in rotation as part of their resistance management programs.

Appendix III Label Amendments for End-use Products Containing Metiram

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 signal words "POTENTIAL SKIN SENSITIZER" are required on the Polyram DF Water dispersible granular Fungicide product label, registration number 20087.

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 3 applications per year is allowed on potatoes at a maximum application rate of 1.40 kg a.i./ha with 7-day application intervals and a 14-day pre-harvest interval using aerial or ground spray only.

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

The following statements are required under the **DIRECTIONS FOR USE** section of the labels for the end-use products Polyram DF Water dispersible granular Fungicide (registration number 20087) and Cabrio Plus (registration number 30395), to be added to GENERAL DIRECTIONS FOR USE after the MIXING INSTRUCTIONS:

> "As this product is not registered for the control of pests in aquatic systems, DO NOT use to control aquatic pests.
>
> DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes."

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 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 terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands), sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats.

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:				
			Freshwater Habitat of Depths:		Estuarine/Marine Habitats of Depths:		Terrestrial habitat
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m	
Field sprayer	Potato		5	3	2	1	1
Aerial	Potato	Fixed wing	450	60	40	15	55
		Rotary wing	225	45	30	10	45

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.

The following statement is required under the **STORAGE** section of the labels for the end-use products Polyram DF Water dispersible granular Fungicide (registration number 20087), and Cabrio Plus (registration number 30395),:

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

Use Precautions:

The words “Potential skin sensitizer” are required.

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 water dispersible granules 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 metiram:

“Wear coveralls over long pants and long-sleeved shirts and 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. Aerial applicators must wear long pants and long sleeved shirts.”

“During open-cab groundboom application, applicators must wear either a respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides OR use a closed-cab tractor that provides respiratory protection (such as dust/mist filtering system and/or vapour/gas purification system) for groundboom application.”

Restricted-Entry Intervals:

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

“DO NOT enter treated areas during the restricted-entry intervals of 30 days after treatment for hand-set irrigation; 5 days after treatment for roguing, and 12 hours after treatment for all other activities.”

The following standard statements are required on the labels for Polyram DF Water dispersible granular Fungicide (registration number 20087) and Cabrio Plus (registration number 30395), under **ENVIRONMENTAL HAZARDS**:

- 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 metiram products (Polyram DF Water dispersible granular Fungicide (registration number 20087) and Cabrio Plus (registration number 30395)) in areas where soils are permeable, particularly where the water table is shallow, may result in ground water contamination.

Add to ENVIRONMENTAL PRECAUTIONS:

TOXIC to aquatic organisms and non-target terrestrial plants. Observe buffer zones specified under DIRECTIONS FOR USE.

Appendix IV Revised Toxicology Assessment

Table 1a Summary of Additional Toxicity Studies for Metiram Submitted in Response to PRVD2014-03

Study Type/Animal/PMRA #	Study Results
2-Generation Dietary Reproductive Toxicity Study Wistar rats PMRA #2458356	**Parental toxicity** **LOAEL = 9 mg/kg bw/ day (♂)** **NOAEL = 9 mg/kg bw/ day (♀)** **≥ 9 mg/kg bw/ day:** ↑follicular hypertrophy/hyperplasia in thyroid glands P/F1 generation, ↑ reticulocyte count F1 (♂). **≥ 31 mg/kg bw/ day:** ↓ body weight in P, F1, ↓ bwg (♂/♀); ↓ T_4 level P and F1, ↑ TSH (P), (♂); ↓ Fc during premating (P, F1), ↑ follicular hypertrophy/hyperplasia in thyroid glands P/F1 generation (♀). **92 mg/kg bw/ day:** ↓ Fc, ↑ thyroid weights (P/F1), ↑ liver weights (P/F1). (♂/♀); ↑ total protein, globulin (F1) and cholesterol level (P/F1), ↑ relative weight of prostate and testes F1, ↑ unilateral follicular cell adenoma in thyroid gland of one, ↑ adrenal abs wt (F1) fatty change in adrenal gland, ↑ multifocal liver necrosis, tubular degeneration of left testicle F1 (♂); ↓ reticulocyte count P (♀). **Reproductive toxicity** **NOAEL: 31 mg/kg bw/ day (♂)** **NOAEL: 92 mg/kg bw/ day (♀)** **92 mg/kg bw/ day:** ↑ % abnormal sperm F1 (♂); No other treatment related effects were observed related to reproductive parameters (estrous cycle length and periodicity, number of testicular spermatids or caudal epididymal sperm). Also, no treatment related effect was observed in reproductive performance parameters (mating index, fertility index, gestation index, gestation interval (days), live birth index. **Offspring toxicity** **NOAEL: 31 mg/kg bw/ day** **LOAEL: 92 mg/kg bw/ day** **≥ 31 mg/kg bw/ day:** ↓ thymus weight F1/F2, (♂/♀). **92 mg/kg bw/ day:** ↓ pup bw during lactation F1/F2, ↓ pup bwg during PND 1-4F1, PND14–21F1 and F2, PND 4-21 F2, ↓ brain weight (♂/♀)F1 PND 21, ↓T4 levels and ↑ TSH level F2 (PND21), F1 PND4(♂/♀) **No sensitivity of the young**
Acute Gavage Neurotoxicity Study Wistar rats PMRA # 2458357	**NOAEL = 500 mg/kg bw/day** 2000 mg/kg bw/day: ↓ bwg (♂/♀) **No evidence of neurotoxicity**

