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Re-evaluation Decision

RVD2020-09

Ethephon and its associated end-use products

Final Decision

(publié aussi en français)

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Re-evaluation decision for ethephon and associated end use products

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

Ethephon is a systemic plant growth regulator intended to promote fruit ripening/maturity, and plant growth and development, through the release of ethylene gas, a natural plant hormone. It is applied to promote early and uniform fruit maturity in apples, tomatoes, blueberries, and cherries; reduces tobacco kiln curing time; and reduces lodging in barley and wheat. Ethephon is used for potted greenhouse ornamental production to ensure uniform flowering for market sales. Currently registered products containing ethephon can be found in the Pesticide [Label Search](#) and in Appendix I.

The Proposed Re-evaluation Decision PRVD2018-01, *Ethephon and Its Associated End-use Products*,¹ containing the evaluation of Ethephon and proposed decision, underwent a 90 day consultation period ending on 26 April 2018. PRVD2018-01 proposed that products containing ethephon are acceptable for continued registration in Canada, provided that the additional proposed risk mitigation measures are in place. The proposed risk mitigation measures included:

- the cancellation of the uses on apple trees when fruit are present;
- revocation of existing maximum residue limits (MRLs) for apple, apple juice, citrus fruit, grape, and raisins;
- requirement for additional personal protection equipment (PPE) and engineering controls when mixing/loading and applying;
- restrictions on amount of active ingredient handled per day; longer restricted-entry intervals (REIs) for some postapplication activities; statements to minimize human exposure from spray drift;
- environmental hazard statements; terrestrial spray buffer zones, and standard runoff statements.

Health Canada received comments (and information) relating to the health and value assessments. Commenters are listed in Appendix II. These comments are summarized in Appendix III along with the responses by Health Canada.

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

The comments and new data/information did result in revisions to the dietary and occupational risk assessments (see Science evaluation update), and did result in changes to the proposed re-evaluation decision as described in PRVD2018-01.

A reference list of information used as the basis for the proposed re-evaluation decision is included in PRVD2018-01, and further information used in the re-evaluation decision is listed in Appendix VIII of this re-evaluation decision. Therefore, the complete reference list of all information used in this final re-evaluation decision includes both the information set out in PRVD2018-01 and the information set out in Appendix VIII herein.

This document presents the final re-evaluation decision² for the re-evaluation of ethephon, including the required amendments (risk mitigation measures) to protect human health and the environment, and any label amendments required to bring labels to current standards. All products containing ethephon that are registered in Canada are subject to this re-evaluation decision.

Re-evaluation decision for ethephon

Health Canada has completed the re-evaluation of ethephon. Under the authority of the *Pest Control Products Act*, Health Canada has determined that continued registration of products containing ethephon is acceptable. An evaluation of available scientific information found that some uses of ethephon products meet current standards for protection of human health and the environment and have acceptable value when used according to revised conditions of registration, which includes new mitigation measures. The following use of ethephon is cancelled since health risks were not shown to be acceptable: use on apple trees when fruit are present. Label amendments, as summarized below and listed in Appendix VII, are required.

Risk mitigation measures

Registered pesticide product labels include specific directions for use. Directions include risk mitigation measures to protect human health and the environment and must be followed by law. The required amendments, including any revised label statements and mitigation measures, as a result of the re-evaluation of ethephon, are summarized below. Refer to Appendix VII for details.

Human health

Risk mitigation:

To protect workers, consumers, and those entering treated areas from dietary and occupational exposure, the following risk-reduction measures are required for continued registration of ethephon in Canada:

- Cancellation of uses on apple trees when fruit are present. The use on apple trees, **when fruit are not present**, is retained.

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

- Revocation of the existing maximum residue limits (MRLs) for apple juice, apples, and citrus fruits such that they will be subject to the general maximum residue limit (GMRL).
- Requirement for additional personal protection equipment (PPE) and engineering controls when mixing/loading and applying to various crops.
- Restrictions on amount of active ingredient handled per day.
- Requirement for longer restricted-entry intervals (REIs) for some postapplication activities.
- Requirement for a statement to promote best management practices to minimize human exposure from spray drift or spray residues resulting from drift.

Environment

Risk mitigation:

To protect the environment, the following risk-reduction measures are required:

- Environmental hazard statements for birds, mammals and non-target plants.
- To reduce the potential for runoff of ethephon to adjacent aquatic habitats, precautionary statements for sites with characteristics that may be conducive to runoff and when heavy rain is forecasted are required. In addition, a vegetative strip between the treatment area and the edge of a water body is required to reduce runoff of ethephon to aquatic areas
- Terrestrial spray buffer zones for the protection of non-target plants.

Next steps

To comply with this decision, the required amendments (mitigation measures and label updates) must be implemented on all product labels no later than 24 months after the publication date of this decision document. Accordingly, both registrants and retailers will have up to 24 months from the date of this decision document to transition to selling the product with the newly amended labels. Similarly, users will also have the same 24-month period from the date of this decision document to transition to using the newly amended labels, which will be available on the Public Registry.

Refer to Appendix I for details on specific products impacted by this decision.

Other information

Any person may file a notice of objection³ regarding this decision on ethephon and its associated end-use products 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 section of the Canada.ca website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (hc.pmra.info-arla.sc@canada.ca).

The relevant confidential test data on which the decision is based (as referenced in PRVD2018-01 and in Appendix VIII of this document) are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please 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 Introduction

Ethephon is a plant growth regulator belonging to the phosphonate family. It is readily absorbed by the plant stimulating release of ethylene, which is a natural plant hormone. Ethylene directly influences several physiological processes (ripening, maturation, etc.).

Ethephon is used on cereals to increase resistance to lodging (stem breakage) through straw shortening and strengthening. It is also used on fruits to promote fruit maturity (early and uniform ripening and colouring of mature fruits) and loosening of fruits for easy harvesting. On tobacco plants it is used to reduce curing time and promote colour development. For greenhouse ornamental production, it is used to stimulate lateral branching leading to fuller plants.

2.0 Revised health risk assessment

2.1 Toxicology summary

Health Canada received toxicology-related comments from Bayer CropScience during the public consultation period for the Proposed Re-Evaluation Decision for Ethephon (PRVD2018-01). The comments pertained to the points of departure selected by Health Canada for the dermal, inhalation, and chronic dietary risk assessments, and included scientific rationales addressing these issues. Based on the comments received, the points of departure for the dog 13-week neurotoxicity and 2-year dietary toxicity studies were revised, and the toxicology reference values for the dermal and inhalation (all durations), and chronic dietary risk assessments were updated. The revised study summaries and toxicology reference values for ethephon are highlighted in Appendix IV.

2.2 Dietary exposure and risk assessment

In PRVD 2018-01, dietary risks for ethephon were not shown to be acceptable, and therefore cancellation of the use on apple trees when fruit are present, and revocation of the existing MRLs for apple juice, apples, citrus fruits, grapes, and raisins were proposed.

Two comments were submitted regarding the use on apples: that the use on apples is limited, and that the label could be amended to disallow use on processing apples (apples intended to be processed into commodities such as juice, sauce). These comments were considered, but did not result in changes to the risk assessment. The registrant submitted three processing studies; however, these studies were not required to complete the re-evaluation as their incorporation would not result in changes to the mitigation measures. Health Canada's responses to specific comments for the dietary assessment are provided in Appendix III.

The dietary risk assessment was updated based on the revised acceptable daily intake (ADI), updated American percent crop treated values, and the Codex MRL for olives (established after the PRVD review). Results of the updated dietary risk assessment are presented in Appendix V.

Based on the current use pattern, the updated acute dietary (food and drinking water) exposure estimates at the 95th percentile for the general population and all subpopulations (including females 13–49 years of age) range from 17–135% of the acute reference dose (ARfD), and therefore risks were not shown to be acceptable. The highest exposed subpopulation was children 1–2 years of age. When apple and citrus commodities are excluded, the acute dietary exposure estimates range from 12–41% of the ARfD, and risks were shown to be acceptable with this mitigation.

Based on the current use pattern, the updated chronic exposure estimates for the general population and all subpopulations range from 39–432% of the ADI, and therefore risks were not shown to be acceptable. The highest exposed subpopulation is children 1–2 years of age. When apple and citrus commodities are excluded, the chronic exposure estimates range from 17–83%, and risks were shown to be acceptable with this mitigation.

