Re-evaluation Decision RVD2020-10

Linuron and its associated end-use products

Final Decision

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Table of Contents

Re-evaluation of linuron 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.

Linuron is a selective systemic herbicide registered for the control of annual and perennial broadleaf and grassy weeds in: corn (field and sweet), soybean, potato, wheat, barley, oats, carrots, parsnip, dill, caraway, coriander, celery, asparagus, sweet white lupins, fruit trees (peach, apple, pear, plum, cherry), chokecherries, Saskatoon berries, and shelterbelts (Western Canada). Currently registered products containing linuron can be found in the Pesticide Label Search and in Appendix I. The Proposed Re-evaluation Decision PRVD2012-02, *Linuron*,[1] containing the evaluation of linuron and proposed decision, underwent a 60-day consultation period ending on 25 September 2012. PRVD2012-02 proposed the cancellation of linuron and its associated end-use products due to health and environmental risks of concern.

Health Canada received comments and information relating to the health, environmental and value assessments. Commenters are listed in Appendix II. These comments are summarized in Appendix III along with responses by Health Canada. These comments and new data/information did result in revisions to the toxicology, dietary, occupational, environmental, and value assessments (see Science evaluation update), and did result in changes to the proposed re-evaluation decision as described in PRVD2012-02.

A reference list of information used as the basis for the proposed re-evaluation decision is included in PRVD2012-02, and further information used in the re-evaluation decision is listed in Appendix XI. Therefore, the complete reference list of all information used in this final re-evaluation decision includes both the information set out in the Reference section of PRVD2012-02 and the information set out in Appendix XI herein.

This document presents the final re-evaluation decision[2] for the re-evaluation of linuron, 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 linuron that are registered in Canada are subject to this re-evaluation decision.

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

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

Re-evaluation decision for linuron

Health Canada has completed the re-evaluation of linuron. Under the authority of the *Pest Control Products Act*, Health Canada has determined that continued registration of products containing linuron is acceptable. An evaluation of available scientific information found that some uses (carrots, parsnip, potato, asparagus, shelterbelts) of linuron products meet current standards for protection of human health and the environment when used according to revised conditions of registration, which include new mitigation measures. The following uses of linuron are cancelled since health risks were not shown to be acceptable:

- Tree fruit (apple, peach, pear, plum/prune, cherry), corn (field and sweet), wheat, barley, oats, soybean, celery, Saskatoon berries, chokecherries, dill, coriander, caraway, sweet white lupins, and pre-emergent combined with post-harvest application to asparagus.

Label amendments, as summarized below and listed in Appendix X, 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/updated label statements and/or mitigation measures, as a result of the re-evaluation of linuron, are summarized below. Refer to Appendix X for details.

Uses not supported by manufacturers for re-evaluation and will be removed from all product labels:

- Field corn (post-emergence);
- Aerial and handheld applications.

Cancelled uses to be removed from all product labels:

- Tree fruit (apple, peach, pear, plum/prune, cherry), corn (field and sweet), wheat, barley, oats, soybean, celery, Saskatoon berries, chokecherries, dill, coriander, caraway, sweet white lupins, and pre-emergent combined with post-harvest application to asparagus.
- Airblast and right-of way application equipment.

Cancelled uses with an extended phase out schedule:

A subset of cancelled uses were found to lack suitable alternatives for the management of weeds, for which growers would face significant challenges:

- Chokecherries (fall seeded plantings), dill, coriander, caraway, celery, and sweet white lupins.

As a result, the implementation of the re-evaluation decision for these cancelled minor specialty crops will be delayed for an additional two years to allow growers to find pest management solutions. During this extended period, the overall exposure to human health and the environment will be significantly reduced by the removal of other cancelled uses, as well as through the implementation of additional interim mitigation measures that will be required when applying linuron to these cancelled minor uses. The risks to human health and the environment are therefore considered acceptable for an additional two years for these cancelled minor uses.

General label improvements:

- Update and/or revise the use directions for retained uses according to required risk mitigation measures.

- Replace ‘guarantee’ with ‘active ingredient’ on all product labels.

Human health

Risk Mitigation:

To protect human health from exposure, the following risk-reduction measures are required for uses with continued registration (carrots, parsnip, potato, asparagus and shelterbelts):

- Revised maximum application rates
  - Limit pre-emergent and post-emergent applications to carrots to a maximum annual application rate of 1.68 kg a.i./ha
  - Limit pre-emergent and post-emergent applications to parsnips to a maximum annual rate of 1.50 kg a.i./ha
  - Limit pre-emergent application to potatoes to a maximum annual rate of 1.78 kg a.i/ha
  - Limit pre-emergent or post-emergent application to asparagus to a maximum annual application rate of 1.63 kg a.i./ha
  - Limit dormant stage application to shelterbelts to a maximum annual application rate of 2.16 kg a.i./ha
- To protect consumers, increase the plant back interval restriction from 4 months to 12 months for carrots, potato, and parsnip.
- To protect mixers/loaders and applicators: increased personal protective equipment (PPE), addition of engineering controls (closed mixing loading and closed cab application), and restrictions on some types of application equipment.
- To protect post application workers: increased restricted-entry intervals (REIs) for all activities.
- To protect bystanders from spray drift: require a statement to promote best management practices to minimize human exposure from spray drift or spray residues resulting from drift.

Interim Risk Mitigation:

To protect human health from exposure, the following interim risk-reduction measures are required for cancelled uses with an extended phase out period (chokecherries, dill, coriander, caraway, celery and sweet white lupins):

- Interim maximum application rates
  - Limit pre-emergent application to chokecherries (fall seeded plantings) to a maximum annual application rate of 1.70 kg a.i./ha
  - Limit pre-emergent and post-emergent applications to dill to a maximum annual rate of 1.50 kg a.i./ha
  - Limit post-emergent application to coriander and caraway to a maximum annual rate of 0.80 kg a.i/ha
  - Limit post-emergent application to celery to a maximum annual application rate of 1.68 kg a.i./ha
  - Limit pre-emergent application to sweet white lupins to a maximum annual application rate of 1.49 kg a.i./ha
- To protect post application workers: increased interim restricted-entry intervals (REIs) for all activities.

Environment

Label improvements to meet current standards:

- Updated discharge of effluent statements;
- Updated storage statements.

Risk Mitigation:

To protect the environment, the following risk-reduction measures are required for uses with continued registration (carrots, parsnip, potato, asparagus and shelterbelts):

- Standard label statements are required to minimize potential risks resulting from runoff;
- Standard hazard statements to inform users of the potential toxic effects to sensitive biota;
- Aerial application is prohibited;
- Buffer zones are required to mitigate risks from spray drift.

Interim Risk Mitigation:

To protect the environment, the following interim risk-reduction measures are required for cancelled uses with an extended phase out period (chokecherries, dill, coriander, caraway, celery and sweet white lupins):

- Interim buffer zones to mitigate risks from spray drift.

Value

Label improvements to meet current standards:

- Remove any vague or non-specific claims that the product can be tank mixed with another pesticide.

- Verify that the resistance management statement on each end-use product label is up-to-date.

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 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 objection[3] regarding this decision on linuron 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 PRVD2012-02 and Appendix XI 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

Based on the comments and additional information received during consultation, Health Canada revised the human health, environmental and value assessments.

1.0 Revised health risk assessment

1.1 Toxicology assessment for linuron

Comments received during the consultation period covered a range of issues pertaining to the toxicology assessment, including: 1) the choice of cancer risk assessment method for the uterine and ovarian tumours; 2) the choice of point of departure (POD), toxic endpoint, and study selected for all toxicology reference values (TRVs) established in PRVD2012-02; and 3) the magnitude of applied uncertainty factors. Newly submitted data for linuron included an acute oral gavage neurotoxicity study in rats, a short-term dietary immunotoxicity study in male rats, and all tier 1 in vitro and in vivo assays conducted for the United States Environmental Protection Agency (USEPA) Endocrine Disruptor Screening Program (EDSP). In addition, USEPA and European Food Safety Authority (EFSA) assessments were cited to support the comments. Additional scientific rationales addressing the issues noted above were also provided by the registrant. A weight of evidence review was conducted with consideration of all newly submitted information and rationales in the context of previously evaluated data. As such, all relevant parts of the toxicology assessment outlined in PRVD2012-02 were revisited. Detailed responses to the comments received as well as any revisions to toxicology reference values are provided in Appendix III. Updated toxicology reference values are provided in Appendix IV, Table 1. The linuron PRVD identified that the technical grade active ingredient is known to contain chlorinated benzenes, and polychlorinated biphenyls, dibenzodioxin and dibenzofurans. Based on comparison of the TRVs of the impurities to those of linuron, and taking into account the levels of these impurities in the technical grade active ingredient, the TRVs for linuron are considered protective of the potential toxicity of these impurities.

1.2 Cumulative assessment

The *Pest Controls Products* Act requires Health Canada to consider cumulative effects of pest control products that have a common mechanism of toxicity or share common metabolites. Linuron is a member of the phenylurea class of herbicides which includes diuron, fluometuron, chloroxuron, metobromuron, monolinuron, and thidiazuron. The only other phenylurea herbicide registered in Canada is diuron, a structural analogue of linuron. As a result of structural similarities, diuron and linuron share several common metabolites such as norlinuron and hydroxy-norlinuron. Recently completed international regulatory toxicology reports of diuron were considered in conducting a screening examination of common effects between linuron and diuron. This screening examination revealed that diuron potentially produces several effects that are similar to those observed in the linuron toxicity database including hematological effects such as methemoglobinemia as well as various endocrine effects and several tumour types. Overall, international regulatory agencies including the USEPA (PMRA# 3081861) have yet to establish a common mechanism group for chemicals structurally similar to linuron, largely due to the lack of mechanistic data to establish the various modes of action (MOAs) that are potentially

responsible for producing the common effects. Thus, for the current re-evaluation, Health Canada did not establish a common mechanism of mammalian toxicity between linuron and other pest control products including diuron. The cumulative risk assessment of this chemical class will be addressed once the re-evaluation of diuron has been completed.

1.3 Dietary exposure and risk assessment

The dietary assessment for linuron was published in PRVD2012-02 with the proposal to cancel all uses due to health (dietary and occupational) and environmental risk concerns. Food residue estimates for linuron were updated in consideration of comments and information submitted following the publication of PRVD2012-02. Considerations include the use of a reduced use pattern based on lower applications rates and limited crop uses, while giving priority to the important uses on carrots and potatoes as identified by the registrant and stakeholders. In addition, the dietary assessment incorporated revised drinking water estimates and toxicology reference values.

Acute and chronic dietary (food and drinking water) exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™; Version 4.02) 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. For more information on the assessment, see Appendix V.

1.3.1 Drinking water estimates

Drinking water modelling was previously conducted in PRVD2012-02. Fate inputs were revisited for the current modelling, which contributed to significantly lower drinking water residue estimates. In addition, 3,4-dichloroaniline (3,4-DCA) was now included in the residue definition.

Level 1 Estimated Environmental Concentrations (EECs) are conservative values intended to screen out pesticides that are not expected to pose any concern related to drinking water. These are calculated using conservative inputs with respect to application rate, application timing, and geographic scenario. Level 1 EECs cover all regions of Canada.

EECs were calculated using the Pesticide Water Calculator model (PWC, version 1.52). Modelling for surface water used a standard Level 1 scenario which is represented by a small reservoir adjacent to an agricultural field. EECs in groundwater were calculated by selecting the highest EEC from a set of standard scenarios representing different regions of Canada.