Table 1b Summary of Additional Toxicity Studies for ETU Submitted in Response to PRVD2014-03

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, ↑ 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 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 T_4 and ↑ in serum TSH levels; ↑creatinine, ↓ reticulocyte count, ↑total cholesterol. (♂); ↑reticulocyte count (♀).

Study Type/Animal/PMRA #	Study Results
	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 ♀/♂
	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, ↑ thyroid follicular cell hypertrophy, ↑ hypertrophy pars distalis/ pituitary (♂). **≥ 2 mg/kg bw/day:** ↓ in T_4 serum, ↓ 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, ↓ prostate, and epididymides Cohort 1A/1B, ↑ proportion of abnormal sperm, ↑ thymus atrophy (♂); ↑ ovarian follicle counts (small, growing, and total) (♀).

Study Type/Animal/PMRA #	Study Results
	<u>Cohorts 1A and 1B – Reproduction, systemic and thyroid toxicity</u> **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 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** **<u>Maternal toxicity</u>** **≥ 1.6 mg/kg bw/day:** ↓ T_4 level (GD16), ↑ thyroid weight, ↑ thyroid marked hyperplasia. (♀) **≥ 2.4 mg/kg bw/day:** ↓bw gain (PND1-17) (♀) No effects on bw, gestation length, post-implantation loss, and litter size were observed **<u>Developmental toxicity</u>** **≥ 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, 17 and 23, ↓bw (PND23-27), ↑ ABR (auditory brain stem response) thresholds by 12–15dB, ↓ Cubic

Study Type/Animal/PMRA #	Study Results
	Distortion Products (CDP) at f2=4kHz by 12–13dB. ↑ total motor activity on PND 64, ↑ radial arm maze-errors in mid and high- dose animals correlated very well with developmental levels of T_4 (PND 16) and maternal T_4 (GD 17). Auditory response in high dose also correlated well with T_4 levels (GD 17 and PND 16).
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 Toxicological Reference Values for Risk Assessment

Table 1a Metiram Revised Toxicology Reference Values

Exposure Scenario	Study	Point of Departure and Endpoint (mg/kg bw/day)	CAF[1] or Target MOE
Acute Reference Dose Females 13-49 years of age	Rat Developmental Toxicity	NOAEL = 80 mg/kg bw/day Post-implantation loss	300
	ARfD Females 13-49 = 0.27 mg/kg bw		
Acute Reference Dose General population, excluding females 13-49 years of age	Acute neurotoxicity study	NOAEL = 500 mg/kg bw Decreased Body Weight Gain	100
	ARfD = 5 mg/kg bw		
Chronic Dietary	One Year Dog Toxicity	NOAEL = 2.5 mg/kg bw/day Thyroid and Thyroid Hormone effects	100
	ADI = 0.03 mg/kg bw/day		
Short- and intermediate term Dermal	**Occupational**		
	90-day Neurotoxicity in Rats	NOAEL = 6.7 mg/kg bw/day Neuromuscular Effects	300
Short, and Intermediate Inhalation	**Occupational**		
	90-day Inhalation Toxicity in Rat	NOAEL = 0.5 mg/kg bw/day Decreased Body Weight	300
Cancer Risk	$q_1^* = 0.0601$ (mg/kg bw/day) $^{-1}$ Based on incidences of liver tumours in a combined chronic/carcinogenicity/reproduction study (ETU)		