Therefore, the mitigation proposed in PRVD2018-01 to cancel uses on apple trees when fruit are present and to revoke the MRLs for apple juice, apples, and citrus fruits remains unchanged. Based on the revised risk assessments, the PRVD proposal to revoke the MRLs for grapes and raisins is no longer required. Label changes resulting from the dietary assessment are included in Appendix VII. Changes to MRLs will be published in a Proposed Maximum Residue Limit (PMRL) document for consultation.

2.3 Occupational and non-occupational exposure and risk assessment

In PRVD2018-01, risks were not shown to be acceptable for several application and postapplication scenarios. For mixer/loader/applicators, additional PPE, engineering controls, and limits to amounts of active ingredient handled per day were proposed. For agricultural workers entering treated sites to conduct hand labour activities, longer REIs ranging from 12 hours to 15 days were proposed. Calculated REIs were considered to be agronomically feasible.

One comment was received regarding the use of gloves for postapplication activities when the proposed REIs present a challenge to crop production. A postapplication study with workers conducting activities on grapes was cited. The scientific basis and the feasibility of using gloves as a mitigation measure for postapplication exposure is being reviewed by Health Canada through the Post Application Exposure Working Group, which also includes grower and industry representatives. At present, adequate scientific data are not available to consider gloves as a mitigation measure for postapplication workers. More information is provided in the Health Canada response to this comment in Appendix III.

The occupational assessment was updated with the revised toxicology reference values (see Section 2.1 Toxicology summary). In addition, the foliar dissipation rate in greenhouses was revised from 2.3–2% as per current policy. As a result, revised mitigation measures to those proposed in PRVD2018-01 are required as follows:

- A closed mixing and loading system for all scenarios, except for handheld equipment. Increased PPE for these scenarios is also required.

- A lower level of PPE is required for manually pressurized handwand and backpack application.
- Increased PPE and a respirator are required for application with a mechanically-pressurized handgun.
- Further restrictions on amount of active ingredient handled per day is required.
- Restriction on the use of a handheld airblast/mistblower (HH AB/MB).
- Longer REIs for some postapplication activities.

Details regarding the revised occupational risk assessment are presented in Appendix VI. Label changes resulting from the occupational assessment are included in Appendix VII.

2.4 Aggregate exposure and risk assessment

For ethephon, the aggregate assessment consisted of combining food and drinking water exposure only, since residential exposure is not expected to occur. The results of the updated dietary assessment include both food and drinking water exposure (see Section 2.2).

3.0 Environmental risk assessment

There were no comments received relating to the environmental risk assessment during the public consultation period for PRVD2018-01. Environmental risks were shown to be acceptable in the PRVD, when used according to the revised label directions, which include advisory statements and spray buffer zones.

4.0 Value assessment

Ethephon is a systemic plant growth regulator, which when applied, influences plant growth and development, including fruit maturity/ripening process. It is registered for use on apples, barley, blueberries, cherries, tomatoes, tobacco, wheat and greenhouse ornamentals. Ethephon is of value as a harvest aid, where it is applied to promote early and uniform fruit maturity in blueberries and cherries, reduce tobacco kiln curing time, and reduce lodging in barley and wheat, in order to improve overall harvesting efficiency. It is used to increase flower bud development in the subsequent season in non-bearing apple trees. Ethephon is of notable value for tomatoes intended for processing, since growers use a one-pass mechanical harvest, and all fruits need to be at the same stage of ripening when harvested. It is necessary for potted greenhouse ornamental production since retailers and importers request that all the exported stocks be treated with ethephon to ensure uniform flowering for market sales.

5.0 Conclusion of science evaluation

Ethephon is of value as a plant growth regulator which influences plant growth and development, including fruit maturity and the ripening process. It is used commercially in a variety of crops including cereals, apples, sweet and sour cherries, blueberries, field tomatoes, tobacco, as well as in potted greenhouse ornamentals. With respect to human health, risks were shown to be acceptable with the cancellation of the use on apple trees when fruit are present and revocation of the existing MRLs for apple juice, apples, and citrus fruit such that they will be subject to the general maximum residue limit (GMRL) of 0.1 ppm (subsection B.15.002(1) of the Food and Drugs Regulations). Additional mitigation measures are required for some of the remaining uses, including longer REIs and increased PPE.

Ethephon can pose potential risks to birds, mammals and terrestrial plants. However, it is unlikely to affect the environment when used according to the revised label directions, which include advisory statements and spray buffer zones.

List of abbreviations

ADI	acceptable daily intake
a.i.	active ingredient
ALAT	alanine aminotransferase
ALP	alkaline phosphatase
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
ATPD	area treated per day
BChE	brain cholinesterase
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CFIA	Canadian Food Inspection Agency
CR	chemical-resistant
DA	dermal absorption
DFR	dislodgeable foliar residue
EChE	erythrocyte cholinesterase
fc	food consumption
GH	greenhouse
GMRL	general maximum residue limit
ha	hectare
Hct	hematocrit
Hgb	hemoglobin
HH AB/MB	Handheld airblast/mistblower
hrs	hours
kg	kilogram
L	liters
LOAEL	lowest-observed-adverse-effect-level
MA	mechanically assisted
mg	milligram
M/L/A	mixer/loader/applicator
MOE	margin of exposure
MPHG	mechanically pressurized handgun
MPHW	manually pressurized handwand
MRL	maximum residue limit
NOAEL	no-observed-adverse-effect-level
PChE	plasma cholinesterase
PCPA	<i>Pest Control Products Act</i>
PDP	Pesticide Data Program
PMRA	Pest Management Regulatory Agency
PMRL	Proposed Maximum Residue Limit
POD	point of departure
PPE	personal protection equipment

ppm	part per million
PRVD	Proposed Re-evaluation Decision
RBC	red blood cells
REI	restricted-entry interval
TC	transfer coefficient
USEPA	United States Environmental Protection Agency
wk	week
yrs	years
♂	male
♀	female
↑	increased
↓	decreased

Appendix I Registered products containing Ethephon in Canada

Table 1 Registered products containing ethephon requiring label amendments¹

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Active ingredient (% g/L)
19205	Technical	Bayer CropScience Inc.	Technical Ethephon	Solid	Ethephon: 90.22%
19206	Manufacturing Concentrate	Bayer CropScience Inc.	Base 250	Solution	Ethephon: 71.3% by weight
11580	Commercial	Bayer CropScience Inc.	Ethrel Liquid Plant Growth Regulator	Solution	Ethephon: 240 g/L
18685	Commercial	Bayer CropScience Inc.	Cerone Brand Plant Regulator Lodging Control for Cereals	Solution	Ethephon: 480 g/L
29593	Commercial	Bayer CropScience Inc.	Florel Plant Growth Regulator	Solution	Ethephon: 240 g/L
30686	Commercial	Bayer CropScience Inc.	Proxy Plant Growth Regulator	Solution	Ethephon: 240 g/L

¹as of 30 June 2020, excluding discontinued products or products with a submission for discontinuation

Appendix II List of commenters to PRVD2018-01

List of commenters' affiliations for comments submitted in response to PRVD2018-01

Category	Commenter
Agricultural Association, NGO	Canadian Horticultural Council
Agricultural Association, NGO	Northwest Horticultural Council/United States Apple Export Council
Government organization	California Table Grape Commission
Pesticide Manufacturer	Nufarm Inc.
Registrant	Bayer Cropscience Inc.

Appendix III Comments and responses

Health Canada received ten written comments during the public consultation for the ethephon proposed re-evaluation decision. Commenters' affiliations are listed in Appendix II. These comments were considered during the final decision phase of this re-evaluation. Summarized comments and Health Canada's responses to them are provided below.

1.0 Comments related to the health risk assessment

1.1 Toxicology

1.1.1 Comment related to the NOAEL in the 13-week dog neurotoxicity study

The registrant indicated that the rationale for the Health Canada NOAEL of 1.8 mg/kg bw/day (70 ppm in the diet) for the dog 13-week neurotoxicity study was unclear, since calculated intakes of ethephon in the study report were 2, 4 or 15/18 mg/kg bw/day in males and females, respectively, and at dietary concentrations of 70, 140 or 525 ppm, respectively. The registrant stated that Health Canada should either select 2 mg/kg bw/day as the NOAEL for the dog 13-week neurotoxicity study, or provide a clear rationale for the selection of the NOAEL of 1.8 mg/kg bw/day.

Health Canada's response:

Health Canada re-examined the dog 13-week neurotoxicity study and agrees that the dose levels were reported incorrectly in PRVD2018-01, and should be revised as recommended by the registrant based on measured dietary concentrations and calculated intakes of ethephon in the study report. Consequently, the NOAEL of 1.8 mg/kg bw/day presented for this study in PRVD 2018-01 will be revised to 2 mg/kg bw/day.