A single annual application rate of 1.78 kg a.i./ha and 1.08 kg a.i/ha were modelled at Level 1. Environmental fate data used in the modelling as well as information on the available water monitoring data are summarized in Appendix VIII.

The annual application 1.78 kg a.i./ha application is reflective of the typical use for potatoes and is higher than the typical rate for the other remaining uses for linuron except for shelterbelts. For shelterbelts, an annual application rate of 2.16 kg a.i./ha is not expected to exceed the modelled potato use scenario due to its relatively smaller area.

The highest daily EEC of 74 µg a.i./ha was used for the acute dietary assessment and the highest yearly EEC of 21 µg a.i/.ha was used for the chronic dietary assessment. Results are provided in Table 1.

Table 1 Level 1 estimated environmental concentrations of the combined residues of linuron in potential sources of drinking water, reported as parent equivalent

Use pattern	Groundwater (µg a.i./L)		Surface water (µg a.i./L)	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]
Single application of 1.78 kg a.i./ha	21	21	74	13
Single application of 1.08 kg a.i./ha	13	13	45	8

1 90th percentile of daily concentrations
2 90th percentile of 365-day moving average concentrations
3 90th percentile of the peak concentrations from each year
4 90th percentile of yearly average concentrations

The 3,4-dichloroaniline transformation product was included in the residue definition as a conservative approach to account for this compound in the dietary risk assessment. The available fate information would not allow for the calculation of separate EECs for 3,4-DCA.

It is however important to note that the revised modelling indicated that the contribution of this compound to the overall EECs is low, as it was found only in small amounts in degradation studies (generally well below 10% of the applied linuron). Therefore, excluding 3,4-DCA from the residue definition would result in minimal changes to the degradation rates and to the resulting EECs. Coupled with the existing information that 3,4-DCA is not readily formed in food commodities, it can be concluded the dietary exposure to 3,4-DCA is minimal and is not of concern.

1.3.2 Exposure from food sources

Food residue estimates were refined to the extent possible based on existing information and the comments received during the consultation period. Residue estimates for food commodities were generally based on field trial data. When field trial data were not available the US Tolerance or the general Maximum Residue Limit (MRL) at 0.1 ppm was used. Chemical specific processing factors were used when available. Percent crop treated information was used in the chronic assessment only, as the refinement was not required for the acute assessment. Refer to Appendix V for additional information on the risk assessment.

In the updated acute dietary assessment, exposure from food alone accounted for less than 10% of the Acute Reference Dose (ARfD) for all population groups and was shown to be acceptable.

In the updated chronic dietary assessment, exposure from food alone accounted for 135% of the Acceptable Daily Intake (ADI) for children 1 to 2 years and was not shown to be acceptable. Dietary exposure was below the ADI for all other population groups. The risk from food alone can be mitigated with the removal of cereal (sweet and field corn, barley, oats, wheat), tree fruits (apple, cherry, peach, pear, plum and prune), soybean, and animal commodities from the assessment. Soybean and tree fruit uses were also removed to reduce drinking water estimates, as these uses have application rates that exceeded the drinking water modelling rate of 1.78 kg a.i./ha. The chronic dietary exposure from food alone, accounted for 7% of the ADI or less, for all population groups when these uses are removed.

Based on additional information obtained during the PRVD2012-02 comment period, a threshold approach was considered appropriate for uterine adenocarcinomas and ovarian tumour risk assessment. The ADI used in the chronic dietary assessment provides a margin of 640-fold to the low dose where there was equivocal evidence of uterine carcinomas and ovarian tumours in female rats.

1.3.3 Exposure from food and drinking water

Exposure from food sources were aggregated with exposure from water sources. Several food commodities were excluded from the chronic food and drinking water assessment in order to mitigate risk concerns from food sources (see Section 1.3.2).

Acute and chronic exposure estimates to linuron from food and drinking water were below 38% of the ARfD and 71% of the ADI for all relevant populations group. Thus, dietary risks to linuron are shown to be acceptable with the consideration of mitigation measures.

1.3.4 Summary of risk mitigation measures related to dietary exposure

The following uses will be cancelled in order to mitigate the health risk concerns to linuron from food and drinking water:

> Tree fruit (apple, cherry, peach, pear, plum/prune), soybean, corn (sweet and field), wheat, barley, and oats.

The following uses will be cancelled due to residue chemistry data deficiencies (these data deficiencies were identified in PRVD2012-02):

> Saskatoon berries, chokecherries, coriander, caraway, dill, sweet white lupins, and tree fruit (apple, cherry, peach, pear, plum/prune).

Note that Saskatoon berries also showed drinking water risk and tree fruit uses showed dietary and drinking water risks.

For the remaining uses, the maximum annual application rate will be reduced to mitigate risk concerns from food and drinking water.

- 1.68 kg a.i./ha for carrot
- 1.50 kg a.i./ha for parsnip

- 1.78 kg a.i./ha for potato
- 1.63 kg a.i./ha for asparagus
- 2.16 kg a.i./ha for shelterbelts

Note that celery was shown to be acceptable in the dietary risk assessment; however, the use will be cancelled due to occupational risk concerns. Additionally, only one application per year is permitted for asparagus (pre-emergent or post-harvest) as more than one application would result in a cumulative yearly rate that exceeds 1.78 kg a.i/ha.

Plant Back Interval Update:

A revised plant back interval (PBI) of 12 months (currently 4 months on existing labels) was identified in PRVD2012-02 based on confined crop rotation data on file. This update was not proposed for implementation in PRVD2012-02 as all uses were proposed for cancellation at that time. Since some uses will be retained, the PBI restriction is now required for carrot, parsnip, and potato uses. The PBI is not applicable to asparagus and shelterbelts.

1.4 Occupational and non-occupational exposure and risk assessment

1.4.1 Toxicology endpoint selection for residential and occupational exposure

See Appendix III, Section 1.1.6.

1.4.2 Non-occupational exposure and risk assessment

There are currently no registered residential uses of linuron; as such a risk assessment for this scenario was not required.

1.4.3 Occupational exposure and risk assessment

In PRVD2012-02, Health Canada had identified many application and post application risks of concern. Calculated restricted-entry intervals (REIs) were not considered to be agronomically feasible for most crops. Since all uses were proposed for cancellation due to drinking water and food risks of concern, mitigation measures were not considered at that time.

Following the publication of PRVD2012-02, additional information was received from the registrant and grower groups. This included use information such as typical application rates and a chemical-specific dislodgeable foliar residue study. This information was incorporated into the revised assessment, to the extent possible. Health Canada responses to specific comments are provided in Appendix III. Details regarding the revised occupational risk assessment are presented in Appendix VI.

The occupational assessment was revised for all uses. The revisions included: updating the dislodgeable foliar residues (DFR) for all crops, incorporation of revised toxicology reference values, and consideration of additional data available to Health Canada and use information from registrants and growers, submitted during the consultation period.

Additional refinements to the use pattern and post application exposure risk assessment were also considered in order to mitigate risks to the general public and workers, while giving priority to the important uses on carrots and potatoes as identified by the registrant and stakeholders.

As a result of the comments and additional information submitted, the outcome of the occupational risk assessment and mitigation proposed in PRVD2012-02 has changed for a few scenarios:

- Most of the agricultural uses previously proposed for cancellation are still of concern and will be removed from the product labels due to dietary risk concerns (food and drinking water; see Section 1.3.4).
- Some remaining uses are now acceptable for continued registration provided the use pattern and mitigation measures outlined in Appendix X are followed:
    - Pre-emergent application to potatoes, asparagus, carrots, and parsnip;
    - Post-emergent application to carrots and parsnip;
    - Post-harvest application to asparagus;
    - Dormant stage application to shelterbelts.
- The following uses were shown to be acceptable in the occupational risk assessment, but will be cancelled due to dietary risk concerns:
    - Pre-emergent combined with post-harvest application to asparagus;
    - Pre-emergent application to field corn, dill, sweet corn, sweet white lupins, chokecherries;
    - Post-emergent application to wheat, barley, oats, dill, coriander and caraway, Saskatoon berries.

Occupational risks of concern continue to be identified for the following uses, which will be cancelled and removed from the labels:

- Pre-emergent application to soybeans;
- Post-emergent application to celery and fruit trees;
- Application using right-of-way sprayer equipment.

The registrant has decided to voluntarily discontinue the following uses. These uses will be removed from the relevant labels:

- Aerial application;
- Application using handheld spray equipment;
- Post-emergent application to field corn.

1.5 Aggregate exposure and risk assessment

There are currently no registered residential uses of linuron; as such a risk assessment for the aggregation of residential and dietary exposures was not required. (Refer to the aggregate assessment for food and drinking water in Section 1.3.2).

1.6 Incident reports

Since the publication of PRVD2012-02, no additional human or domestic animal incidents involving linuron were submitted to Health Canada (in other words, 27 July 2012 to 6 June 2020).

2.0 Revised environmental risk assessment

Estimated environmental concentrations (EECs) were recalculated based on decreased application rates and fewer applications. In addition, comments and studies submitted following the publication of PRVD2012-02 were considered in the revised risk assessment.

2.1 Fate and behaviour in the environment

New studies were submitted (aerobic soil biotransformation and aerobic water/sediment biotransformation) and the results indicate shorter half-lives in these compartments compared to those reported in PRVD2012-02. These half-lives were combined with existing data and used in water modelling, buffer zone calculations, and in the risk assessment for the calculation of EECs. Recent foreign reviews [EFSA 2015 (PMRA# 3038894, PMRA# 3038895, PMRA# 3038896), USEPA 2016 (PMRA# 3038898) and USEPA 2019 (PMRA# 3038899)] contained relevant information which was also incorporated into this revised risk assessment. A summary of the available data on the fate of linuron is presented in Appendix VII, Tables 1 and 2.

Linuron is slightly to moderately persistent and is slightly to moderately mobile in the terrestrial environment. Leaching was not observed in field studies and carryover into the following growing season is not expected to be a concern.

Linuron may enter aquatic environments through spray drift and run-off from the application site. Linuron is classified as being non-persistent to slightly persistent in both aerobic and anaerobic aquatic whole systems. Due to the similarity of chemical structures and formation of major transformation products in the aquatic environment, two transformation products, norlinuron and desmethoxy linuron, were included as residues of concern (RoC) for drinking water and the aquatic risk assessment.

Linuron was detected in 12% of 10 016 Canadian surface water samples, with a maximum concentration of 960 µg/L. For surface water that is a potential source of drinking water, linuron was detected in 6.4% of 6024 samples with a maximum concentration of 18.4 µg/L. In ground water, linuron was detected in 0.32% of 15 106 samples, with a maximum concentration of 1.1 µg/L. Detection of linuron transformation products in groundwater and surface water was infrequent; however, available data is very limited.

2.2 Effects on non-target species

Additional information on the toxic effects to non-target terrestrial and aquatic biota (submitted to Health Canada during the comment period for PRVD2012-02, available in foreign reviews or in published literature) was incorporated into the revised risk assessment. A summary of the available toxicity information is presented in Appendix VII, Tables 3 and 4.

2.3 Environmental risk assessment

Tables 5 to 12 (Appendix VII) report the results of the risk assessment on terrestrial biota. In the terrestrial environment, linuron poses a risk to beneficial arthropods, non-target plants, birds and small wild mammals. Label statements are required to warn users of the potential hazards and buffer zones are required to reduce potential exposure to non-target plants.