[1]CAF (Composite assessment factor) refers to the total of uncertainty and PCPA factors for dietary risk assessment. MOE refers to target MOE for occupational assessments.
[2]Since an oral NOAEL/LOAEL was selected, a dermal absorption factor of 7% is used in a route-to-route extrapolation.
[3]Since an oral NOAEL/LOAEL was selected, an inhalation absorption factor of 100% (default value) is used in route-to- route extrapolation.

Table 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* = 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
	PRVD2014-03	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 United States national drinking water monitoring survey. ETU residues could be from both mancozeb and metiram uses.
Food only	9×10^{-6}	3.2×10^{-6}	• Domestic uses of EBDC fungicides 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 apples and grapes for metiram. • An EEC[1] value of 0.57 ppb was derived from the 2002–2003 EBDC/ETU Task Force United States national drinking water monitoring survey. ETU residues could be from both mancozeb and metiram uses.
Food and Drinking Water	12×10^{-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 United States 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 Metiram

Population Subgroup	Potatoes only			
	Acute (99.9th percentile)		Chronic	
	Exposure (mg/kg bw)	%ARfD[1]	Exposure (mg/kg bw)	%ADI[2]
General Population	N/A	N/A	0.000000	0.0
All Infants (< 1 year old)	0.001683	2.1	0.000000	0.0
Children 1–2 years old	0.002380	3.0	0.000001	0.0
Children 3–5 years old	0.001554	1.9	0.000001	0.0
Children 6–12 years old	0.001234	1.5	0.000001	0.0
Males 13–19 years old	0.000750	0.9	0.000000	0.0
Males 20–49 years old	0.000632	0.8	0.000000	0.0
Adults 50–99 years old	0.000575	0.7	0.000000	0.0
Females 13–49 years old	0.000608	0.2	0.000000	0.0

[1]Acute Reference Dose (ARfD) of 0.27 mg/kg bw for females 13–49 years old and 5 mg/kg bw for all other populations (including children).
[2]Acceptable Daily Intake (ADI) of 0.03 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 Metiram Mixing/Loading and Applying Short- to Intermediate-Term Exposure and Risk Assessment

Use Site Category	Crop	Formulation	Application Equipment	Application Rate [a] (kg a.i./ha)	Area Treated per Day [b]	Daily Exposure [c, d] (mg/kg bw/day)		Margin of Exposure [e, f] (MOE)	
						Dermal	Inhalation	Dermal	Inhalation
USC 14: Terrestrial Food Crops (High Acreage Field and Vegetable Crops)	Potato	Water dispersible granules in water soluble packaging	Aerial Mixer/loader	1.40	400	3.9E-03	1.3E-03	1700	400
			Aerial Applicator			1.3E-03	6.8E-05	5100	7400
			Groundboom (farmer) Open Cab		107	6.2E-03	3.5E-04	1100	140
			Groundboom (custom) Open Cab		360	9.8E-03	1.2E-02	690	43
			Groundboom (farmer) Closed Cab		107	4.3E-03	4.5E-04	1600	1100
			Groundboom (custom) Closed Cab		360	5.4E-03	1.5E-03	1200	330

Wearing personal protective equipment: coveralls over long pants, long sleeved shirt, chemical-resistant gloves (except during farmer groundboom and aerial application).
[a] Refined application rate in kilograms of active ingredient per hectare (kg a.i./ha).
[b] Based on default assumptions.
[c] Where dermal exposure mg/kg bw/day = (unit exposure × area treated × application rate × 7% dermal absorption)/80 kg bw.
[d] Where inhalation exposure mg/kg bw/day = (unit exposure × area treated × application rate)/80 kg bw.
[e] Based on the short- to intermediate-term- term dermal NOAEL of 6.7 mg/kg bw/day from the 90-day neurotoxicity study, target MOE of 300.
[f] Based on the short- to intermediate-term inhalation NOAEL of 0.5 mg/kg bw/day from the 90-day inhalation toxicity study, target MOE of 300. Shaded cells indicate MOEs that are below the target MOE.