1.1.2 Comment related to the point of departure used for the chronic dietary risk assessment

The registrant disagreed with the NOAEL of 0.86 mg/kg bw/day for the dog 2-year dietary toxicity study presented in PRVD2018-01. This NOAEL was used by Health Canada for chronic dietary risk assessments in all populations, based on decreased body weight, soft stool, clinical chemistry changes (decreased erythrocyte cholinesterase [EChE] activity, increased glucose levels and decreased alkaline phosphatase [ALP] activity) and effects in the gastrointestinal tract (thickening and hypertrophy of the smooth muscle in the stomach and duodenum) at the LOAEL of 7.6/8.4 mg/kg bw/day in males and females, respectively. The registrant indicated that the NOAEL for this study should be 7.6/8.4 mg/kg bw/day, since the effects noted at 7.6/8.4 mg/kg bw/day were not clearly treatment-related or adverse based on the following:

a) The registrant noted the lack of confirmation of a treatment-related increase in microscopic changes in the gastrointestinal tract of dogs in the dog 2-year toxicity study based on a re-evaluation of tissue samples from the stomach, duodenum, jejunum, and ileum in female dogs according to modern pathological criteria and practices (PMRA# 2889465). Only tissues from female dogs were re-examined since the original pathological evaluation identified effects primarily in females, with only one high-dose male identified with smooth muscle hypertrophy of

the duodenum. Original histology slides of the stomach, duodenum, jejunum, and ileum were provided by the conducting laboratory's archives; however, "the age of the slides, faded staining and separation of coverslips did not allow proper evaluation of the majority of tissues".

Therefore, new slides (number not specified) were prepared as needed from original paraffin-embedded tissues; additional details related to slide preparation were not presented. In the microscopic re-evaluation, smooth muscle hypertrophy was not observed in the duodenum and stomach of female dogs, as previously described in the original study report. The pathologist performing the re-evaluation concluded that the original histopathological analysis did not take into consideration the plane of sectioning, which may have affected the appearance of tissues. Additionally, the pathologist noted that tissue contraction may have contributed to the previous observations of tissue thickening.

b) The registrant did not consider the effects on body weight, stool, ALP activity, EChE activity and glucose levels in dogs at the Health Canada LOAEL of 7.6/8.4 mg/kg bw/day to be toxicologically significant. The slight change in body weight noted by Health Canada in dogs treated with 7.6/8.4 mg/kg bw/day of Source B ethephon was considered by the testing laboratory to be within acceptable limits and comparable to control values. Further, body weight was only marginally decreased during the initial weeks of the study in dogs treated with the highest tested dose level of Source A ethephon in this study. The observed changes in ALP activity were within the range of normal laboratory limits and were only statistically significant at week 26 in males. The changes in glucose levels were not considered to be of biological significance due to the lack of dose-response and consistency, and differences in mean values that were driven by "one or two high normal values in the groups". The incidence of soft stool at 7.6/8.4 mg/kg bw/day was comparable to controls, EChE inhibition was not considered to be biologically adverse in studies of longer duration, and the inhibition of brain cholinesterase (BChE) activity was not observed in this study.

c) The registrant noted the absence of toxicologically significant effects on body weight, clinical chemistry parameters and microscopic pathology in the gastrointestinal tract of dogs of either sex in a more recent (1989) guideline dog 1-year dietary toxicity study conducted at dose levels up to 27/30 mg/kg bw/day in males and females, respectively (PMRA# 1161192).

d) The observation of higher NOAELs in long-term dietary toxicity studies in rodents, compared to those in studies conducted in dogs, was also noted by the registrant.

The registrant suggested that the revised NOAEL of 7.6 mg/kg bw/day from the 2-year dog dietary toxicity study be used as the point of departure for the chronic dietary risk assessment, and recommended an ADI of 0.025 mg/kg bw/day. The ADI was derived by dividing the NOAEL of 7.6 mg/kg bw/day by a composite assessment factor (CAF) of 300, which included an additional threefold uncertainty factor for database deficiencies.

Health Canada's response:

Health Canada conducted a critical review of the comments and additional information provided by the registrant, a re-analysis of available data in the dog 13-week, 1-year and 2-year dietary toxicity studies, as well as an analysis of information presented in published foreign reviews. It was concluded that although some of the findings at the dose level of 7.6/8.4 mg/kg bw/day,

including decreased EChE activity in both sexes, increased glucose levels in males and gastrointestinal histopathology in females, may be treatment-related, they were not toxicologically significant or adverse. In reconsidering the available information related to body weight changes and the incidence of soft stool, which was limited to the conclusions of foreign agency reviews, Health Canada concluded that treatment-related effects on these parameters occurred at the highest tested dose level only.

Therefore, in agreement with the registrant, the NOAEL for the dog 2-year dietary toxicity study will be revised from 0.86 mg/kg bw/day to 7.6/8.4 mg/kg bw/day (in males and females, respectively). This is based on decreased body weight and food consumption, clinical signs (soft stool, emesis) and clinical chemistry changes (increased glucose levels, increased ALAT (alanine aminotransferase) activity, and decreased EChE activity) in both sexes, in addition to decreased red blood cell parameters in females, at the LOAEL of 42/48 mg/kg bw/day in males and females, respectively.

Re-assessment of toxicology reference values

As a result of the change to the point of departure (POD) for the dog 2-year dietary toxicity study, which was critical in the previous human health risk assessment, it was necessary to re-visit the toxicology reference values previously selected for ethephon. In PRVD2018-01, the previous NOAEL of 0.86 mg/kg bw/day from the dog 2-year dietary toxicity study was the lowest point of departure in the ethephon toxicology database and was selected for the assessment of chronic dietary and long-term dermal and inhalation risk in all populations. However, the revised NOAEL of 7.6 mg/kg bw/day for the dog 2-year dietary toxicity study, based on the registrant's comments, is no longer the lowest POD in the ethephon database. The more recent and more robust dog 13-week neurotoxicity study with an updated NOAEL of 2 mg/kg bw/day (as explained in the preceding comment) was considered most appropriate for the assessment of chronic dietary risk, as well as long-term dermal and inhalation risk. Based on Health Canada's current approach to human health risk assessment, a benchmark dose (BMD) analysis was conducted using the brain and erythrocyte cholinesterase data for various time points in the critical dog 13-week neurotoxicity study. The lowest BMDL₁₀ of 1.39 mg/kg bw/day, based on the inhibition of BChE activity in female dogs at 13 weeks, was selected for risk assessment purposes. Accordingly, the toxicology reference values for chronic dietary and long-term dermal and inhalation risk assessment were updated as detailed below.

In PRVD2018-01, the NOAEL of 1.8 mg/kg bw/day from the dog 13-week neurotoxicity study was critical for the assessment of short- and intermediate-term dermal and inhalation risk in all populations. However, as BMD analyses have now been conducted for this study, as prompted by the revision of the NOAEL in the dog 2-year toxicity study (as explained above), and consistent with Health Canada's current approach to human health risk assessment, the corrected NOAEL of 2 mg/kg bw/day for this study is no longer the lowest POD for these exposure scenarios. The BMDL₁₀ of 1.39 mg/kg bw/day derived for this study, based on the inhibition of BChE activity in female dogs at 13 weeks, was considered to be the most appropriate POD for the assessment of risk for each of these exposure scenarios.

The relevant toxicology reference values were updated as follows:

Acceptable daily intake (ADI)

To estimate risk following repeated dietary exposure in all populations, the BMDL₁₀ of 1.39 mg/kg bw/day from the dog 13-week dietary neurotoxicity study was selected, based on decreased BChE activity in females at termination. As discussed in the *Pest Control Products Act* Hazard Characterization section of PRVD2018-01, the PCPA factor was reduced to onefold and a threefold database uncertainty factor was applied due to the lack of cholinesterase inhibition data in the young animal. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were selected, resulting in a CAF of 300. The resulting ADI is 0.005 mg/kg bw/day.

Dermal and inhalation – all durations

For the assessment of dermal and inhalation risk of all durations, the BMDL₁₀ of 1.39 mg/kg bw/day from the dog 13-week dietary neurotoxicity study was selected. This point of departure was based on the inhibition of BChE activity in females at termination. Repeat-dose dermal and inhalation toxicity studies that assessed the critical endpoint (BChE inhibition) in the most sensitive species were not available. For residential scenarios, the PCPA factor was reduced to onefold, as discussed in the *Pest Control Products Act* Hazard Characterization Section of PRVD2018-01. For both occupational and residential scenarios, a threefold database uncertainty factor was applied due to the lack of cholinesterase inhibition data in the young animal, as also discussed in PRVD2018-01. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were selected, resulting in a target margin of exposure (MOE) of 300. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and unborn children of exposed women.