In the absence of mitigative measures, linuron poses a potential risk to most aquatic organisms (Appendix VII, Tables 13 to 15). The inclusion of transformation products in the RoC for aquatic biota did not result in significant changes to the risk assessment compared to the risk assessment conducted with linuron alone (Appendix VII, Table 16).

The USEPA determined that linuron has the potential to affect the endocrine systems in rats, fathead minnow, rainbow trout and sticklebacks (USEPA 2015, PMRA# 3038901); however, prior to concluding on the endocrine disruption potential of linuron, they requested higher tier studies. A study from the open literature, PMRA# 3033298, satisfies the requisite studies and clearly demonstrates anti-androgenic activity in amphibians. The risk assessment conducted with the endocrine endpoints from PMRA# 3033298 and the currently modelled EECs indicate there is a potential for endocrine disruption in Canadian aquatic systems. Buffer zones are expected to mitigate the risk from drift. For runoff, the RQ value for the highest relevant field application rate for effects to the amphibian endocrine system is 34. Standard run-off statements will be required on product labels.

When used according to the revised use pattern and revised label mitigation measures, linuron poses acceptable risks to terrestrial and aquatic organisms. Buffer zones are required to protect sensitive habitats and toxicity statements are required to warn users of the potential risks to sensitive species.

2.4 Environmental incident reports

Since the publication of PRVD2012-02, one incident report associated with a short-term fathead minnow reproduction study for linuron was reported in Canada (PMRA# 2185692). This study was reviewed and was included in the toxicity assessment for freshwater fish.

3.0 Pest control product policy considerations

3.1 Assessment of the active ingredient under the toxic substances management policy (TSMP)

The results of the TSMP assessment in PRVD2012-02 indicated that linuron and its transformation products do not meet all Track 1 TSMP criteria. These conclusions have not changed.

3.2 Formulants and contaminants of health or environmental concern

The conclusion of the formulants and contaminants assessment in PRVD2012-02 have not changed as a result of the updated risk assessment. The review of the recently submitted new batch data indicated the need to reduce the levels of impurities in linuron technical products. The

registrant will be required to change their manufacturing method to reduce impurities, and provide supporting analytical data from at least five batches of the technical grade active ingredient, as a condition of registration under section 12 of the *Pest Control Products Act*f.

4.0 Revised value assessment

Linuron has value to users as an herbicide to control a broad-spectrum of broadleaf and grassy weeds on a wide range of sites. During the consultation of PRVD2012-02, a number of stakeholders emphasized that linuron is an essential and critical herbicide for certain crop production in Canada. It is a unique fit in many crop production practices due to its efficacy, weed spectrum, crop safety, crop rotation characteristics, and use as an herbicide resistance management tool.

Based on the health and environmental risk assessments, the following uses are to be retained: carrot, potato, parsnip, asparagus and shelterbelts, provided the use pattern is amended and all risk mitigation measures specified are implemented. For these retained uses, the use pattern amendments include implementing lower rates of application. These amended rates of application are still within the range of labelled rates (see Appendix IX). In addition, a longer re-entry interval (REI) for post application activities, especially for scouting, is also required for certain uses. Consultation with stakeholders indicated that these REIs are considered agronomically feasible for most producers for these retained crops, but not for all producers across Canada, unless modification to certain production practices are adopted. Considering the unique benefits provided by linuron, there is value in retaining the revised use pattern with the longer REIs for those growers who are able to integrate it into their production practices.

The following uses will be cancelled as a result of the re-evaluation: wheat, barley, oats, corn (field and sweet), soybean, Saskatoon berries, fruit trees and minor use specialty crops including dill, coriander and caraway, celery, sweet white lupins and chokecherries. An assessment of the registered products determined that suitable alternatives are available for wheat, barley, oats, corn (field and sweet), soybean, Saskatoon berries and fruit trees. No registered alternatives are available for chokecherries (fall-seeded plantings) as linuron is the only herbicide registered for this use. For dill, coriander, caraway, celery, and sweet white lupins, no suitable alternatives are available, as all alternatives combined do not cover the weed control spectrum and duration of control provided by linuron.

5.0 Conclusion of science evaluation

Following the consultation on the proposed re-evaluation decision of linuron, Health Canada revised the dietary, occupational, environmental, and value assessments based on the comments and information received. As a result, the health and environmental risks from linuron and its associated end-use products have been shown to be acceptable for the following uses when used according to the revised conditions of registration, which include new mitigation measures (Appendix X):

- Carrots, parsnip, potato, asparagus, and shelterbelts.

The following uses of linuron are cancelled since health risks were not shown to be acceptable:

- Tree fruit (apple, peach, pear, plum/prune, cherry), corn (field and sweet), wheat, barley, oats, soybean, celery, Saskatoon berries, chokecherries, dill, coriander, caraway, sweet white lupins, and pre-emergent combined with post-harvest application to asparagus.

A subset of cancelled uses were found to lack suitable alternatives for the management of weeds, for which growers would face significant challenges:

- Chokecherries (fall seeded plantings), dill, coriander, caraway, celery, and sweet white lupins.

As a result, the implementation of the re-evaluation decision for these cancelled minor specialty crops will be delayed for an additional two years to allow growers to find pest management solutions. During this extended phase out period, the overall exposure to human health and the environment will be significantly reduced by the removal of other cancelled uses, as well as through the implementation of additional interim mitigation measures (Appendix X) that will be required when applying linuron to these cancelled minor uses. The risks to human health and the environment are therefore considered acceptable for an additional two years for these cancelled minor uses.

List of abbreviations

%	percent
>	greater than
<	less than
≤	less than or equal to
1/n	exponent for the Freundlich isotherm
˚C	degrees Celsius
3,4-DCA	dichloroaniline
a.i.	active ingredient
ADI	acceptable daily intake
AGD	anogenital distance
AHETF	Agricultural Handler Exposure Task Force
APVMA	Australia Pesticide and Veterinary Medicines Authority
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
atm	atmosphere
ATPD	area treated per day
BAF	bioaccumulation factor
BCF	bioconcentration factor
bw	body weight
CAF	composite assessment factor
CARC	Cancer Assessment Review Committee
CC	Carbohydrate concentrate
CD	caesarean-derived
CEPA	*Canadian Environmental Protection Act*
CHC	Canadian Horticulture Council
cm	centimetre
CSFII	Continuing Survey of Food Intake by Individuals
CT	Crop Treated
Ctl	control
d	day(s)
DA	dermal absorption
DACO	data code
DEEM-FCID	Dietary Exposure Evaluation Model – Food Consumption Intake Database
DFOP	double first-order in parallel
DFR	dislodgeable foliar residue
DNT	developmental neurotoxicity
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
dw	dry weight
DW	drinking water
EC	European Commission or emulsifiable concentrate
EC_{10}	effective concentration on 10% of the population
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily exposure

EDSP	Endocrine Disruptor Screening program
EEC	Estimated environmental concentrations
EFSA	European Food Safety Authority
ELS	early life stage
EP	end-use product
EPI	Estimation Program Interface
ER_{50}	Effective rate on 50% of the population
EU	European Union
F_1	first generation
F_2	second generation
FDS	field dissipation study
fw	fresh weight
FW	freshwater
FOB	functional observational battery
g	gram
GAP	good agricultural practice
GD	gestation day
Gm/dL	grams per deciliter
h	hour(s)
ha	hectare
HAFT	highest average field trial residue
Hb	hemoglobin
HC	historical control
HC_{05}	hazardous concentration to 5% of the species
hr	hour
IARC	International Agency for Research on Cancer
IC_{25}	inhibitory concentration on 25% of the population
IC_{50}	inhibitory concentration on 50% of the population
IORE	indeterminate order rate equation
IR	incident reports
JMPR	Joint Meeting on Pesticide Residues
Kad	adsorption equilibrium constant for the substance
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
K_{Foc}	Freundlich organic-carbon partition coefficient
kg	kilogram(s)
K_H	Henry's law Constant
Koa	Octanol-air partition coeffficient
K_{oc}	organic-carbon partition coefficient
K_{ow}	n–octanol-water partition coefficient
kg	kilogram
L	litre
LC_{10}	lethal concentration 10%
LC_{25}	lethal concentration 25%
LC_{50}	lethal concentration 50%
LC_{90}	lethal concentration 90%
LD_{50}	lethal dose 50%
LOAEC	lowest observed adverse effect concentration

LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOEC	low observed effect concentration
LOQ	limit of quantitation
LSC	liquid scintillation counting
m	metre(s)
MARTA	Middle Atlantic Reproduction and Teratology Association
M/E	marine/estuarine
MetHb	methemoglobin
mg	milligram
mL	millilitre
MLA	mixer/loader/applicator
MOA	mode of action
MOE	margin of exposure
MTD	maximum tolerated dose
MRL	maximum residue limit
MS	mass spectroscopy
MTDB	maximum theoretical dietary burden
N	North
NA	not available
NASS	National Agricultural Statistics Service
NHANES	National Health and Nutrition Examination Survey
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
OC	organic carbon
OECD	Organisation for Economic Co-operation and Development
ORD	Office of Research and Development
PBI	plant back interval
PC	Protein concentrate
PCPA	*Pest Control Product Act*
PCT	percent crop treated
PF	processing factor
PHI	pre-harvest Interval
pKa	dissociation constant
PND	postnatal day
POD	point of departure
ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
PRVD	Proposed Re-evaluation Decision Document
PTEN	phosphatase and tensin homolog
PWC	Pesticide in Water Calculator
R	Roughage
RAC	Raw agricultural commodity
RBC	red blood cell
REI	restricted-entry interval
Repro	reproduction

RQ	risk quotient
SPF	specific pathogen free
SPN	Science Policy Note
SSD	species sensitivity distribution
STMdR	supervised trial median residue
SulfHb	sulfhemoglobin
SW	saltwater
T	testosterone
$t_{1/2}$	half-life
$T_{1/2\ rep}$	representative half-life
$t_{1/2soil}$	half-life in soil
TC	transfer coefficient
TFD	terrestrial field dissipation
TLC	thin layer chromatography
TRV	toxicology reference value
TSH	thyroid stimulating hormone
T4	thyroxine
UF_{DB}	database uncertainty factor
UF_L	LOAEL to NOAEL extrapolation factor
USEPA	United States Environmental Protection Agency
µg	microgram
WHO	World Health Organization
yr	year(s)

Appendix I Registered linuron products in Canada

Table 1 Registered linuron products in Canada requiring label amendments[1]

Registration number	Marketing class	Registrant	Product name	Formulation type	Guarantee
16279	Commercial	Tessenderlo Kerley, Inc.	Lorox L Herbicide	Suspension	480 g/L
16363	Commercial	Adama Agricultural Solutions Canada Ltd.	Afolan F Herbicide	Suspension	450 g/L
19696	Technical	Tessenderlo Kerley, Inc.	Linuron Flake Technical	Wettable Granules	96.9%
27852	Technical	Tessenderlo Kerley, Inc.	Linurex Technical	Dust or Powder	96.8%

[1] as of 4 June 2020, excluding discontinued products or products with a submission for discontinuation

Appendix II List of commenters to PRVD2012-02

List of commenters' affiliations for comments submitted in response to PRVD2012-02.