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

Use Site Category	Crop	Formulation	Application Equipment	Application Rate [a] (kg a.i./ha)	Area Treated per Day [b]	Daily Exposure (mg/kg bw/day)				Combined MOE [g]
						ETU Tank Mix [c, d]		Metabolic conversion from MTR [e]	Total ETU [f]	
						Dermal	Inhalation			
USC 14: Terrestrial Food Crops (High Acreage Field and Vegetable Crops)	Potato	Water dispersible granules in water soluble packaging	Aerial Mixer/loader	1.40	400	2.3E-05	1.3E-06	3.9E-04	4.1E-04	12000
			Aerial Applicator			1.7E-05	1.4E-07	1.0E-04	1.2E-04	42000
			Groundboom (farmer) Open Cab		107	6.1E-05	7.0E-06	7.2E-04	7.9E-04	6300
			Groundboom (custom) Open Cab		360	1.0E-04	2.2E-05	1.6E-03	1.7E-03	2900
			Groundboom		107	3.7E-05	1.0E-06	3.6E-04	3.9E-04	13000

			(farmer) Closed Cab							
			Groundboom (custom) Closed Cab		360	4.8E-05	2.0E-06	5.2E-04	5.7E-04	8800

Wearing personal protective equipment: coveralls over long pants, long sleeved shirt, chemical-resistant gloves (except during farmer groundboom and aerial application).
ETU = ethylenethiourea; MTR = metiram; MOE = margin of exposure
[a] Refined application rate in kilograms of active ingredient per hectare (kg a.i./ha).
[b] Based on default assumptions.
[c] Where dermal exposure mg/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 mg/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 mg/kg bw/day = total exposure to metiram (as expressed in Table 1, dermal exposure + inhalation exposure) × metabolic conversion of metiram to ETU (7.5%).
[f] Total daily exposure to ETU mg/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 Estimates

Use Site Category	Crop	Formulation	Application Equipment	Application Rate[a] (kg a.i./ha)	Area Treated per Day[b]	ETU Absorbed Daily Dose[c] (mg/kg bw/day)	Lifetime Average Daily Dose[d] (mg/kg bw/day)	Cancer Risk[e]
USC 14: Terrestrial Food Crops (High Acreage Field and Vegetable Crops)	Potato	Water dispersible granules in water soluble packaging	Aerial Mixer/loader	1.40	318	4.1×10^{-4}	1.7×10^{-5}	1×10^{-6}
			Aerial Applicator			1.2×10^{-4}	5.0×10^{-6}	3×10^{-7}
			Groundboom (farmer) Open Cab		60	7.2×10^{-4}	7.6×10^{-4}	2×10^{-6}
			Groundboom (custom) Open Cab		240	1.7×10^{-3}	7.1×10^{-5}	4×10^{-6}
			Groundboom (farmer) Closed Cab		60	3.8×10^{-4}	1.6×10^{-5}	1×10^{-6}
			Groundboom (custom) Closed Cab		240	5.5×10^{-4}	2.3×10^{-5}	1×10^{-6}

Wearing personal protective equipment: coveralls over long pants, long sleeved shirt, chemical-resistant gloves (except during farmer groundboom and aerial application).
ETU = ethylenethiourea
[a] Refined application rate in kilograms of active ingredient per hectare (kg a.i./ha).
[b] Based on default assumptions.
[c] Represents total daily exposure to ETU expressed in mg/kg bw/day, as presented in Table 2 and adjusted for the lower default ATPD values for cancer risk assessments.
[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 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	Analyte	Slope[b]	Linear Equation[c]	Daily Dissipation[d] (%)	Correlation Coefficient (R^2)	Canadian Crops
Apples	California	5.38	3 applications, 6 weeks apart	MTR	0.9775	y = -0.0228x + 1.3543	2.25	0.7903	Potatoes
				ETU	0.9829	y = -0.0172x-2.3848	1.71	0.7837	