In conclusion, as a result of the re-consideration of the NOAELs for the dog 13-week neurotoxicity study and the dog 2-year dietary toxicity study, Health Canada has revised the toxicology reference values for the dermal and inhalation (all durations), and chronic dietary risk assessments. There were no changes to the ARfDs. The revised study summaries and toxicology reference values for ethephon are highlighted in Appendix IV.

1.2 Dietary exposure

1.2.1 Relative use of ethephon on apples

A comment was received from the Canadian Horticultural Council indicating that ethephon has a relatively small area of use and limited use pattern for fresh market apple production.

Health Canada's response

The limited usage was included in the risk assessment in PRVD2018-01 via a percent crop treated factor of 5% for all domestically cultivated apples. The same value was used in the updated risk assessment.

1.2.2 Revoking the grape MRLs

A comment from the California Table Grape Commission was received about the importance of maintaining the grape MRLs for ethephon due to the large exportation of grapes from California to Canada.

Health Canada's response

The revocation of the grapes and raisins MRLs proposed in the PRVD is no longer required, as risks were shown to be acceptable in the revised dietary assessments with the inclusion of grape commodities.

1.2.3 Updated USEPA usage analysis information

A comment was received from Nufarm, Inc., which referenced updated USEPA usage analysis for ethephon.

Health Canada's response

The ethephon risk assessment has been updated to include the most recent USEPA usage analysis.

1.2.4 USEPA reliance on Pesticide Data Program (PDP) monitoring data

A comment was received from the Northwest Horticultural Council, jointly with the American Apple Export Council, which noted that the American Pesticide Data Program (PDP) data for apples were used in the USEPA review of ethephon in 2016.

Health Canada's response

Available PDP data were considered in the ethephon review; however, the data were from the year 2004 only and are more than 10 years old. They are therefore not appropriate to include in the risk assessment. No additional Canadian Food Inspection Agency (CFIA) or PDP monitoring data are available.

1.2.5 Refinements suggested by the registrant

Bayer CropScience Inc. submitted three processing studies (one for grape, and two for wheat), and proposed the removal of blackberry from the risk assessment (that is, revoking the blackberry MRL) in favour of retaining the grape MRL. The registrant did not submit refinement options for apples.

Health Canada's response

The PMRA has taken into account the registrant's proposed refinement options.

As there were no refinement options proposed for apples and there were no changes to the acute toxicology reference values, the use on apples will be cancelled and the MRLs will be revoked for apples and apple juice, as proposed in the PRVD.

In consideration of the updated acceptable daily intake reference value, the cancellation of the use on apple trees when fruit are present, and the revocation of the existing MRLs for apple juice, apples, and citrus fruit, dietary risks were shown to be acceptable in the revised chronic risk assessment.

As grape and raisin uses are now shown to be acceptable, these MRLs will be retained. The registrant's proposed mitigation for blackberries is not required.

The three processing studies submitted during the comment period were screened. However, as these would not affect the outcome of the risk assessment, they were not considered further under this re-evaluation.

1.3 Occupational and non-occupational exposure

1.3.1 Postapplication PPE

A comment was received from Bayer CropScience regarding the use of protective gloves for postapplication activities when the proposed REI presents a challenge to crop production. A study with workers conducting postapplication activities on grapes was cited. Based on the study results, Bayer CropScience believes that gloves appear to be a feasible option for postapplication exposure mitigation and managing the current proposed REIs.

Health Canada's response

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

Before Health Canada can estimate risk to workers wearing gloves, worker exposure studies comparable to those currently used by Health Canada are required. Studies that are currently used are discussed in the Regulatory Proposal PRO2014-14, *Updated Agricultural Transfer Coefficients for Assessing Occupational Postapplication Exposure to Pesticides*. Most, if not all, studies conducted by the Agricultural Re-entry Task Force (ARTF), submitted by registrants, or available in the scientific literature and used to determine Health Canada's transfer coefficients did not include gloves as a basis to estimate exposure. Gloves may have been worn in some of the studies; however, they were used as dosimeters to measure hand exposure without gloves, rather than exposure as a result of protection from the gloves, such as the case with the study submitted by Bayer. While one limited study showed significant reduction in hand exposure when wearing gloves during tomato harvesting (Rech et al., 1989), a number of other available studies suggest that exposure may actually increase when gloves are worn (Brouwer, 2000; Boman et al., 2005; Garrigou et al., 2011; Graves et al., 1995; Keifer, 2000; Rawson et al., 2005).

Health Canada is currently participating in a working group that also includes grower and industry representatives. The purpose of the working group is to investigate:

- a) the potential use of gloves as a risk mitigation option for postapplication workers in pesticide treated areas, and
- b) more efficient ways to gather postapplication worker information to ensure that risk assessments are kept up-to-date in reflecting activities that occur in the field.

The scope of this information gathering includes both agricultural crops and ornamentals. The role of Health Canada on this working group is to provide regulatory advice and direction for any proposals suggested by the working group to meet the project goals. Currently, the working group is considering conducting studies to estimate the degree of protection offered by chemical-resistant gloves while performing activities in various crops for the purpose of determining a default protection factor of gloves for postapplication workers. Based on the outcome of these studies, Health Canada may consider gloves as a mitigation measure for postapplication workers in the future. Presently, such data are not available.

3.0 Comment related to the value assessment

3.1 Apples

In response to the proposed cancellation of ethephon on trees bearing apples, the Canadian Horticultural Council highlighted the value of ethephon, particularly for use in fresh market apple production and for apples going to farmer's markets. They noted that there are no alternatives to ethephon for the use of promoting early ripening in apples.

Health Canada's response

The PMRA recognizes the value of ethephon as a harvest aid used in the fresh market production of apples. However, dietary health risks remain a concern for ethephon use on apples. Health Canada recognizes that cancellation of this use may have an impact on producers who grow apples for the fresh market. Health Canada recommends that apple growers contact Agriculture and Agri-Food Canada, or their provincial Minor Use Coordinator, to discuss the options for registration of new products to address their pesticide needs.

4.0 Comment related to the use pattern

4.1 Label mitigation to remove processing apple uses

A comment was received from the Canadian Horticultural Council suggesting that the label could be amended to disallow use on processing apples.

Health Canada's response

The dietary risks were not shown to be acceptable based on the existing use pattern, and exposure from apple commodities was identified as a significant contributor to the unacceptable risk. Health Canada considered the measurable risk from processed apples and implication on MRLs,

along with potential compliance issues (difficult to confirm apples will not be used for processing), and has determined that removing apples meant for processing from the use pattern for ethephon is not a feasible measure for risk mitigation purposes.

Appendix IV Updated toxicology reference values for ethephon

Table 1 Toxicology reference values for use in the human health risk assessment for ethephon

(Note: Revised toxicology reference values are indicated with shading)

Exposure scenario	Study	Point of departure (POD) and endpoint	CAF or target MOE ¹
Acute Dietary	Developmental toxicity study – rabbit	Females 13–49 yrs: Developmental NOAEL = 50 mg/kg bw/day ↑ number of early resorptions and ↓ number of live fetuses	1000
	ARfD ♀ 13–49 yrs = 0.05 mg/kg bw		
	Developmental toxicity study – rabbit	General Population (excluding females 13–49 yrs): Maternal NOAEL = 50 mg/kg bw/day ↑ number of mortalities in dams	300
	ARfD general population (excluding females 13–49 yrs) = 0.17 mg/kg bw		
Repeated Dietary (all populations)	13-wk dietary neurotoxicity study – dog	BMDL ₁₀ = 1.39 mg/kg bw/day inhibition of brain cholinesterase activity	300
	ADI = 0.005 mg/kg bw/day		
Short-, Intermediate- and Long-Term Dermal² (all populations)	13-wk dietary neurotoxicity study – dog	BMDL ₁₀ = 1.39 mg/kg bw/day inhibition of brain cholinesterase activity	300
Short-, Intermediate- and Long-Term Inhalation³ (all populations)	13-wk dietary neurotoxicity study – dog	BMDL ₁₀ = 1.39 mg/kg bw/day inhibition of brain cholinesterase activity	300
Cancer	Equivocal increase in thymic lymphosarcomas in female mice. Toxicology reference values selected for the non-cancer risk assessment are protective of any residual concerns regarding carcinogenic potential.		