Category	Commenter
Registrant	Tessenderlo Kerley Inc.
	Novafito
Government Organization	Crops Knowledge Centre (Manitoba)
	PEI Department of Agriculture and Forestry
	Ontario Ministry of Agriculture, Food and Rural Affairs
	BC Ministry of Agriculture
	Manitoba Agricultural, Food and Rural Initiatives
Non-Government Organization	University of Guelph
	Poplar Council of Canada
Agricultural Association	Keystone Potato Producers Association
	Potato Growers of Alberta
	Horticulture Nova Scotia
	Canadian Horticultural Council
	Conseil québécois de l'horticulture
	BC Potato and Vegetable Growers Association
	Productions maraîchères Breizh Inc.
	Alberta Farm Fresh Producers Association
	Agronomy Company of Canada Ltd.
	PEI potato Board
	Ontario Apple Growers
	Fédération des producteurs de cultures commerciales du Québec
	Ontario Tender Fruit producers
	TerraLink Horticultures Inc.
	Thompsons Ltd
	Comité asperges du Québec
	Le Comité carotte
	Keystone Agricultural Producers
	Fédération des producteurs maraîchers du Québec
	Ontario Processing Vegetable Growers
	Maraîchers HCD
	Quebec Produce Grower Association
	Ontario Fruit and Vegetable Growers' Association
	PEI Federation of Agriculture
	PEI Horticultural Association Inc
	Holland Marsh Growers' Association
	Jeffries Brothers Vegetable Growers Inc.
Grower/Stakeholder/Public	Producteur de carrottes
	Schuyler Farm Limited
	Hillview Farms Limited
	Les Fermes André Bérard Inc.
	Carrot Farming
	Connery's Riverdale Farms Ltd

Category	Commenter
	R H MC Lean Farms Inc
	Jamor Farms Ltd.
	Birch Farms Ltd.
	Ferme JFC Gagnon Inc.
	Producteur de carottes et panais
	Les Fermes du Soleil Inc.
	Monaghan Farms
	Ferme B. Cousineau et Fils
	H. J. VanderZaag Farms Ltd.
	Don Chapman Farms Limited
	Ferme Denis Coulombe
	Les Fermes Majalyn
	Ferme C.J. Duval
	Les Fermes Guilbault
	Fermes Rochon et Frères
	Fermin Joubert-Fertinor Inc
	Denis Leguerrir, fils et fille
	Bragg Lumber Company Ltd.
	Erdmann's Gardens & Greenhouse
	Dyke View Farms Ltd
	Ferme Sylvain Brouillette
	Sapec Inc.
	WD Potato Limited
	McCain Foods (Canada)
	La Coop fédérée
	Bradford Co-operative Storage Ltd.
	Max Underhill's Farm Supply Ltd.
	Setterington's Fertilizer Service Ltd.
	Peak of the Market
	Perennia
	Consu Pak Inc
	Ralph A Carpenter & Sons

Appendix III Comments and responses

Health Canada received 97 written comments during the public consultation for the linuron proposed re-evaluation decision, PRVD2012-02. 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 Comments related to toxicology

1.1.1a Comment – cancer risk assessment

The registrant commented that the cancer risk assessment should be based on a margin of exposure (MOE)/threshold approach rather than a linear dose extrapolation approach, as used by the USEPA. The registrant noted that the incidence of uterine and ovarian tumours was observed in only 1 of the 4 chronic rodent oncogenicity studies and was not statistically significant at doses that exceed the maximum tolerated dose (MTD). Furthermore, at doses below the MTD, the incidence of uterine and ovarian tumours falls within the historical control range for these tumours. Based on this information, the registrant requested that Health Canada revise its cancer assessment.

1.1.1b Health Canada response

As part of the re-evaluation of linuron, Health Canada used a weight of evidence approach to assess the relevance of the observed uterine adenocarcinomas and sex-cord stromal cell (ovarian) tumours in Wistar rats after chronic exposure to linuron (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321). Since the uterine adenocarcinomas were present in higher incidences than the sex-cord stromal cell tumours, the focus was largely on the former tumour group.

The following represents some of the considerations in the analysis of the tumour data:

1. Was a dose-response relationship observed?
2. What tumour-type was observed?
3. How do the tumour incidences of experimental animals compare to concurrent and historical control tumour rates?
4. Was hyperplasia observed?
5. Were the changes in tumour incidences statistically significant and/or biologically relevant?
6. What was the relationship of the tumour incidences to the MTD?
7. What were the incidences of related effects in other animal species and strains?
8. Does linuron have a structure-activity relationship similar to other compounds/metabolites?
9. Was linuron mutagenic?
10. Other (hormonal mode of action)

In light of the comments provided to PRVD2012-02, Health Canada has revisited its analysis of the tumour data, considering both previously available and newly obtained information. The following discussion represents Health Canada's position regarding the carcinogenic potential of linuron.

1) Was a dose-response relationship observed?

A dose-response relationship was apparent starting at the lowest dose tested for both ovarian and uterine tumours. As well, all treatment groups had higher incidences of uterine adenocarcinomas and ovarian tumours than either of the concurrent controls. Table 1 summarizes the incidences of ovarian sex-cord stromal cell tumours and uterine adenocarcinomas:

Table 1 Incidences (incidence rates) of uterine adenocarcinomas and ovarian sex-cord stromal cell tumours in Wistar rats after 24 months of exposure to linuron

mg/kg bw/day (ppm)	Ctl A (vehicle control)	Ctl B (vehicle control)	1.6 (25 ppm)	13.6 (200 ppm)	109 (1600 ppm)
Uterine Adenocarcinomas	1/58 (1.72 %)	0/59 (0%)	3/63 (4.76 %)	4/59 (6.78 %)	20/57 (35.1 %)
Combined sex-cord stromal cell tumours	0/58 (0 %)	0/59 (0 %)	1/63 (1.6 %)	2/59 (3.4 %)	5/58 (8.6 %)

2) What tumour-type was observed?

The ovarian tumours were benign, malignant or indeterminate. According to the WHO and IARC histological classification for ovarian tumours, theca cell tumours and granulosa/theca cell tumours (sex-cord stromal cell tumours) can be grouped together when considering dose-response relationships (PMRA# 1828507).

All uterine adenocarcinomas were malignant. Although the study pathologist differentiated the different types of adenocarcinomas (scirrhous, polypoid), these tumours have the same histologic origin from glandular epithelium, and therefore can be grouped together when considering dose response relationships.

3) How do the tumour incidences compare to concurrent and historical control tumour rates?

The concurrent control group is the most relevant comparator for determining treatment-related effects in a study.

In the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321), two sets of concurrent control animals were available. Control A was a negative control and control B was a vehicle control (acetone). The pathology results in these groups of animals were comparable to one another and the health of those animals did not appear to be compromised or influenced by the vehicle (acetone). Together, these concurrent controls provide the best indication of what effects should be considered spontaneous.

For completeness, appropriate historical control data were requested from the registrant. However, this information was not available since the conducting laboratory (Hoechst) was no longer operating as an Agrochemical company.

Instead, Health Canada was referred to a document (PMRA# 1986633) which identified a study conducted by Deerberg et al., (1981) also cited in the original study report, as a rationale for disregarding the increased uterine adenocarcinomas in the treated animals. Furthermore, Elsinghorst et al., (1984) referred to the Deerberg study as evidence for the spontaneous occurrence of uterine adenocarcinomas. However, the following identifies several noteworthy limitations that preclude the acceptance of the animal data in the Deerberg study as adequate historical control information:

a) In the Deerberg study, Han:Wistar rats were used, as opposed to HOE:WISKf (SPF 71) rats from the SPF Hoechst breeding colony in the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321), which appear to be a different stock of Wistar rats. Standard guidance specifies that historical control data originate from animals of the same breeding colony.

b) The Deerberg study was not conducted in the same facility as the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321). Historical control data should originate from animals examined at the same facility as the study animals.

c) The authors did not note this tumour type in a second study using retired breeding females of the Han:Wistar stock, suggesting a low spontaneous occurrence of uterine adenocarcinomas.

d) There is a degree of uncertainty as to the date the study began and whether it was conducted within 5 years of the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321), since the authors reported that animals were from a colony that was started in their institute more than 10 years before the published date. Ideally, historical control data originate from studies that have been examined within ± 5 years of the study under consideration to account for genetic drift.

e) In the Deerberg study, 320 animals were monitored from weaning until their natural death (up to 48 months). Since the animals in the Deerberg study were not sacrificed, only those that died within the first two years would be “comparable” to the animals in the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321), that were sacrificed after 24 months of treatment.

f) The authors identified that animals were from their specified-pathogen-free colony. However, they also noted that Escherichia coli 07:K1:H7 was a prevalent pathogenic bacterium in their colonies of rats and mice, and that a relationship may exist with the purulent infections seen regularly in the tumour tissue, which was mainly caused by Escherichia coli 07. Such a finding would affect the utility of this data.

In light of these limitations, the historical control data from the Deerberg study were not considered to be adequate.

According to a broader literature search, Sabra and Donryu rats have been suggested to be susceptible to the spontaneous development of uterine adenocarcinomas (Nagoaka et al., 1990; Mor and Lutsky, 1986; Ando-Lu et al., 1998). Further, two detailed reviews of spontaneous neoplasms in control Wistar rats (Poteracky and Walsh, 1998; Walsh and Poteracky, 1994) suggested that the incidence of spontaneous uterine adenocarcinomas in Wistar rats was lower than that observed in each of the treatment groups in the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321).

The 1994 review examined 1370 control Wistar rats (685 each males and females) from 10 carcinogenicity bioassays conducted between 1980 and 1990, with animals from Charles River Laboratories and Hilltop Laboratory Animals. Some of these studies would have been conducted within 5 years of the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321). A total of 1857 neoplasms were identified, of which 582 were in female rats. Only 1.6 % of females (11/685) had uterine adenocarcinomas (% range = 0-4%).

The 1998 review examined 930 control Wistar rats (465 each males and females) from five carcinogenicity bioassays conducted between 1990 and 1995, and compared results with review findings in studies between 1980 and 1990. A total of 1599 neoplasms were diagnosed in 361 male and 415 female rats. Of these, none were identified as uterine adenocarcinomas. Animals were sourced from Charles River Laboratories.

More recent historical control data from Charles River Laboratories (2003) identified 13 uterine adenocarcinomas out of 565 Wistar Han rats examined (2.3 %). Six studies out of the 10 examined showed this tumour type, with a range of 1.6 to 5.5 %.

The registrant provided additional data (Harlan Laboratories, 2011; Charles River, 2011) in which the upper ranges for the uterine adenocarcinomas exceeded that found in the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321). However, in these studies, it is important to note that, similar to those cited above, the mean incidences were lower than those observed in all treatment groups in the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321). In the Charles River Laboratories data, 30 incidences of uterine adenocarcinomas were identified out of 1217 animals (2.5 %). In the Harlan laboratories data, 104 out of 3818 (2.9 %; range 0-11%) or 101 out of 3594 (2.1 %; range 0-11%) animals had uterine adenocarcinomas. The mean incidences are considered low and support the validity of using the concurrent controls in the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321).

Although much of this data originated from animals examined beyond the 5-year range relative to the study in question, the overall indication supports the low incidence of this tumour type over approximately two decades. Furthermore, the incidences in all treatment groups exceeded the mean historical control data in all studies conducted in Wistar rats (discussed above).

More recently, Health Canada located a chronic-cancer study (PMRA# 1199540; #1199520) that was conducted in the same facility (Hoechst Aktiengeseflschaft Pharma Forschung Toxikologie) as the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321), with the same stock of animals (HOE:Wfskf (SPF71)), and within 5 years of each other.