MTR = Metiram, ETU = ethylenethiourea
[a] Mean study application rate of metiram in kilograms of active ingredient per hectare.
[b] Calculated from the equation of the line: y = mx + b, where m refers to the slope. EXP (m) corresponds to the fraction remaining after one day of dissipation and is calculated from e_m.
[c] The linear equation was calculated by plotting the natural logarithms (In) of DFR versus dissipation time (postapplication interval)
[d] Percent dissipation per day was calculated from the following equation: (1- EXP (m))*100

Table 5 Metiram 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	1.40	3	7	Hand-set Irrigation	1750	3.61	0.044	150	30
				Roguing	1100		0.028	240	5[h]
				All other activities	210		0.005	1300	0.5

TC = Transfer coefficient; DFR = Dislodgeable foliar residues; REI = Restricted-Entry Interval; MOE = Margin of Exposure.
[a] Refined application rates expressed in kilograms a.i./ha.
[b] Refined number of applications per season and application interval for registered crops.
[c] Transfer coefficients are based on PMRA default values.
[d] Based on chemical-specific dislodgeable foliar residue data on day 0 using the minimum interval between applications.
[e] Dermal Exposure = DFR × TC × 8 hr × DA (7%)/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 metiram. Calculated using the dermal short- to intermediate-term NOAEL of 6.7 mg/kg bw/day from the 90-day neurotoxicity study, target MOE of 300.
[g] Restricted-entry interval (REI) refers to the day following application that metiram residues are less than the target DFR and calculated MOEs exceed the target of 300.
[h] An REI of 5 days results in an MOE of 270 which is approaching the target. However, to fully reach the target MOE of 300, an REI of 10 days is required.

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)	MTR REI [d] (days)	MTR Exposure [e] (mg/kg bw/day)	ETU Exposure (mg/kg bw/day)			MOE[i]
							Dermal[f]	Metabolic Conversion from MTR[g]	Total[h]	
USC 14: Terrestrial Food Crops										
Potato	1.40	3	Hand-set Irrigation	1750	30	0.022	2.63×10^{-3}	1.68×10^{-3}	4.31×10^{-3}	1200
			Roguing	1000	5	0.023	2.32×10^{-3}	1.69×10^{-3}	4.01×10^{-3}	1200
			All other activities	210	0.5	0.005	5.30×10^{-4}	3.98×10^{-4}	9.28×10^{-4}	5400

TC = Transfer coefficient; DFR = Dislodgeable foliar residues; ETU = Ethylenthiourea; MTR = metiram; REI = Restricted-Entry Interval; MOE = Margin of Exposure.
[a] Refined application rates expressed in kilograms a.i./ha.
[b] Refined number of applications per season and number of applications proposed by registrants for registered crops.
[c] Transfer coefficients are based on PMRA default values.
[d] Metiram REI refers to the day following application that metiram residues are less than the target DFR and calculated MOEs exceed the target of 300, as presented in Table 5.
[e] Refers to metiram dermal exposure on the REI day, calculated as Dermal exposure = [MTR DFR × TC × MTR Dermal absorption (7%) × 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 metiram, calculated by multiplying metiram exposure on the REI day by 7.5%.
[h] Refers to total ETU exposure on the metiram 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 metiram REI day, calculated using the short to intermediate-term dermal NOAEL of 5 mg/kg bw/day from the oral developmental toxicity study and target MOE of 1000.

Table 7 ETU Postapplication Cancer Exposure and Risk Estimates

Crop	Rate[a] (kg a.i./ha)	Number of Applications	Activity	TC[b] (cm^2/hr)	RE [c] (days)	ETU Absorbed Daily Dose[d] (mg/kg/day)	ETU Lifetime Average Daily Dose[e] (mg/kg bw/day)	Cancer Risk[f]
USC 14: Terrestrial Food Crops								
Potato	1.40	3	Hand-set Irrigation	1750	30	4.31×10^{-3}	1.38×10^{-4}	8×10^{-6}
			Roguing	1000	5	4.01×10^{-3}	1.28×10^{-4}	8×10^{-6}
			All other activities	210	0.5	9.28×10^{-4}	2.96×10^{-5}	2×10^{-6}

TC = Transfer coefficient; DFR = Dislodgeable foliar residues; ETU = Ethylenthiourea; REI = Restricted-Entry Interval; MOE = Margin of Exposure.
[a] Refined application 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 metiram and ETU exposure exceed the target MOE, as presented in Table 6.