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

² Since an oral BMDL₁₀ was selected, a dermal absorption factor (see Section 3.4.1.1 in PRVD 2018-01) was used for route-to-route extrapolation.

³ Since an oral BMDL₁₀ was selected, an inhalation absorption factor of 100% (default value) was used for route-to-route extrapolation.

Table 2 Updated toxicology study summaries for ethephon

Effects observed in both sexes are presented first followed by sex-specific effects in males, then females, each separated by semi-colons.

Study type/animal/PMRA#	Study results
<p>13-Week Oral Neurotoxicity (dietary)</p> <p>Beagle dogs</p> <p>PMRA# 1548710</p>	<p>BMDL₁₀ (↓ BChE at termination) = 1.39 mg/kg bw/day (♀)</p> <p>≥4/4 mg/kg bw/day: ↓ EChE activity (♂: days 25-87; ♀: days 10-87)</p> <p>15/18 mg/kg bw/day: ↓ EChE activity (♂: days 10-87; ♀: days 3-87); ↓ bwg (♂); ↓ BChE activity (♀)</p> <p>EChE inhibition is considered to be adverse up to 28 days. BChE activity was not inhibited in ♂s at any dose level.</p>
<p>2-Year Oral Toxicity (dietary)</p> <p>Beagle dogs</p> <p>PMRA# 1540652, 1540653, 1618450, 1677465, 1677466, 1677467</p>	<p>NOAEL = 7.6/8.4 mg/kg bw/day (♂/♀)</p> <p>Source A</p> <p>≥7.6/8.4 mg/kg bw/day: ↓ EChE activity (assessed starting wk 6) (♂/♀); ↑ glucose (♂); ↑ incidence of thickening and hypertrophy of the smooth muscle of the stomach and duodenum (♀); <i>not considered to be adverse</i></p> <p>42/48 mg/kg bw/day: ↑ incidence of soft stool, ↑ incidence of emesis, ↓ bw and fc (wks 1-4), ↑ ALAT activity (♂/♀); ↑ glucose, ↓ Hgb, ↓ Hct and ↓ RBC (♀)</p> <p>Source B</p> <p>7.6/8.4 mg/kg bw/day: ↓ PChE and ↓ EChE activity (assessed starting wk 6) (♂/♀); ↑ glucose (♂); <i>not considered to be adverse</i></p> <p>BChE activity was not inhibited at any dose level in either sex.</p>

Appendix V Dietary exposure and risk estimates for ethephon

Details for the revised risk assessment are included in this appendix. Please refer to PRVD2018-01 for additional information.

Table 1 Acute exposure and risk assessment (deterministic, 95th percentile) – food and drinking water based on current use pattern

Population Subgroup	Dietary Exposure (mg/kg bw/day)	% ARfD
All Infants (<1 year old)	0.144238	85
Children 1–2 years old	0.229932	135
Children 3–5 years old	0.147096	87
Children 6–12 years old	0.072375	43
Male 13–19 years old	0.036840	22
Male 20–49 years old	0.030850	18
Adults 50–99 years old	0.029253	17
Female 13–49 years old	0.031546	63

Acute Reference Dose (ARfD): Females 13–49 = 0.05 mg/kg bw; General population (excluding females 13–49) = 0.17 mg/kg bw

Table 2 Acute exposure and risk assessment (deterministic, 95th percentile) – food and drinking water, with apple and citrus commodities removed

Population subgroup	Dietary exposure (mg/kg bw/day)	% ARfD
All Infants (<1 year old)	0.046011	27
Children 1–2 years old	0.064198	38
Children 3–5 years old	0.051541	30
Children 6–12 years old	0.032117	19
Male 13–19 years old	0.020868	12
Male 20–49 years old	0.020575	12
Adults 50–99 years old	0.019980	12
Female 13–49 years old	0.020343	41

Acute Reference Dose (ARfD): Females 13–49 = 0.05 mg/kg bw; General population (excluding females 13–49) = 0.17 mg/kg bw

Table 3 Chronic (cancer and non-cancer) exposure and risk assessment – food and drinking water based on current use pattern

Population subgroup	Dietary exposure (mg/kg bw/day)	% ADI
General Population	0.003396	68
All Infants (<1 year old)	0.010006	200
Children 1–2 years old	0.021577	432
Children 3–5 years old	0.013738	275
Children 6–12 years old	0.005124	103
Youth 13–19 years old	0.002249	45
Adults 20–49 years old	0.001886	38

Population subgroup	Dietary exposure (mg/kg bw/day)	% ADI
Adults 50–99 years old	0.001924	39
Female 13–49 years old	0.001938	39

Acceptable Daily Intake (ADI): 0.005 mg/kg bw/day

Table 4 **Chronic (cancer and non-cancer) exposure and risk assessment – food and drinking water, with apple and citrus commodities removed**

Population Subgroup	Dietary Exposure (mg/kg bw/day)	% ADI
General Population	0.001237	25
All Infants (<1 year old)	0.001380	28
Children 1–2 years old	0.004145	83
Children 3–5 years old	0.003588	72
Children 6–12 years old	0.001655	33
Youth 13–19 years old	0.000847	17
Adults 20–49 years old	0.000942	19
Adults 50–99 years old	0.001056	21
Female 13–49 years old	0.000957	19

Acceptable Daily Intake (ADI): 0.005 mg/kg bw/day

Appendix VI Occupational mixer/loader/applicator (M/L/A) and postapplication exposure and risk estimates for ethephon

Details for the revised risk assessment are included in this appendix. Please refer to PRVD2018-01 for additional information.

Toxicology reference values

The toxicology reference values have been updated since the PRVD2018-01. See Appendix IV for updated values). All human health risk assessments have been updated as necessary using the revised values.

Table 1 Summary of mitigation measures for mixer, loader, and applicators based on the updated risk assessment

Scenario	Mix/load required PPE/engineering controls	Application required PPE/engineering controls	Amount handled per day restriction
Open Cab Airblast	Closed Mix/Load, Maximum PPE	Open Cab, Maximum PPE, CR hat, Respirator	36 kg a.i./day
Closed Cab Airblast	Closed Mix/Load, Maximum PPE	Closed Cab, Mid-level PPE	53 kg a.i./day
Open Cab Groundboom	Closed Mix/Load, Maximum PPE	Open Cab, Maximum PPE, Respirator	54 kg a.i./day
Closed Cab Groundboom	Closed Mix/Load, Maximum PPE	Closed Cab, Mid-level PPE	57 kg a.i./day
Aerial	Closed Mix/Load, Maximum PPE	Closed Cockpit, Baseline PPE	For mixer/loaders: 59 kg a.i./day
MPHW – GH	Open Mix/Load, Baseline PPE		Not required
Backpack – GH	Open Mix/Load, Baseline PPE		Not required
MPHG – GH	Open Mix/Load, Maximum PPE, Respirator		0.25 kg a.i./day

PPE = personal protection equipment; CR = chemical-resistant; GH = greenhouse; MPHW = manually-pressurized handwand; MPHG = mechanically-pressurized handgun

Baseline PPE = Long-sleeved shirt, long pants, CR gloves (gloves not required in closed cab)

Mid-Level PPE = Coveralls over long-sleeved shirt, long pants, CR gloves (gloves not required in closed cab)

Maximum PPE = CR coveralls over long-sleeved shirt, long pants, CR gloves

Table 2 Short- to intermediate-term exposure and risk assessment with mitigation for mixer/loaders and applicators