Incidences of uterine adenocarcinomas in control animals for this study were compared with control data from the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321), which are noted in Table 2.

Table 2 Incidences of uterine adenocarcinomas in the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321), and other Hoechst control animals

mg/kg bw/day (ppm)	Ctl A (vehicle control)	Ctl B (vehicle control)	1.6 (25 ppm)	13.6 (200 ppm)	109 (1600 ppm)
Study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321),					
Combined chronic/cancer	1/58 (1.72 %)	0/59 (0%)	3/63 (4.76 %)	4/59 (6.78 %)	20/57 (35.1 %)
Chronic-cancer study (Hoechst Control Animals)					
Chronic portion	0/20 (0%)	Duration on study: 24 months			
Cancer portion	2/59 (3.4%)	Duration on study: 28 months			

The incidences in all treatment groups exceeded the control data in a comparable study conducted in HOE:Wfskf (SPF71) rats.

In summary, due to the limitations in the Deerberg study, notably the questionable health of the animals, and lack of reproducibility within their same stock of animals, and given that the two sets of concurrent controls reported only one occurrence of a uterine adenocarcinoma, as well as the fact that the majority of historical control data supports the low spontaneous incidence of uterine adenocarcinomas in Wistar rats, the weight of evidence suggests that the observed tumours in the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321), were more likely treatment-related than spontaneous.

However, in light of the recently examined control data from the Hoechst lab, the incidences at the low dose level are considered equivocal, while the incidences at the mid-and high-dose levels are considered treatment related.

4) Was hyperplasia observed?

There was no obvious dose-response relationship for ovarian or endometrial hyperplasia within the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321).

In a different 2-year rat study using CD rats exposed to linuron (PMRA# 1430980), an increase in cystic hyperplasia of the uterine endometrium and an increase in endometrial stromal cell polyps of the uterus were noted after 24 months of exposure. However, this dose level was considered excessive due to severe weight loss in females.

Conflicting evidence exists in the scientific literature with regards to the appearance of uterine endometrial hyperplasia as a precursor for uterine endometrial adenocarcinomas.

5) Were the changes in tumour incidences statistically significant and/or biologically relevant?

The statistical analyses cited in PRVD2012-02 were those of the study authors. No additional statistical analyses were conducted by Health Canada. In light of the comments received, Health Canada has revisited the statistical analyses for this study.

Based on the study authors' assessment, uterine adenocarcinomas were statistically increased from controls in the mid- ($p < 0.05$) and high-dose groups ($p < 0.001$). The total number of ovarian tumours was significantly increased in the high dose group ($p < 0.001$). A slightly increased incidence of these tumours at the mid-dose level was not significant with the Fisher's exact test and significant only at the 95 % level with the CHI^2 test. In their analysis, the study authors combined the incidences from controls A (no acetone) and B (with acetone).

The registrant provided a statistical re-analysis of the uterine and ovarian tumour incidences using a Fisher's exact test (one-tailed and two-tailed). These data were assessed using the incidences in control group B, but excluded those in control group A. Their results using the one-tailed test (which is the standard test for comparing tumour incidences) indicated that the uterine adenocarcinomas and ovarian tumours were only statistically significantly increased from controls at the high dose level.

Generally, different control groups are not combined for use in statistical analyses (Organisation for Economic Co-operation and Development (OECD) Guidance Document 116). The concurrent control group that differed from the test groups by the absence of the test substance only (control B) was the most appropriate for the comparison with the test groups. However, following the publication of PRVD2012-02, the registrant submitted a Peto analysis and linear trend tests with the control groups combined. Based on their calculations, a positive trend by Peto analysis was observed overall and a positive trend by linear trend test was observed when the high dose level was either included or excluded. Further to this, Health Canada conducted a Cochrane-Armitage trend test examining the trend with and without the high dose group, and relative to control B (without combining the two controls). The results indicated statistical significance when the high dose group was included and no statistical significance when the high dose group was excluded.

While Health Canada is in agreement with the registrant that the study authors made an error in their statistical analysis, the data obtained from control A animals remains important to the interpretation of the tumour incidences. In fact, the results from control A animals are the best suited "historical control" data, given that they were obtained from animals of the same facility and animal colony, and examined in parallel to the other dose groups (see point 3, above).

Despite the lack of statistical significance at the mid- and low- dose levels, the single incidence of a uterine adenocarcinoma in control group A further supports the low spontaneous incidence of these tumours.

6) What was the relationship of the tumour incidences to the MTD?

In the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321), the high dose level exceeded the MTD.

Body weight was adversely affected at the high dose level. However, these effects were presumed to be at least in part due to a decrease in palatability at the beginning of the study (see below) and decreased food consumption throughout the study.

A 35% decrease in body weight gain was noted in the first 3 months which may have been due, in part, to a palatability problem, especially since there was only an 8% decrease in body weight gain between 3 and 6 months of treatment. On average, high dose females did not gain weight in the second year of treatment, as opposed to a 34% increase in body weight gain for controls. Most of this discrepancy can be attributed to treatment between 12 and 18 months, as a small increase in weight gain was noted at the high-dose level, but amounted to only 30% of the weight gained by control B. At the end of the study, between 18 and 24 months, high-dose level and control animals lost weight in comparable amounts. Furthermore, body weight parameters were not affected at the low- and mid-dose levels, while the incidences of uterine adenocarcinomas were increased relative to both control groups at all dose levels.

Although the relationship between the observed uterine adenocarcinomas and the effects on body weight is not clear as noted in PRVD2012-02, the high-dose level females experienced physiological stress.

In addition to body weight effects, high-dose level animals showed:

1) Increased toxic change including necrosis to the liver (primarily in females) with the majority of reported cases classified as very slight, slight, mild, or unclassified, while only a few were considered moderate, marked, or severe effects;

2) Increased liver necrosis without toxic change in males;

3) Increased incidence of hemosiderin deposition in the liver (males), spleen (males), lymph nodes (males), and kidneys (females);

4) Slight normochromic anemia (females) and leukocytosis (but no change in differential blood count);

5) Decreased relative and absolute weights in seminal vesicles and prostate;

6) Increased mortality (discussed below).

According to OECD Guidance Document 116, results from a rat carcinogenicity bioassay can be considered acceptable if survival is not less than 50% in all groups at 24 months (OECD Guidance Document 116). In the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321), survival was 63% (36/57) at the high dose level compared to 90% (53/59) in Control group B. Additionally, no more than 10% of any group should be lost due to autolysis, cannibalism, or management problems (OECD Guidance Document 116). Severe autolysis, to the extent that tissues were no longer able to be examined, was observed in 7% (4/57) of the high dose animals. Thus, the results of the high dose group should not be dismissed on the basis of decreased body weight and mortality. In fact, the mortality in this group deserves further scrutiny.

Health Canada agrees with the registrant that mortality was increased in females at the high dose level. Excess deaths compared to controls were the result of tumors.

Eight of the nine rats that had scirrhous-type uterine adenocarcinomas did not survive to the end of the study and displayed extensive metastases to other parts of the body. These high dose rats with metastatic adenocarcinomas of the uterus were found dead between 17-24 months of treatment. The majority were found dead by 21 months, thus indicating that they developed these tumours earlier on during the treatment, but after 12 months (since no uterine tumours were noted at the interim sacrifice). At the mid-dose level, one rat with a metastatic adenocarcinoma was found dead after 21.5 months of treatment.

As discussed in point 5, the registrant submitted a Peto analysis and linear trend tests with the control groups combined. Based on their calculations, a positive trend by Peto analysis was observed overall and a positive trend by linear trend test was observed when the high dose was either included or excluded. Further to this, Health Canada conducted a Cochrane-Armitage trend test examining the trend with and without the high dose groups, and relative to control B (without combining the controls). The results of these tests were statistically significant when including the high dose group and not statistically significant when excluding the high dose group.

Health Canada agrees that, in some cases, endocrine-mediated tumours may be due to age related changes in hormonal signaling, as the registrant noted with respect to ovarian and pituitary cancers. However, given the duration of time on treatment prior to death and the extent and severity of tumour metastasis indicated in the pathology report for those animals, Health Canada disagrees that these tumours are related to aging. Furthermore, as with other spontaneous tumours of aging, higher incidences of uterine adenocarcinomas across all dose levels and controls as well as consistently across chronic/oncogenicity studies would be expected if these were age related tumours. Since the majority of historical control data, as well as the studies on file for linuron do not reflect these characteristics, Health Canada does not support the registrant's position that the uterine adenocarcinomas seen in the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321), were spontaneous tumours of aging.

The uterine adenocarcinomas in the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321), are considered treatment-related at the mid- and high-dose levels, and equivocal at the low dose level. Although mortality was increased at the high dose level, 8/21 (38%) appeared to have died with metastatic uterine adenocarcinomas. While Health Canada recognizes that the high dose level animals were stressed (MTD was exceeded), given the severity of the observed tumours, concern remains regarding the potential relevance and aggressiveness of this tumour type in humans (see point 10 below).

7) What were the incidences of related effects in other animal species and strains?

Health Canada agrees with the comment that within the linuron database, the evidence for uterine adenocarcinomas, as well as other uterine cancers, was limited primarily to the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321).

Uterine cancer was observed in both rats and mice, albeit in variable incidences. However, the studies were supplemental and the evidence was not robust.

In mice, uterine endometrial sarcomas were noted starting at the low dose level and exceeded levels in both concurrent and historical controls, although not statistically significant (PMRA# 1223427). At the low dose level, these neoplasms occurred in the absence of systemic toxicity but in the presence of other tumours in females that were considered equivocal in nature. Given the lack of a dose-response and animal health concerns in this study, the toxicological relevance was uncertain.

In rats, a slight increase in uterine adenocarcinomas was noted in a chronic/post three-generation study with CD BR rats (PMRA# 1224447). A progression of these tumours was noted from hyperplasia at lower dose levels to adenocarcinomas at the high dose level. Excessive systemic toxicity was evident at the high dose level but not at lower dose levels where hyperplasia was observed. Data from this study were deemed inconclusive because of the small sample size.

As discussed in PRVD2012-02, in point 1 above, and as shown in Table 1, ovarian tumours were also observed in the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321), with a dose-related increase starting at the lowest dose tested (statistically significant at the mid-dose level); however, without prior evidence of hyperplasia.

8) Does linuron have an structure-activity relationship similar to other compounds/metabolites?

Diuron, another substituted urea herbicide, is structurally similar to linuron. It is also thought to have the ability to directly antagonize the androgen receptor, with lower affinity than linuron.

The California Department of Pesticide Regulation review of a chronic/carcinogenicity study with diuron reported an increase in uterine adenocarcinomas at 203 mg/kg bw/day in Wistar rats (Cal-DPR Draft report 2002). In this study, the MTD was not exceeded at the high dose level. A 2011 Australian review for diuron (Australian Pesticides and Veterinary Medicines Authority (APVMA) 2011) also reported these tumours from the same study but indicated that they were within the range of historical control data provided by the conducting laboratory (2-20%).

Vinclozolin is an anti-androgen that is structurally similar to linuron. In a 24-month chronic-cancer study in Wistar rats (PMRA# 1146930), vinclozolin induced a statistically significant increase in uterine adenocarcinomas at the high dose level (180 mg/kg bw/day) in the presence of systemic toxicity.

9) Was linuron mutagenic?

Linuron was negative in most mutagenicity studies. The weight of evidence suggests that linuron is not genotoxic, but rather that it generates its effects by a cytotoxic mode of action.