[d] ETU Absorbed Daily Dose (ADD) expressed in µg/kg bw/day on the REI day.
[e] ETU LADD (Lifetime Average Daily Dose, mg/kg/bw/day) calculated using the following formula:

$$\text{LADD} = \frac{\text{Absorbed Daily Dose ETU (mg/kg bw/day)} \times \text{Exposure Days (30 days/yr)} \times \text{Working Duration (40 yrs/lifetime)}}{\text{365 days/yrs} \times \text{Life Expectancy (78 yrs)}}$$

[f] Lifetime cancer risk, calculated using the following formula: Cancer Risk = LADD (mg/kg bw/day) × q_1^* (0.0601 (mg/kg bw/day)$^{-1}$

Appendix VIII Revised Environmental Endpoints

Table 1 New environmental endpoints incorporated into the environmental risk assessment

Study Type	Test substance	Endpoint value	Comment	PMRA Number
Environmental Fate				
Aerobic Water/sandy loam sediment Rhine River system	Metiram Complex (dissipation based on evolved CO_2)	t½ or DT_{50} = 134 d DT_{90} = 445 d		2458375
Aerobic Water/ loam sediment Pond system	Metiram Complex (dissipation based on evolved CO_2)	t½ or DT_{50} = 118 d DT_{90} = 392 d		
Environmental Toxicology				
Toxicity to foliar dwelling predatory mite *Typhlodromus pyri*	BAS 222 28 F WG (70% metiram)	LR_{50} = 266.8 g EUP/ha (186.76 g a.i./ha)	83.3% corrected mortality at the highest dose tested (800 g EUP/ha).	2458377
Effects of BAS 222 28 F on predatory mites (*Acar: Phytoseiidae*) in apple orchard	3 applications of BAS 222 28 F at rates of 2.3 kg/ha in 700 L/ha and 2.3 kg/ha in 800 L/ha	Percent reduction in population relative to control at 1 to 4 weeks after application: -1.9% to 34.5% and 1.3 to 39.9% 26 days after the last late application: 10 to 27%		2458378 2458379 2458380 2458381
Plant toxicity: 4 monocots (onion, ryegrass, wheat, and corn) and; 6 dicots (bean, oilseed rape, cabbage, soybean, lettuce and tomato)	Seedling emergence (3657 g a.i./ha – highest dose tested)	ER25 = 138 g a.i./ha NOER = 45.5 g a.i./ha	Significant effect on seedling emergence, survival, shoot height or shoot dry weight of tomato, the most sensitive species tested.	2458405
	Vegetative vigour (3663 g a.i./ha – highest dose tested)	ER25 = >3663 g a.i./ha NOER = 3663 g a.i./ha	No adverse effects observed	2458407
Freshwater invertebrate *Daphnia magna*	Acute BAS 222 29F (91.6% ai)	48 h EC50 = 634 µg/L (mean measured) NOEC = 201 µg a.i./L (immobilization)		2458382
	Chronic BAS 222 29F (91.6% a.i.)	21-d NOEC = 55 µg a.i./L (mean measured) (survival)		2458383
Fathead Minnow (*Pimephales promelas*)	Acute BAS 222 29F (91.6% a.i.)	96-h LC50 > 607 µg a.i./L (mean measured) NOEC = 607 µg/L		2458387
	Early Life-Stage BAS 222 29F (91.6% a.i.)	NOEC = 13 µg/L (mean measured)		2458389
Freshwater Green Algae *Ankistrodesmus bibraianus*	Acute Metiram	72-h EC50 = 0.054 mg a.i./L (nominal concentration) NOEC = 0.01 mg a.i./L	Highly toxic	1589711
Freshwater diatom (*Navicula pelliculosa*)	Acute BAS 222 29F (72.5% a.i.)	96-h EC_{50} = 6.4 µg a.i./L (mean measured) NOEC = 0.83 µg a.i./L		2458398
Vascular plant Duckweed (*Lemna gibba*)	Acute BAS 222 29F (91.6% a.i.)	7-d EC_{50} > 517 µg a.i./L NOEC = 517 µg/L (mean measured)		2458404
Chironomus tentans	10- day Acute Spike Sediment BAS 222 29F (91.6% a.i.)	10-d EC_{50} > 150 mg a.i./kg (nominal) (> 144 mg a.i./kg initial Sed. Conc.) 10-d NOEC = 38 mg a.i./kg		2458365