Application equipment	Max rate	ATPD	Exposure (mg/kg bw/day)		MOE			Restriction on amount handled ^e
			Dermal ^a	Inhalation ^b	Dermal ^c	Inhalation ^c	Combined ^d	
M/L: Closed M/L, Max PPE; A: Open Cab A, Max PPE (CR hat for airblast application), Respirator								
Airblast	3.36 kg a.i./ha	20 ha/day	0.0079	0.0009	180	1600	160	36 kg a.i./day
Groundboom (farmer – fruit and vegetable)	2.04 kg a.i./ha	26 ha/day	0.0043	0.0002	320	7500	310	Not required
Groundboom (custom)	0.6 kg a.i./ha	360 ha/day	0.0177	0.0008	79	1900	75	54 kg a.i./day
M/L: Closed M/L, Max PPE; A: Closed Cab A, Mid-level PPE								
Airblast	3.36 kg a.i./ha	20 ha/day	0.0056	0.0004	250	3800	240	53 kg a.i./day
Groundboom (farmer - fruit and vegetable)	2.04 kg a.i./ha	26 ha/day	0.0042	0.0001	330	12 000	320	Not required
Groundboom (custom)	0.6 kg a.i./ha	360 ha/day	0.0171	0.0005	81	3000	79	57 kg a.i./day
M/L: Closed M/L, Max PPE; A: Closed Cockpit A, Baseline PPE (wheat, barley, lowbush blueberry, field tomatoes)								
Aerial – M/L ^f	2.04 kg a.i./ha	200 ha/day	0.0316	0.0006	44	2500	43	59 kg a.i./day
Aerial – A ^f			0.0004	4.9E-05	3400	28 000	3000	Not required
Aerial – M/L	0.6 kg a.i./ha	400 ha/day	0.0186	0.0003	75	4200	74	59 kg a.i./day
Aerial – A			0.0002	2.9E-05	5900	48 000	5200	Not required
Open M/L, Baseline PPE								
MPHW	0.000499 kg a.i./L	150 L/day	0.0007	4.2E-05	2000	33 000	1900	Not required
Backpack			0.0041	5.8E-05	340	24 000	340	
Open M/L, Max PPE, Respirator								
MPHG	0.000499 kg a.i./L	3800 L/day	0.0347	0.0004	40	3900	40	0.25 kg a.i./day

ATPD = area treated per day; MOE = margin of exposure; PPE = personal protection equipment; M/L = mix/load; A = apply; CR = chemical-resistant; MPHW = manually pressurized handwand; MPHG = mechanically pressurized handgun; Max = maximum; DA = dermal absorption

Shaded cells indicate target MOE not met.

Baseline PPE = Long-sleeved shirt, long pants, CR gloves (gloves not required in closed cab)

Mid-Level PPE = Coveralls over long-sleeved shirt, long pants, CR gloves (gloves not required in closed cab)

Max PPE = CR coveralls over long-sleeved shirt, long pants, CR gloves

^a Where dermal exposure (mg/kg bw/day) = unit exposure (µg/kg ai) × area treated per day (ha/day) × DA (80% for M/L, 3% for A) × max application rate (kg a.i./ha) × 0.001 mg/µg/80 kg bw. A DA value of 80% was used for MPHW, backpack, and MPHG handheld scenarios, as it was not possible to separate the PHED unit exposure values into a

mixer/loader component and an applicator component.

^b Where inhalation exposure (mg/kg bw/day) = unit exposure (µg/kg ai) × area treated per day (ha/day) × max application rate (kg a.i./ha) × 0.001 mg/µg/80 kg bw.

^c Based on a short-, intermediate-, long-term BMDL₁₀ of 1.39 mg/kg bw/day from a 13-week dietary neurotoxicity study in dogs and a target MOE of 300. MOE = BMDL₁₀/exposure.

^d Based on a short-, intermediate-, long-term BMDL₁₀ of 1.39 mg/kg bw/day from a 13-week dietary neurotoxicity study in dogs and a target MOE of 300. Combined MOE = BMDL₁₀/(Exp_{dermal} + Exp_{inhalation}).

^e Restriction on amount handled: kg ai handled/day to reach target MOE = max application rate × ATPD × MOE/Target MOE.

^f Based on data from the Census of Agriculture, the 95th percentile for lowbush blueberries and field tomato farms are 63.1 ha and 3.6 ha, respectively. Therefore, it was considered unlikely that more than 200 ha would be treated per day by aerial application equipment to those crops.

Table 3 Postapplication exposure and risk assessment

Crop	Max rate (kg a.i./ha)	Activity	TC (cm ² /hr)	Peak DFR (µg/cm ²) ^a	Dermal exposure (mg/kg bw/day) ^b	Dermal MOE (Day 0) ^c	REI (days) ^d
Apple (fruit not present) ^e	3.36	Hand Pruning, Scouting, Training	580	8.40	0.0146	95	10
		Transplanting	230		0.0058	240	2
		Maintenance, Propping, Weeding	100		0.0025	550	12 hrs
Highbush Blueberry	2.04	Hand Set/Hand Line irrigation related activities involving foliar contact	1750	5.10	0.0268	52	16
		Hand Harvesting	1400		0.0214	65	14
		Bird Control, Frost Control, Hand Pruning, Scouting, Hand Weeding	640		0.0098	140	7
		Transplanting	230		0.0035	400	12 hrs
Lowbush Blueberry	2.04	Hand Set/Hand Line irrigation related activities involving foliar contact	1750	5.10	0.0268	52	16
		Hand Harvesting, Scouting	1100		0.0168	83	12
		Transplanting	230		0.0035	400	12 hrs
		Hand Weeding	70		0.0011	1300	
Cherry (Sour)	0.66	Hand Harvesting	1400	1.65	0.0069	200	3
		Hand Pruning, Scouting, Training	580		0.0029	480	12 hrs
		Transplanting	230		0.0011	1200	
		Bird Control, Maintenance, Propping, Hand Weeding	100		0.0005	2800	
Cherry (Sweet)	1.32	Hand Thinning	3000	3.30	0.0297	47	17
		Hand Harvesting	1400		0.0139	100	10
		Hand Pruning, Scouting, Training	580		0.0057	240	2
		Transplanting	230		0.0023	610	12 hrs
		Maintenance, Propping, Weeding	100		0.0010	1400	
Spring Barley	0.48	Scouting	1100	1.20	0.0040	350	12 hrs
Wheat (Spring, Winter)	0.6	Scouting	1100	1.50	0.0050	280	12 hrs
		Weeding	70		0.0003	4400	

Crop	Max rate (kg a.i./ha)	Activity	TC (cm ² /hr)	Peak DFR (µg/cm ²) ^a	Dermal exposure (mg/kg bw/day) ^b	Dermal MOE (Day 0) ^c	REI (days) ^d
Tobacco	0.9	Hand Set/Hand Line irrigation related activities involving foliar contact	1750	2.25	0.0118	120	8
		Canopy Management, Hand Harvesting, MA Harvesting	800		0.0054	260	1
		Transplanting	230		0.0016	900	12 hrs
		Scouting, Hand Weeding	90		0.0006	2300	
Field Tomato	1.536	Hand Set/Hand Line irrigation related activities involving foliar contact	1750	3.84	0.0202	69	13
		Hand Harvesting, Tying/Training	1100		0.0127	110	9
		Transplanting	230		0.0027	530	12 hrs
		Scouting	210		0.0024	580	
		Hand Pruning, Hand Weeding	70		0.0008	1700	
Greenhouse Ornamentals not for cut flowers	0.5	All Activities	230	3.79	0.0026	530	12 hrs

TC = transfer coefficient; DFR = dislodgeable foliar residue; MOE = margin of exposure; REI = restricted-entry interval; MA = mechanically-assisted; Max = maximum; DA = dermal absorption

Shaded cells indicate where MOE is below the target MOE.

^a Peak DFR (µg/cm²) calculated on the day of application for all field crops (max number of applications is 1) and the day of the 4th application assuming a 10 day minimum interval for greenhouse ornamentals (maximum number of applications for greenhouse ornamentals is 4 with a 10 day minimum interval). DFR values calculated using the standard 25% of the application rate, with a 10% daily dissipation for outdoor crops or a 2% daily dissipation in greenhouse crops.

^b Dermal Exposure (mg/kg bw/day) = Peak DFR (µg/cm²) × TC (cm²/hr) × Duration (8 hrs) × DA (3%)/Body Weight (80 kg)

^c Dermal MOE on Day = 0. Calculated using the short-to-intermediate term BMDL₁₀ of 1.39 mg/kg bw/day from the 13-week dietary neurotoxicity study in dogs, target MOE of 300.

^d Refers to restricted-entry level and is the number of days following application that workers can enter treated areas to perform postapplication activities, when risk is considered to be acceptable (target MOE achieved). Minimum REI is 12 hours.

^e As the high application rate of 3.36 kg a.i./ha is only for use to increase flowering of young (non-bearing) apple trees, hand fruit thinning and hand harvesting were not assessed, as these activities are not expected to occur.

Appendix VII Label amendments for products containing ethephon

Information on approved labels of currently registered products should not be removed unless it contradicts the label statements provided below.

1.0 Label amendments for technical ethephon products

The following information should appear on the labels of technical ethephon products:

The skull and crossbones symbol enclosed in the inverted triangle border accompanied by the signal word “Poison”; the signal word and hazard statement “Danger - Corrosive to Eyes and Skin”.