10) Other (hormonal mode of action):

Typically, uterine endometrial cancer can be either type 1, which is estrogen-related, or type II, which does not appear to be estrogen-related and tends to present with more aggressive disease. Some type II tumours can have molecular alterations found in type I tumours such as K-ras, PTEN, β-catenin and microsatellite instability. Therefore, it is possible that type II tumours may arise from de-differentiation of a pre-existing type I cancer (Plataniotis and Castiglione, 2010).

Linuron is known to perturb the homeostasis of several hormones, including estrogen. Although Health Canada data on file pertaining to modifications in estrogen levels were derived from linuron-treated males, it can be postulated that there may be potential for linuron-induced estrogen modulation in females, either directly or indirectly via alterations in signalling pathways. However, this mode of action in females has not been characterised for linuron.

Furthermore, given the aggressiveness of several observed uterine adenocarcinomas in the study under consideration (PMRA# 1074302, PMRA# 1074320, and PMRA# 1074321), these tumours appear more similar to type II in origin and thus may be un-responsive to estrogen. However, additional information would be required to determine the mode of action of linuron on the uterus.

In 2015, the USEPA completed a weight of evidence assessment evaluating the results of the EDSP (PMRA# 3038901) and concluded that linuron does not appear to interact with the estrogen pathway based on Tier 1 assays. Results from the aromatase assay were equivocal. However, linuron was anti-androgenic both in vitro and in vivo. There was evidence of potential interaction with the thyroid pathway as characterized by thyroid hormone changes in the female pubertal assay. Therefore, the USEPA draft human health risk assessment (PMRA# 3081860) recommended a special thyroid assay in pregnant, postnatal, and adult animals to generate data that may be used in human health risk assessment in protecting the developing nervous system from thyroid hormone disrupting chemicals. However, in 2019, the USEPA (PMRA# 3081862) accepted the registrant submitted data waiver for this assay. Currently, the revised Health Canada ARfD (females 13+) and ADI provide a margin of 4,000-fold and 20,000-fold, respectively, to the low dose level of 50 mg/kg bw/day that resulted in reduction of serum T4 and TSH in female pubertal assay.

Health Canada's conclusion regarding the carcinogenic potential of linuron:

Based on the weight of evidence noted above, sufficient concern remains that linuron may be related to increased incidences of uterine adenocarcinomas and ovarian tumours in rats, and, thus, relevant for human health risk assessment.

In summary, tumours were observed in rats in a 24-month chronic-cancer study. The dosing was considered adequate at the low- and mid-dose levels; however, the high dose level in this study was deemed excessive. Compared to concurrent and adequate historical controls, incidences of uterine adenocarcinomas were considered treatment-related and not spontaneous at the mid- and high-dose levels, while equivocal at the low dose level. Incidences at the mid-dose level, although not statistically significant, were considered biologically relevant based on a comparison of incidences to the vehicle controls, negative controls, and historical controls. Finally, the onset of tumour related mortality and associated severity of metastasis suggested an aggressive tumour type.

A linear low dose extrapolation (q_1*) approach is frequently recommended for the cancer risk assessment in the absence of a sufficient weight of evidence and mode of action data to support a proposed threshold-based approach. However, in this case, several considerations were identified that rendered this approach overly conservative. Those considerations are identified below:

1) Uterine adenocarcinomas were only statistically significant at the high dose level and a positive trend was observed only when the high dose level was included in the calculations. However, a dose level between the high dose level and mid dose level would be expected to produce statistically significantly findings below the MTD.

2) The high dose level exceeded the MTD, thus the animals were considered physiologically stressed.

3) Linuron was not genotoxic.

4) Incidence at the low dose level was considered equivocal based on incidences in historical controls.

5) These tumours did not appear in another chronic-cancer study for linuron.

Therefore, Health Canada will depart from the proposed linear low dose extrapolation approach and support a threshold approach for the cancer assessment for uterine adenocarcinomas. This approach is also considered to be sufficiently protective of the onset of ovarian sex-cord stromal cell tumours at all dose levels.

1.1.2a Comment – acute reference dose (ARfD)

The submitted comments requested revision to the acute dietary endpoint (ARfD- for all populations). The use of elevated levels of methemoglobin (MetHb) and sulfhemoglobin (SulfHb) from a one-year dog study was contested to be highly conservative, inappropriate and inconsistent with historical Health Canada decisions and scientific approach. The comments suggested using the ARfD determined by the 2012 USEPA assessment, which was the most recent USEPA assessment at the time these comments were submitted.

1.1.2b Health Canada response

As a part of the re-evaluation of linuron, Health Canada (PRVD2012-02) conducted a weight of evidence assessment to establish an ARfD on the basis of elevated levels of methemoglobin (MetHb) and sulfhemoglobin (SulfHb) observed in a one-year dog study.

In light of the comments provided to PRVD2012-02, Health Canada has revisited this information, and considered newly obtained information. The following discussion represents the revised Health Canada position regarding the selection of a toxicity endpoint to establish an ARfD.

1) Brief Literature Overview of MetHb and SulfHb

2) Relevance of MetHb for Setting an ARfD

3) Historical Health Canada decisions re: elevated MetHb levels

4) Evaluation of Elevated Levels of MetHb in One-Year Dog Study

5) Implication of Elevated MetHb on the 3-fold PCPA Factor

6) Conclusions of Part 2: Re-consideration of the ARfD identified in the PRVD2012-02

1) Brief literature overview of MetHb and SulfHb

MetHb binds oxygen more strongly than hemoglobin (Hb) and therefore does not effectively deliver oxygen to tissues. In addition, the presence of methemoglobin in a hemoglobin tetramer has allosteric effects that increase the affinity of oxyhemoglobin for oxygen and therefore significantly impairs the delivery of oxygen to tissues. SulfHb is much less common than MetHb and generally requires the formation of MetHb and then binding of sulfur to the heme (Bloom and Brand, 2001).

In humans, the concentration of MetHb is generally maintained at less than 1% of total Hb by enzymatic reductive pathways (MetHb reductase). In beagle dogs, the background levels of MetHb are around 0.5-2.0% of total Hb. In addition, rats and mice are considered less sensitive to formation of MetHb compared to dogs and humans (Mueller, 2006). An oxidizing xenobiotic that overwhelms these pathways can elevate levels of MetHb in the blood (Bloom and Brand, 2001).

The impact of the elevated MetHb levels on the health of animals and humans depends on the extent of MetHb formation. MetHb at low levels (<10% of total Hb) are clinically asymptomatic in humans. However, a blue/gray appearance of the extremities (nails, nose, fingertips and skin) may already occur at slightly raised MetHb levels (≥6% of total Hb) in animals and humans. Clinical symptoms of hypoxia due to elevated MetHb levels include cyanosis, dyspnoea, fatigue, headache, weakness, dizziness, tachycardia and chocolate brown blood, which appear when MetHb levels reach 15-40% of total Hb. Levels of MetHb exceeding 50% of total Hb can result in death. Individuals with a higher risk for developing methemoglobinemia are likely those with a hereditary deficiency of MetHb reductase (enzyme catalyzes MetHb reduction) and infants, as their MetHb reductase activity is low (Muller, 2006).

SulfHb cannot be reduced to Hb, persisting for the life of the RBC. However, the symptoms and clinical signs associated with elevated levels of SulfHb tend to be milder than with MetHb because the non-sulfated Hb units can unload oxygen to tissues more readily as opposed to MetHb (Wolf and Wright, 2004).

2) Relevance of MetHb for setting an ARfD

An effect, or endpoint, relevant to an acute exposure scenario may be identified from any study in a standard toxicology database developed for a pesticide. This acute effect may be used to establish an ARfD. For hematological parameters, if changes are observed early in a repeat-dose study and do not appear to progress during the course of the study, then such effects can be considered to result from acute exposure to the substance (JMPR, 2004). Additionally, in the standard toxicity data package required for the evaluation of a pesticide, hematology is generally not conducted in the single dose studies. MetHb levels were not determined in single dose studies in the linuron database; the earliest measurements of MetHb levels were after 3 months in the one-year dog study in the linuron toxicity database. Since MetHb levels of ≥ 6% of total Hb

appear to be associated with clinical signs of toxicity, the MetHb levels of 4% above background level in dogs, or a statistically significant increase relative to the background level in rodents is considered to be relevant in setting an ARfD (JMPR, 2004; Solecki et al., 2005). The subsequent, JMPR, WHO and EU guidance documents for setting an ARfD refer to this discussion as the primary reference for setting an ARfD based on MetHb. Considering all these known facts at the time of the re-evaluation of linuron, MetHb was considered a relevant endpoint for setting an ARfD when assessed in repeat-dose studies.

3) Historical Health Canada decisions re: elevated MetHb levels

Key guidance documents on setting ARfD values were published by the JMPR, EU and WHO in 2004/2005. Prior to these publications, the evaluation of pesticides in Canada (prior to 2005) did not generally consider elevated levels of MetHb as a potential basis for an ARfD.

Hematological effects were demonstrated in the linuron toxicology database in both rats and dogs. These effects included methemoglobinemia, anemia, Heinz bodies, bilirubin, hemosiderin deposition in the spleen, and changes in the spleen weights observed in both rats and dogs. Overall, these effects were suggestive of methemoglobin-induced hemolytic anemia. The aniline moiety of linuron is known to cause hematological effects including elevated levels of MetHb. Since changes in the hematopoietic system were one of the two primary effects in the linuron database, regulating on MetHb was considered appropriate.

4) Evaluation of Elevated Levels of MetHb in One-Year Dog Study

Previously, Health Canada considered statistically significant increases of MetHb and SulfHb levels at 4.17/3.49 mg/kg bw/day as a treatment-related and adverse effect. The ARfD was established based on a NOAEL of 0.77 mg/kg bw/day for elevated levels of MetHb and SulfHb observed at 4.17/3.49 mg/kg bw/day in the one-year dog study. Statistically significant increased levels of MetHb and SulfHb were observed at 3 months starting 4.17/3.49 mg/kg bw/day. This was the first measurement of MetHb and SulfHb in this study. In humans, clinical signs of toxicity are associated with MetHb levels that reach 6% or greater of total Hb (as discussed above). The comparison of clinically significant levels in humans to dogs appears valid since similar background activity of methemoglobin reductase exists in dogs and humans. Dog and human erythrocytes also have similar circulating lifespans. The mean values for MetHb and SulfHb results for dogs in this study do not approach the clinically significant levels in humans. The highest individual MetHb concentrations were 6.1% or 0.9 gm/dL and 4.1% or 0.6 g/dL in a male (#2525 at 9 months) and a female (#2552 at 12 months) dog, respectively.

The elevated levels of MetHb and SulfHb should be considered treatment-related and biologically significant starting at 0.79/0.77 mg/kg bw/day (♂/♀). However, since they do not approach the clinically significant levels in humans (6% of total Hb) and the ‘4% of total Hb’ threshold in dogs set by international guidance documents, these levels of MetHb and SulfHb were not considered toxicologically adverse. At the high dose level of 18.6/16.1 mg/kg bw/day (♂/♀), these levels likely reached the cusp of toxicological adversity.

5) Implication of the elevated MetHb levels on the 3-fold PCPA factor

The PCPA 10-fold uncertainty factor is applied by default to protect the unborn, infants, and children. This factor may be reduced based on reliable scientific data. Relevant effects across the entire toxicology database, and other uncertainties, may affect the magnitude of the retained PCPA factor.