Study Type	Test substance	Endpoint value	Comment	PMRA Number
		10-d EC_{50} > 0.659 mg a.i./L (Initial concentration of overlying water)		
		10-d EC_{50} > 17.2 mg a.i./L (initial pore water concentration)		
Mysid shrimp (*Americamysis bahia*)	Acute: BAS 222 29F (91.6%)	96-h EC_{50} = 25 µg a.i./L (mm) 96-h NOEC = 7.1 µg a.i./L		2458385
	Chronic, life cycle, flow-through; BAS 222 29F (91.6 % a.i.)	40-d NOEC = 3.1 µg a.i./L (nominal) 40-d LOEC = 6.3 µg a.i./L	NOEC based on significant reductions in reproduction when compared to solvent control.	2458388
Eastern Oyster (*Crassosea virginica*)	Acute; 96 hour Shell deposition: BAS 222 29F (91.6% a.i.)	96-h EC_{50} = 140 µg/L (mean measured) 96-h NOEC = 4.2 µg/L		2458386
Sheepshead minnow (*Cyprinodon variegatus*)	Acute; BAS 222 29F (91.6% ai)	96-h LC_{50} > 673 µg a.i./L (mean measured) 96-h NOEC = 673 µg a.i./L		2458384
Marine diatom (*Skeletonema costatum*)	Acute: BAS 222 28F (72.3% a.i.)	96-h EC_{50} = 21.3 µg a.i./L (mean measured) 96-h NOEC = 4.4 µg a.i./L		2458403
Leptocheirus plumulosus	Acute Spiked Sediment; BAS 222 29F (91.6%)	10-d EC_{50} > 5 mg a.i./kg (nominal) 10-d NOEC = 5 mg a.i./kg (> 2.07 mg a.i./kg initialsediment concentration) 10-d EC50 > 0.013 mg a.i./L (Initial concentration of overlying water) 10-d EC50 > 0.621 mg a.i./L (initial pore water concentration)		2458368

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
2458356	2011. Two-Generation Reproduction Toxicity Study in Wistar Rats Administration via the Diet. DACO: 4.5.1
2458357	2010. Acute Oral Neurotoxicity Study in Wistar Rats - Administration via Gavage. DACO: 4.5.12

B. Additional Information Considered

Published Information

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
2849954	2005. R. Thomas Zoeller & Kevin M. Crofton Mode of Action: Developmental Thyroid Hormone Insufficiency—Neurological Abnormalities Resulting From Exposure to Propylthiouracil, Critical Reviews in Toxicology, 35:8-9, 771-781. DACO: 4.5.14

Dietary

A. List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
2458361	2014. Residue Summary. DACO 7.1
2458362	2014. Residue Summary: Trials on Grape, Apple, Potatoes and tomatoes. DACO 7.4.1
2458363	2010. Confined rotational crop study with 14C-BAS 222 F.
2458364	2009. Confined rotational crop study with 14C-BAS 222 F.
2364293	2013. Comprehensive Data Summaries - Response of Mancozeb Task Force - on proposed re-evaluation decision for Mancozeb 2004-0189.