The active ingredient on the technical label should be revised from “90.22%” to “91.7%”.

The following information should appear on the labels of technical and manufacturing concentrate ethephon products:

Remove the following statement under the “**PRECAUTIONS:**”

- Do not contaminate any body of water.

And **add** the following statement:

- DO NOT discharge effluent containing this product into sewer systems, lakes, streams, ponds, estuaries, oceans or other waters.

Add the following title “**ENVIRONMENTAL PRECAUTIONS**” before the section entitled **STORAGE** and add the following statement:

- TOXIC to non-target terrestrial plants, birds and small mammals

Remove the following statement under the “**DISPOSAL**”

- Canadian formulators of this technical should dispose of unwanted active and containers in accordance with municipal or provincial regulations. For information on disposal of unused, unwanted product, contact the manufacturer or the provincial regulatory agency. Contact the manufacturer and the provincial regulatory agency in the case of a spill, and for clean-up of spills.

and **add** the following statement:

- Canadian manufacturers should dispose of unwanted active ingredients and containers in accordance with municipal or provincial regulations. For additional details and clean-up of spills, contact the manufacturer or the provincial regulatory agency.

2.0 Label amendments for commercial-class end-use products containing ethephon

2.1 PRINCIPAL PANEL

Replace “guarantee” with “active ingredient”

2.2 PRECAUTIONS

2.2.1 General label improvements

Spray drift statement:

In order to promote best management practices to minimize human exposure from spray drift or spray residues resulting from drift, the following statement must be added to the **PRECAUTIONS** all commercial end-use product labels:

“Apply only to agricultural crops when the potential for drift to areas of human habitation and 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.”

Greenhouse restrictions:

“DO NOT apply in greenhouses, except on ornamentals not for cut flowers.”

“DO NOT apply using handheld mistblower/airblast or handheld fogging equipment in greenhouses.”

2.2.2 Engineering controls and personal protective equipment

Label statements must be amended (or added) to include the following directions to the appropriate labels, unless the current label mitigation is more restrictive:

Open cab airblast and groundboom mixing/loading/application

“Closed mixing/loading systems are required. A closed system means removing a pesticide from its original container, rinsing, mixing, diluting, and transferring the pesticide through connecting hoses, pipes, and couplings that are sufficiently tight to prevent exposure of any person to the pesticide or rinsing solution. Rinsing is not required when the pesticide is used without dilution.”

“Wear chemical-resistant coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, socks, chemical-resistant footwear, and protective eyewear (goggles or face shield) during mixing, loading, application, cleanup and repair.”

“During application using an open cab tractor, wear a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH-approved canister approved for pesticides.”

“Wear chemical-resistant headgear during open cab airblast application. Chemical-resistant headgear includes Sou’Wester hat, chemical-resistant rain hat or large brimmed waterproof hat and hood with sufficient neck protection.”

“DO NOT handle more than 36 kg active ingredient per person in a day when using open cab airblast equipment.” [36 kg a.i. to be reported as a product equivalent value on product label]

“DO NOT handle more than 54 kg active ingredient per person in a day when using open cab groundboom equipment.” [54 kg a.i. to be reported as a product equivalent value on product label]

Closed cab airblast and groundboom mixing/loading/application

“Closed mixing/loading systems are required. A closed system means removing a pesticide from its original container, rinsing, mixing, diluting, and transferring the pesticide through connecting hoses, pipes, and couplings that are sufficiently tight to prevent exposure of any person to the pesticide or rinsing solution. Rinsing is not required when the pesticide is used without dilution.”

“Wear chemical-resistant coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, socks, chemical-resistant footwear, and protective eyewear (goggles or face shield) during mixing, loading, cleanup, and repair.”

“During application, use a closed cab that provides both a physical barrier and respiratory protection (such as dust/mist filtering and/or vapour/gas purification system). The closed cab must have a chemical-resistant barrier that totally surrounds the occupant and prevents contact with pesticides outside the cab.”

“During application, wear coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, socks, and shoes. Gloves are not required during application within a closed cab.”

“DO NOT handle more than 53 kg active ingredient per person in a day when using closed cab airblast equipment.” [53 kg a.i. to be reported as a product equivalent value on product label]

“DO NOT handle more than 57 kg active ingredient per person in a day when using closed cab groundboom equipment.” [57 kg a.i. to be reported as a product equivalent value on product label]

Aerial application

“Closed mixing/loading systems are required. A closed system means removing a pesticide from its original container, rinsing, mixing, diluting, and transferring the pesticide through connecting hoses, pipes, and couplings that are sufficiently tight to

prevent exposure of any person to the pesticide or rinsing solution. Rinsing is not required when the pesticide is used without dilution.”

“Wear chemical-resistant coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, socks, chemical-resistant footwear, and protective eyewear (goggles or face shield) during mixing, loading, clean-up, and repair.”

“During application, wear a long-sleeved shirt, long pants, socks and shoes.”

“DO NOT handle (during mixing and loading) more than 59 kg active ingredient per person per day.” [59 kg a.i. to be reported as a product equivalent value on product label]

Manually-pressurized handwand and backpack application

“Wear long-sleeved shirt and long pants, chemical-resistant gloves, socks, chemical-resistant footwear, and protective eyewear (goggles or face shield) during mixing, loading, application, clean-up and repair.”

Mechanically-pressurized handgun application

“Wear chemical-resistant coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, socks, chemical-resistant footwear, and protective eyewear (goggles or face shield) during mixing, loading, application, clean-up and repair. In addition, a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH-approved canister approved for pesticides MUST be worn.”

“DO NOT handle more than 0.25 kg active ingredient per person in a day.” [0.25 kg a.i. to be reported as a product equivalent value on product label]

2.2.3 Restricted-entry intervals

“DO NOT enter or allow worker entry into treated areas to perform postapplication activities during the intervals specified in the following table:”

Crop	Activity	REI and/or PHI (Days)
Greenhouse Ornamentals not for cut flowers	All Activities	12 hrs
Apples – non-bearing	Hand Pruning, Scouting, Training	10
	Transplanting	2
	All Other Activities	12 hrs
Highbush Blueberries	Hand Set/Hand Line irrigation related activities involving foliar contact	16
	Hand Harvesting	14
	Hand Pruning, Hand Weeding, Scouting, Bird Control, Frost Control,	7

Crop	Activity	REI and/or PHI (Days)
	Mechanical Harvesting	
	All Other Activities	12 hrs
Lowbush Blueberries	Harvesting (Mechanical and Hand)	42
	Hand Set/Hand Line irrigation related activities involving foliar contact	17
	Scouting	13
	All Other Activities	12 hrs
Sour Cherries	Harvesting (Mechanical and Hand)	7
	All Other Activities	12 hrs
Sweet Cherries	Hand Fruit Thinning	17
	Hand Harvesting	10
	Mechanical Harvesting	7
	Hand Pruning, Scouting, Training	2
	All Other Activities	12 hrs
Spring Barley	Harvesting	35
	All Other Activities	12 hrs
Wheat (Spring, Winter)	Harvesting	35
	All Other Activities	12 hrs
Tobacco	Hand Set/Hand Line irrigation related activities involving foliar contact	8
	Harvesting (Mechanical and Hand)	3
	Canopy Management	1
	All Other Activities	12 hrs
Field Tomatoes	Harvesting (Mechanical and Hand)	14
	Hand Set/Hand Line irrigation related activities involving foliar contact	13
	Tying/Training	9
	All Other Activities	12 hrs

REI = restricted-entry interval; PHI = pre-harvest interval; hrs = hours

2.2.4 Environmental label amendments

Add the following title “ENVIRONMENTAL PRECAUTIONS” to replace “ENVIRONMENTAL HAZARDS”:

Add to ENVIRONMENTAL PRECAUTIONS:

- TOXIC to non-target terrestrial plants.
- TOXIC to birds and small mammals.

The following is required as a standard label statement for runoff:

- 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.

Add to GENERAL DIRECTIONS FOR USE

The following statement is required for all agricultural and commercial pesticide products.

- 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) coarse classification. Boom height must be 60 cm or less above the crop or ground.

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

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

Buffer zones:

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).