With respect to MetHb formation, the unborn and infants are more sensitive than older children and adults. Older children and adults are able to convert MetHb back to normal Hb, using the enzyme MetHb reductase. In infants, however, the enzyme is not fully functional (Muller, 2006; Gregory Cope, 2004). This consideration is integrated in the discussion of the PCPA factor (see Health Canada response to comment 1.1.4).

Conclusion

Treatment-related effects on MetHb levels following repeat-dose studies are relevant for establishing an ARfD. The elevated levels of MetHb in the linuron one-year dog study are considered a treatment-related effect. However, the levels of MetHb in this study were not associated with any clinical signs of toxicity at 4.17/3.49 mg/kg bw/day. In addition, according to the internationally accepted published guidance documents on MetHb, the levels of MetHb in this study did not exceed toxicologically relevant levels (4% of total Hb in dogs) and therefore were not considered toxicologically adverse. As such, the NOAEL for the study was established at 4.17/3.49 mg/kg bw/day; however following receipt of comments and additional information during the comment period for PRVD2012-02, an alternate study was selected for establishing an ARfD (see Section 1.1.5 Revised Toxicology Endpoints for Dietary Risk Assessment).

1.1.3a Comment – short-term endpoint

The submitted comments requested that the endpoint selected for short-term dermal and inhalation risk assessments be revised. Using an endpoint from a two-generation reproduction study was contested as inappropriate for this exposure scenario. The commenters also requested revision of the NOAEL and LOAEL values for offspring and reproduction toxicity in the two-generation reproduction toxicity study. The commenter viewed the toxicological effects identified by Health Canada at the LOAEL as non-adverse. For the reproduction toxicity, the comments suggested using the NOAEL and LOAEL from the 2012 USEPA assessment.

1.1.3b Health Canada response

As a part of the re-evaluation of linuron, Health Canada (PRVD2012-02) conducted a weight of evidence assessment to establish an endpoint for short-term dermal and inhalation risk assessments on the basis of adverse effects observed in the guideline two-generation reproduction toxicity study. In light of the comments provided to PRVD2012-02, Health Canada has revisited this information, and considered newly obtained information. The following discussion represents the position of Health Canada regarding the NOAEL values in the two-generation reproduction toxicity study and the short-term endpoint for occupational risk assessments of linuron.

1) Re-consideration of Offspring NOAEL/LOAEL identified in the PRVD2012-02

2) Re-consideration of Reproduction NOAEL/LOAEL identified in the PRVD2012-02

3) Re-consideration of the Endpoint Selected for Short-term Risk Assessment

1) Re-consideration of the offspring NOAEL/LOAEL

Both Health Canada and the USEPA established a LOAEL at the mid-dose level and a NOAEL at the low-dose level based on statistically significantly decreased body weight in F_1 pups.

Statistically significantly reduced body weights were observed in F_1 pups at birth and throughout lactation starting at 5.8 mg/kg bw/day. The litter size at the mid-dose level of 5.8 mg/kg bw/day was increased, which may account for some of the reduction observed in F_1 pup body weights. In addition, the mean total litter weights were comparable between the mid-dose group and the control group. In general, pup body weight is inversely related to litter size, at least in pre-weaning animals (OECD Guidance Document 43). The variation in pup body weight can generally be corrected by the standardization of litter size ("culling"). Although, this study standardized litter size on PND 4, the variation in body weight was not completely corrected. A comparison of F_1 pup body weights at the end of lactation to their birth weights showed that the "rate of growth" was comparable between the mid-dose group and that of the control group. No other effects were noted in the offspring and no treatment-related effects were noted on F_2 pup body weights at this dose level, although not many other parameters were assessed including microscopic histopathology. Finally, decreased fetal body weight was observed at higher dose levels elsewhere in the linuron toxicity database. In conclusion, given the strength and weight of the evidence, the reduction in the fetal body weight at 5.8 mg/kg bw/day is not considered an adverse effect.

In summary, the offspring NOAEL was revised from 0.74/0.92 mg/kg bw/day to 5.8/7.3 mg/kg bw/day based on effects at the high dose level, which included decreased body weight, litter size, percent born alive, viability index, and lactation index.

2) Re-consideration of the reproduction NOAEL/LOAEL

PRVD2012-02 reported a LOAEL for reproduction toxicity at 5.8 mg/kg bw/day on the basis of increased incidences of testicular effects including minimal arteritis, moderate-severe atrophy, minimal intratubular granuloma/fibrosis and minimal Leydig cell hyperplasia. Effects on epididymides at this dose level included increased incidence of interstitial/perivascular lymphoid foci, minimal focal inflammation/tubular degeneration, and moderate unilateral oligospermia. Other effects at this dose level included increased incidence of minimal inflammation in ductus deferens/ampulla. These effects were increased in incidence and severity at the high dose level. The effects at the high dose level have been considered treatment-related and toxicologically adverse unanimously by the study author, study sponsor, Health Canada and the USEPA.

In order to re-evaluate the changes in the reproductive system of F_1 male rats at the LOAEL, Health Canada examined the incidence of males with one or more of these changes which required examination of the individual animal data. This analysis showed that the two animals exhibited a cluster of changes mainly characterized as testicular and epididymal effects (testes: unilateral and bilateral atrophy, unilateral intratubular granuloma/fibrosis, epididymides:

unilateral oligospermia) at 5.8 mg/kg bw/day. Two additional animals showed epididymal inflammation/focal tubular degeneration that were not present in the control animals. No historical control data were available. Overall, five more animals showed adverse histopathological changes in reproductive tissues at 5.8 mg/kg bw/day compared to controls. Four of these animals showed changes in their reproductive systems that were not present in the control animals. F_2 animals were not examined microscopically. Thus, it was concluded that a treatment-related increased incidence and severity of reproductive effects in the F_1 male rats occurred at, and above, 5.8 mg/kg bw/day in two-generation reproduction toxicity study.

Health Canada further re-examined the toxicological significance of these findings within the context of available toxicity data for linuron. The published literature offered numerous non-guideline, modified reproduction/developmental toxicity studies characterizing the toxicity of linuron in utero in rats, further supporting the toxicity to the male reproductive system noted in guideline studies. In addition to many of the effects noted above and following in utero exposure, some adult male rats displayed flattened Sertoli cells and an increased number of Leydig cells (McIntyre et al., 2000). Malformations, namely decreased anogenital distance, increased retention of areola/nipples, and malformed epididymides were common to both pups and adults (McIntyre et al., 2000, 2002a and 2002b; Wolf et al., 1999). Other developmental defects were specific to adults following in utero exposure, such as hypoplastic testes and epididymides, cryptorchid testes, partial to complete agenesis of the epididymides and/or vasa deferentia, hypospadias, and retention of a vaginal pouch (Turner et al., 2003; McIntyre et al., 2000 and 2002b; Wolf et al., 1999). Male rats that were exposed through weaning, young adulthood, and mating, but not in utero, showed delayed preputial separation as well as reduced accessory sex organ weights (Wolf et al., 1999). Non-guideline studies clearly demonstrated that in utero exposure to linuron resulted in developmental toxicity to male reproductive tissues during the period of male sexual differentiation/reproductive system development (late in gestation). Guideline developmental toxicity studies did not cover the period of male reproductive system differentiation/development. Although the two-generation reproduction toxicity study in rats did expose animals in this sensitive developmental period, a microscopic examination of the male pup reproductive tissues was not conducted.

A study not captured in the PRVD2012-02 showed that in utero exposure to linuron on gestation days (GD) 13-18 (5 days) reduced fetal testosterone (T) production at dose levels as low as 12.5 mg/kg bw/day (Wilson et al., 2009). Similarly, another pivotal study (McIntyre et al. 2000) exposed pregnant animals to linuron at dose levels as low as 12.5 mg/kg bw/day. This study showed in utero exposure to linuron during late gestation (GD12 to 21) resulted in increased incidence and severity of pathological findings in testes (seminiferous tubular degeneration, dilation, and interstitial edema) and in the epididymides (ductular hypoplasia and epithelial hyperplasia) starting at the lowest dose tested in adult male rats. The lower dose levels tested in the studies conducted by Wilson et al., (2009) and McIntyre et al., (2000) were in a similar range as the mid and high dose levels employed in the guideline two-generation reproduction toxicity study (published studies: 12.5, 25, 50, and 75 mg/kg bw/day vs. two-generation reproduction study: 0.74, 5.8, and 36 mg/kg bw/day). These published studies conducted by the USEPA Office of Research and Development (ORD) were designed to provide insight into the effects observed in the two-generation reproduction toxicity study. The study by McIntyre et al. (2000) also showed that the linuron-induced changes in the male reproductive system resulted in abnormal/absence of spermatogenesis when the affected animals were assessed during adulthood. A clear NOAEL for these effects was not demonstrated in these studies.

In summary, based on a weight of evidence assessment of the linuron toxicity database including the anti-androgen activity of linuron, the male F_1 histopathological findings at 5.8 mg/kg bw/day observed in the two-generation reproduction toxicity study were considered treatment-related. In addition, given that non-guideline published studies conducted by the USEPA ORD (Wilson et al. 2009, and McIntyre et al. 2000) reported similar effects on the male reproductive system following prenatal exposure to linuron and showed that these effects led to absence/abnormal spermatogenesis in adulthood, the reproduction NOAEL was retained at the low dose level of 0.74 mg/kg bw/day.

3) Re-consideration of the endpoint selected for the short term dermal and inhalation risk assessments

The selection of toxicological studies and points of departure (PODs) for risk assessment are based on relevancy of study duration and route of exposure. However, observations in other toxicological studies may influence this choice, as can availability of studies of the appropriate duration and route.

The available 2-week inhalation and 29-day dermal studies did not assess the identified endpoints of concern, namely, effects in pups following pre-natal and/or post-natal exposure, and thus were not selected for use in the risk assessment. Conversely, the rat reproduction study assessed an endpoint of concern which occurred following short-term exposure of the fetus and pup to linuron. As this study has the lowest NOAEL of potentially relevant studies for short-term exposures, it was selected for occupational short-term dermal and inhalation risk assessment.

In the two-generation reproductive toxicity study, rats exposed to linuron during development and adulthood showed gross and microscopic lesions of the testes, soft and small epididymides, microscopic lesions in the epididymides, and systemic toxicity. These effects did not occur in the parental generation. Treatment during pre-and postnatal development produced these effects, indicating that these effects occur following short term dosing. Developmental effects in the male reproductive system seen in non-guideline studies in the published literature were consistent with those reported in this study. As the effects on male reproductive organs were considered to result from a short-term exposure, they are relevant for short term risk assessment.

1.1.4a Comment – The *Pest Control Products Act* (PCPA) hazard characterization

The submitted comments requested that Health Canada reduce the PCPA factor to 1-fold. With respect to completeness of the database, the commenters contested the requirement of a developmental neurotoxicity study and a rabbit developmental toxicity study to address development in late gestation. With respect to pre- and post-natal toxicity, the commenters indicated that no increased sensitivity of the young or residual uncertainty will remain if there were revisions to the ARfD, as well as to the NOAEL and LOAEL of the reproduction toxicity study, and with further consideration of toxicity data (published and applicant submitted) in the linuron database. To reduce the PCPA factor to 1-fold, the commenters also suggested that Health Canada use the USEPA's rationale (published in 2012) for reducing the FQPA factor to 1-fold for linuron.

1.1.4b Health Canada Response

In light of the comments provided on the Health Canada assessment published in PRVD2012-02, Health Canada has revisited this information, and considered newly obtained information. The following discussion represents the revised Health Canada position regarding the PCPA hazard characterization.