Occupational /Residential

A. List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
2115788	2008. Data Submitted by the Agricultural Reentry Task Force 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
2572743	2014. Agricultural Handler Exposure Scenario Monograph: Open Cab Airblast Application of Liquid Sprays. DACO 5.4, 5.
2172938	2012. Agricultural Handler Exposure Scenario Monograph: Closed Cockpit Aerial Application of Liquid Sprays. DACO 5.4, 5.5
2572746	2015. Agricultural Handler Exposure Scenario Monograph: Closed Cab Airblast Application of Liquid Sprays.
1913109	2009. Agricultural Handler Exposure Scenario Monograph: Open Cab Groundboom Application of Liquid Sprays. DACO 5.4, 5.5

Studies considered in the Updated Environmental Assessment

A. List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
2458365	2010, Metiram: A 10-day flow-through survival and growth sediment toxicity test with *Chironomus tentans* using spiked sediment, DACO: 8.2.2.2

2458368 2010, Metiram: A 10-day flow-through whole sediment toxicity test with *Leptocheirus plumulosus* using spiked sediment, DACO: 8.2.2.2

2458375 1993, Metiram: Degradation and metabolism in aquatic systems, DACO: 8.5

2458377 2003, Effects of BAS 222 28 F on the predatory mite *Typhlodromus pyri* (Acari: Phytoseiidae) in a laboratory trial - Dose response, DACO: 9.2.5

2458378 2011, A non-GLP field study to evaluate the effects of BAS 222 28 F on predatory mites (Acari: Phytoseiidae) in an apple orchard in Germany - 3 early applications, DACO: 9.2.5

2458379 2011, A non-GLP field study to evaluate the effects of BAS 222 28 F on predatory mites (Acari: Phytoseiidae) in an apple orchard in Germany - 3 late applications, DACO: 9.2.5

2458380 2011, A non-GLP field study to evaluate the effects of BAS 222 28 F on predatory mites (Acari: Phytoseiidae) in an apple orchard in Germany - 3 early applications, DACO: 9.2.5

2458381 2011, A non-GLP field study to evaluate the effects of BAS 222 28 F on predatory mites (Acari: Phytoseiidae) in an apple orchard in Germany - 3 late applications, DACO: 9.2.5

2458382 2010, Metiram: A 48-hour flow-through acute toxicity test with the Cladoceran (*Daphnia magna*), DACO: 9.3.2

2458383 2010, Metiram: A flow-through life-cycle toxicity test with the Cladoceran (*Daphnia magna*), DACO: 9.3.3

2458384 2010, Metiram: A 96-hour flow-through acute toxicity test with the sheepshead minnow (*Cyprinodon variegatus*), DACO: 9.4.2

2458385 2010, Metiram: A 96-hour flow-through acute toxicity test with the saltwater mysid (*Americamysis bahia*), DACO: 9.4.2

2458386 2010, Metiram: A 96-hour shell deposition test with the eastern oyster (*Crassostrea virginica*), DACO: 9.4.2

2458387 2010, Metiram: A 96-hour flow-through acute toxicity test with the fathead minnow (*Pimephales promelas*), DACO: 9.4.2

2458388 2010, Metiram: A flow-through life-cycle toxicity test with the saltwater mysid (*Americamysis bahia*), DACO: 9.4.5

2458389 2010, Metiram: An early life-stage toxicity test with the fathead minnow (*Pimephales promelas*), DACO: 9.5.3.1

2458397 2008, Polyram (BAS 222 28 F): A 96-hour toxicity test with the freshwater alga (*Anabaena flos-aquae*), DACO: 9.8.2

2458398 2008, Polyram (BAS 222 28 F): A 96-hour toxicity test with the freshwater diatom (*Navicula pelliculosa*), DACO: 9.8.2

2458399 2009, Polyram (BAS 222 28 F): A 96-hour toxicity test with the freshwater alga (*Pseudokirchneriella subcapitata*), DACO: 9.8.2

2458403 2013, Polyram (BAS 222 28F): A 96-hour toxicity test with the marine diatom (*Skeletonema costatum*), DACO: 9.8.3

2458404 2010, Metiram: A 7-day static-renewal toxicity test with duckweed (*Lemna gibba* G3), DACO: 9.8.5

2458405 2008, Polyram (BAS 222 28 F): A toxicity test to determine the effects of the test substance on seedling emergence of ten species of plants, DACO: 9.8.6

2458407 2008, Polyram (BAS 222 28 F): A toxicity test to determine the effects of the test substance on vegetative vigor of ten species of plants, DACO: 9.8.6

2364293 2013. Comprehensive Data Summaries - Response of Mancozeb Task Force - on proposed re-evaluation decision for Mancozeb 2004-0189.