Buffer zones required to protect terrestrial habitats

Method of application	Crop		Buffer zone required for the protection of terrestrial habitat (m)
Field sprayer	Lowbush blueberry and field tomato		1
	Tobacco		1
	Winter wheat, spring barley and spring wheat		1
	Apple, non-bearing type	Late growth stage	10
	Highbush blueberry	Late growth stage	5

Method of application	Crop		Buffer zone required for the protection of terrestrial habitat (m)
	Sweet cherry	Late growth stage	3
	Sour cherry	Late growth stage	2
Aerial	Lowbush blueberry	Fixed wing	20
		Rotary wing	20
	Winter wheat and spring barley	Fixed wing	15
		Rotary wing	15
	Spring wheat	Fixed wing	15
		Rotary wing	10

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners. The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site.

Add to STORAGE

The following statement is required on all agricultural product labels under the **STORAGE** heading.

“Store this product away from food or feed.”

Add to DISPOSAL or RECYCLABLE CONTAINER DISPOSAL

The following statements should be used for commercial and restricted class products used in agriculture and non-crop land.

“For recyclable containers”

The following statement would apply to plastic or metal containers that contain agricultural and non-crop land uses (for example, forestry) pesticide products, and that are designed to contain 23 L or less of product.

“Disposal of Container:

DO NOT reuse this container for any purpose. This is a recyclable container, and is to be disposed of at a container collection site. Contact your local distributor/dealer or municipality for the location of the nearest collection site. Before taking the container to the collection site:

1. Triple- or pressure-rinse the empty container. Add the rinsings to the spray mixture in the tank.
2. Make the empty, rinsed container unsuitable for further use.

If there is no container collection site in your area, dispose of the container in accordance with provincial requirements.”

3.0 Additional label amendments for ethrel liquid plant growth regulator (PCP# 11580) with use on apples:

On the Primary Panel, revise the list of uses to read:

“Accelerates tomato ripening, accelerates blueberry colouring and fruit maturity, increases flowering of young apple trees, loosens cherries for easier harvest, promotes colour and reduces curing time of flue cured tobacco, and reduces lodging in spring and winter wheat.”

Under USE PRECAUTIONS, add “DO NOT use on apple trees when fruit are present.”

Under DIRECTIONS FOR USE, add “Apply ETHREL Plant Growth Regulator once per season”

Under DIRECTIONS FOR APPLES, revise to read:

“DIRECTIONS FOR APPLES:

ETHREL Plant Growth Regulator can be used to increase flower bud development in both spur and nonspur type trees. Thorough uniform spray coverage of leaves is important. A wetting agent may improve spray coverage. Treat when air temperatures are between 16°C and 32°C. However, applications may be made at 10°C if applied under rising temperature conditions.

TO INCREASE FLOWERING OF YOUNG NON-BEARING APPLE TREES:

Apply a foliar spray of ETHREL Plant Growth Regulator to non-bearing apple trees, 1 to 2 weeks after peak bloom period (determined by fruit-bearing apple trees in the area). On young orchard trees just beginning to initiate a few flowers, delay applications until 3 to 5 weeks after full-bloom to avoid overthinning and misshapen fruit (calyx and pinched). Vegetative growth is reduced during the season of application, promoting flower bud development the following spring. Ensure trees are large enough to support a crop of apples before treating. Consult your local Fruit Specialist for recommendations on different varieties.

For spur type trees, mix 2 litres ETHREL Plant Growth Regulator in 1000 litres of water (6 litres in 3000 litres) and apply as a normal dilute spray to the point of runoff. For non-spur type trees, mix 4.25 litres of ETHREL Plant Growth Regulator in 1000 litres of water (12.75 litres in 3000 litres) and apply as a normal dilute spray to the point of runoff.

For concentrate sprayers, apply 7 litres ETHREL Plant Growth Regulator per hectare for spur types or 14 litres per hectare for non-spur types, in 500 litres of water. This rate may completely defruit the current crop from trees, particularly when applied earlier than 4 weeks after full bloom.”

Under Airblast Application, revise the first bullet to read:

“AIRBLAST APPLICATION:

For application to non-bearing apple trees, sweet cherries, sour cherries and highbush blueberries.”

Under Buffer Zones, remove “apples (to promote early red colouring, apple ripening, and to loosen processing apples for easier harvesting)” from the table.

Under RATE OF APPLICATION, remove the “cultivar” column from the table.

3.1 Additional Label Amendments for CERONE BRAND PLANT REGULATOR (PCP# 18685)

Under DIRECTIONS FOR USE, add “Apply CERONE Plant Growth Regulator once per season”

3.2 Additional Label Amendments for FLOREL PLANT GROWTH REGULATOR (PCP# 29593)

Under DIRECTIONS FOR USE, add “Apply FLOREL Plant Growth Regulator a maximum of 4 applications per crop cycle”

3.3 Additional Label Amendments for PROXY (PCP# 30686)

Under DIRECTIONS FOR USE, add “Apply PROXY once per season”

Appendix VIII References considered following publication of PRVD2018-01

Note that the following includes only references that were not previously considered in PRVD2018-01.

A. Information Considered in the Updated Toxicological Assessment

List of studies/information submitted by registrant

PMRA Document Number	Title
2889465	Experimental Pathology Laboratories (EPL). 2018. 104-Week Chronic Administration in Male and Female Dogs. Final Pathology Report. Review of Gastrointestinal Tissues from Female Dogs. Test Item - Ethephon. EPL Project Number 770-007. EPL, Sterling, VA. Report dated June 12, 2018. Unpublished.
2889466	Bayer Crop Science. 2018. Point of Departure for the Chronic Dietary Assessment and Refined Acute and Chronic Dietary Assessments for Ethephon. Report ID US0735. Report dated June 14, 2018. Unpublished.
2885640	Bayer Crop Science. 2018. Comments on the PRVD for Ethephon (PRVD2018-01). Report date not specified. Unpublished.

Additional information considered

Published Information

PMRA Document Number	Title
3010209	JMPR, 2015. Toxicological Evaluation for Ethephon, pg. 227-273. Joint FAO/WHO Meeting on Pesticide Residues, Geneva, Switzerland. Dated September 24, 2015. DACO 12.5.4.
3010213	EFSA, 2017. Draft Re-Assessment Report (RAR) and proposed decision for ethephon. Rapporteur Member State: The Netherlands. European Food Safety Authority. Dated December 2017. DACO 12.5.4.
3045317	U.S. EPA, 2015. Ethephon: Human Health Risk Assessment for Registration Review of Ethephon. Office of Chemical Safety and Pollution Prevention, United States Environmental Protection Agency. Dated October 1, 2015. DACO 12.5.4.

B. Information Considered in the Updated Dietary Assessment

Published information

PMRA Document Number	Title
2998017	USEPA, 2016. Revised Screening Level Usage Analysis (SLUA) for Ethephon (099801) in Support of Registration Review. EPA-HQ-OPP-2010-0098-0024. DACO: 12.5
2998028	USEPA, 2016. Characterization of Ethephon Use, Usage and Importance on Apples, Blackberries, Cherries, Grapes and Turf (PC Code #099801). EPA-HQ-OPP-2010-0098-0027. DACO: 12.5

C. Information Considered in the Updated Occupational and Non-Occupational Assessment

Published information

Reference
Brouwer, D.H., de Vreede, S.A.F., Meuling, W.J.A., van Hemmen, J.J. 2000. Determination of the efficiency for pesticide exposure reduction with protective clothing: a field study using biological monitoring. Chapter 5 In: Assessment of Occupational Exposure to Pesticides in Dutch Bulb Culture and Glasshouse Horticulture. Doctoral Thesis of D.H. Brouwer. pp.158-179.
Boman, A., Estlander, T., Wahlburg J.E., Maibach, H.I. 2005. Protective Gloves for Occupational Use Second edition. CRC Press LLC.
Garrigou, A., Baldi I., Le Frious P., Anselm R., Vallier M. 2011. Ergonomic contribution to chemical risks prevention: an ergotoxicological investigation of the effectiveness of coverall against plant pest risk in viticulture. 42: 321-330.
Graves, C.J., Edwards, C., Marks R. 1995. The effects of protective occlusive gloves on stratum corneum barrier properties. Contact Derm 33: 183-187.
Keifer, M.C., 2000. Effectiveness of Interventions in Reducing Pesticide Overexposure and Poisonings. American Journal of Preventive Medicine. 18 (4S); 80-89.
Rawson, B.V., Cocker, J., Evans, P.G. Wheeler, J.P. and Akrill, P.M. 2005. Internal contamination of Gloves: routes and Consequences. Am. Occup. Hyg. 49 (6): 535-541.
Rech, C., Bissell, S., Margotich, S. 1989. Worker Exposure to Chlorothalonil Residues during the harvest of fresh market pole tomatoes. Report HS-1456. California Department of Food and Agriculture. June 19, 1989.