For assessing risks from potential residues in food or from products used in or around homes or schools, the PCPA requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential pre- and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database, many guideline and non-guideline studies were available that have investigated the developmental, reproductive, and hormonal effects of linuron. In addition, new data from the EDSP Tier 1 assays and a non-guideline developmental mechanistic study became available since the publication of PRVD2012-02. Many of the sensitive indicators of toxicity relevant to the mode of action of linuron as an anti-androgen were assessed in published studies (AGD, nipple retention, estrous cyclicity, sexual maturation). These same indicators were not assessed at relevant dose levels in the available two-generation reproduction toxicity studies. A clear NOAEL for these sensitive indicators of toxicity was not established in published studies.

The dosing period in the available rabbit developmental toxicity study, as discussed in PRVD2012-02, did not encompass the period of male reproductive system differentiation and early development. In rats, this sensitive period was covered in the guideline two-generation reproduction toxicity study and by many published non-guideline studies conducted by the USEPA ORD. Therefore, Health Canada has waived the requirement for a rabbit developmental toxicity study encompassing the period of male sexual differentiation and development.

The available toxicology database for linuron did not indicate neurotoxic potential for linuron. Due to the lack of identified neurotoxic potential in the toxicology database and the lack of neurotoxic mode of action, a DNT study is no longer required. The USEPA also waived this data requirement in their 2019 assessment.

With respect to potential pre- and post-natal toxicity, rare malformations were observed in the absence of maternal toxicity in the rabbit developmental toxicity study. They were considered equivocal due to the lack of a clear dose-response. However, the incidence of these findings exceeded the laboratory-specific historical control (HC) data. Standard guidance (Harris and DeSesso (1994) for interpretation of developmental toxicity studies) recommends using laboratory-specific HC data to determine the spontaneous background rate for rare effects. The registrant additionally submitted less relevant HC data extracted from MARTA and Charles River databases. Overall, the level of concern was low for these findings as the revised ARfD (females 13+) and the ADI provided margins of 400-fold and 2000-fold, respectively to the dose level of 5 mg/kg bw/day showing equivocal evidence of rare malformations.

The linuron toxicology database identified serious developmental effects on the male reproductive system. These effects included increased incidence of hypoplastic testes, epididymides and seminiferous tubular degeneration, decreased fetal testosterone, decreased

anogenital distance, increased retention of nipples/areola and abnormal or absence of spermatogenesis – all observed following pre-natal exposure. PRVD2012-02 indicated a concern for evidence of sensitivity in neonates and infants in converting elevated levels of MetHb back to normal Hb. Older children and adults are able to convert MetHb back to normal Hb, using the enzyme MetHb reductase, for example. In infants, however, the enzyme is not fully functional (Muller, 2006; Gregory Cope, 2004). Following consideration of the submitted comments to PRVD2012-02 and as discussed in response to comment 1.1.2, the concern for elevated levels of MetHb was considered low, since developmental effects on the male reproductive system are observed at lower dose levels in a non-guideline developmental toxicity study and, therefore, selection of this study for acute risk assessment for females 13-49 years of age (see section 1.1.5 below) would be protective of any potential MetHb effects during development.

In summary, with regards to the PCPA factor, the toxicity data are considered complete. The changes in the development of the male reproductive system observed in the study by McIntyre et al. (2000), and findings supported by many guideline and non-guideline studies, were considered serious. However, the concern regarding the serious nature of this effect was tempered by the presence of toxicity in adult animals at similar dose levels elsewhere in the database. Therefore, the PCPA factor was reduced to 3-fold when this endpoint was used to establish the point of departure. For all other scenarios, the PCPA factor was reduced to 1-fold.

1.1.5 Revised toxicology reference values for dietary risk assessment

Revised acute reference dose (ARfD)

Females 13-49 years of age:

To estimate acute dietary risk (1 day), a non-guideline 5-day developmental mechanistic study (McIntyre et al. 2000) was selected for risk assessment. A NOAEL was not determined. The LOAEL was 12.5 mg/kg bw/day based on increased incidences of hypoplastic testes and epididymides, and seminiferous tubular degeneration. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The PCPA factor was reduced to 3-fold, based on the rationale provided in the updated PCPA hazard characterization section. To take into account the lack of a NOAEL, an additional 3-fold uncertainty factor (UF_L) was applied resulting in a composite assessment factor (CAF) of 1000. The ARfD is calculated according to the following formula:

$$\textbf{ARfD} = \frac{\textbf{LOAEL}}{\textbf{CAF}} = \frac{\textbf{12.5 mg/kg bw/day}}{\textbf{1000}} = \textbf{0.0125 mg/kg bw of linuron}$$

General population (excluding females 13-49 years of age):

To estimate acute dietary risk (1 day), the acute neurotoxicity study was selected for risk assessment. A NOAEL of 20 mg/kg bw/day was determined. The LOAEL was 100 mg/kg bw/day based on decreased motor activity and increased incidences of functional observational battery (FOB) findings and clinical signs of toxicity. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The PCPA factor was reduced to 1-fold, based on the rationale provided in the updated PCPA hazard characterization section.

Therefore, the composite assessment factor (CAF) is 100. The ARfD is calculated according to the following formula:

$$\textbf{ARfD} = \frac{\textbf{NOAEL}}{\textbf{CAF}} = \frac{\textbf{20 mg/kg bw}}{\textbf{100}} = \textbf{0.2 mg/kg bw of linuron}$$

Revised acceptable daily intake (ADI)

To estimate risk from repeat dietary exposure, a two generation reproduction toxicity study with a NOAEL of 0.74 mg/kg bw/day was selected for risk assessment. Decreased body weight in both generations and increased incidences of slight but numerous effects in the reproductive system of the F_1 male pups were noted starting at 5.8 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. An additional 3-fold uncertainty factor for database deficiencies was applied to account for the lack of information on sperm measurements (motility, count, and morphology) and examination of the onset of puberty in males with repeat-dosing (effects that are expected to be relevant to linuron's hazard characterization). Therefore, the composite assessment factor (CAF) is 300.

The ADI is calculated according to following formula:

$$\textbf{ADI} = \frac{\textbf{NOAEL}}{\textbf{CAF}} = \frac{\textbf{0.74 mg/kg bw/day}}{\textbf{300}} = \textbf{0.0025 mg/kg bw of linuron}$$

This ADI provides a margin of 640 to the dose level of 1.6 mg/kg bw/day showing equivocal evidence of uterine adenocarcinoma in female rats in the 27-month long term toxicity study in rats, and a margin of 2000 to the dose level of 5 mg/kg bw/day showing equivocal evidence of rare malformations in the rabbit developmental toxicity study.

1.1.6 Revised toxicology reference values for occupational risk assessments

For **occupational risk assessments for short- and intermediate term dermal and inhalation routes**, a two generation reproduction toxicity study with a NOAEL of 0.74 mg/kg bw/day was selected. Increased incidences of effects in the reproductive system of the F_1 male pups were noted. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. An additional 3-fold uncertainty factor for database deficiencies was applied to account for the lack of information on sperm measurements (motility, count, and morphology) and examination of the onset of puberty in males with repeat dosing. Therefore, the target **MOE is 300-fold**.

1.2 Comments related to dietary exposure

Comments were received on PRVD2012-02 relating to the residue chemistry database and the dietary exposure and risk assessment; detailed comments were received from the registrant, Tessenderlo Kerley Incorporated (TKI) on all parts of the assessment, while the Canadian Horticulture Council (CHC) and other stakeholders provided comments related to the Canadian use pattern of linuron.

The dietary exposure and risk assessment for linuron were updated in consideration of comments submitted during the consultation period. Additional refinements to the use pattern were considered in order to mitigate dietary risks, while giving priority to the important uses on carrots and potatoes as identified by the registrant and stakeholders. The refined use pattern of reduced rates, limiting application to pre-emergent use only, and the removal of cereal (sweet and field corn, barley, oats, wheat), tree fruits (apple, cherry, peach, pear, plum and prune), soybean, and animal commodities, addressed dietary risks. In addition, the dietary risk assessment was revised to reflect updated dietary endpoints, current dietary intake estimates and revised drinking water estimates.

1.2.1 Canadian Horticulture Council (CHC) comments

The CHC provided Health Canada with percent crop treated (PCT) information and typical rates for linuron on several commodities. This information was gathered from growers across Canada and was considered in the updated food and drinking water exposure and risk assessment. See also Appendix V.

Health Canada response

In consideration of the data provided, PCT estimates were revised for the following crops.

- Asparagus: 95% CT (average PCT in Ontario) was used for the updated chronic dietary assessment. The previous estimate was 7% CT. The typical seasonal rate is lower than carrots and potatoes.

- Carrots: The 100% CT assumed in the PRVD assessment is reflective of the use information provided by the Canadian Horticulture Council (PCT = 100% in Eastern Canada, Quebec, and Ontario and 96% in Manitoba). As such, no change to the PCT for carrots was made for the updated risk assessment. The typical seasonal rates range of 0.15 to 3.24 kg/ha across provinces were considered in the drinking water model estimates.

- Parsnip: 100% CT was assumed in the updated chronic dietary assessments based on available information in Manitoba and British Columbia. The previous estimate was 1% CT. It is noted that the typical seasonal rate for parsnips is lower than for carrots and potatoes.

- Potatoes: 37% CT (lower range of national average PCT) was used for the updated chronic assessment. The typical rates range from 0.96 to 2.16 kg a.i./ha and were considered in drinking water models.

- Tree Fruits: The PCT of 18% (average of Ontario and Quebec PCT) was used for the revised chronic dietary assessment. The previous estimate was 2% CT for all tree fruits except pears, and 17% CT for pears. The seasonal rate is 4.3-8.52 kg a.i./ha.

1.2.2 Registrant comments

Comments were provided by the registrant on technical errors, PCT estimates, and food residue estimates. These are summarized below. Details on the dietary assessment can be found in Appendix V.

General registrant comments

TKI provided comments to correct technical errors as well as recommendations to clarify study conclusions. In addition, the registrant submitted an updated residue analytical method and an independent laboratory validation study for enforcement.

Health Canada response

The evaluation was updated to reflect the corrections and clarifications where they could be substantiated. For example, commodity forms such as popcorn, which has no registered uses, were removed.

Comment: use of PCT to refine residue estimates

The registrant provided PCT estimates for Canada, and recommended that the Canadian and US PCT estimates be updated.

Health Canada Response

Canadian PCT estimates were provided by CHC, as noted in response 1.2.1. above. The PCT information from CHC was used in preference to registrant provided estimates as it was determined to be more reflective of grower use practices in Canada. Information reported in the USEPA Screening level usage analysis published in 2015 was used to update the US PCT estimates.

Comment: Consideration of lowered application rates and processing factors (PF)

The registrant proposed revised application rates and recommended that residue estimates be adjusted to reflect lower rates for several commodities. Comments were also received regarding the use of certain processing factors.

Health Canada response

Residue estimates were adjusted to account for rates where this was supported by data. Similarly, the use processing factors for specific food forms were revised. Refer to Appendix V for details.

Comment: use of updated consumption data and DEEM

The registrant recommended updated consumption data from the US National Health and Nutrition Examination Survey (NHANES) 2003-2008 be used in the dietary exposure assessment.

Health Canada response

The dietary exposure and risk assessment presented in PRVD2012-02 was conducted using DEEM-FCID version 2.03 and the Continuing Survey of Food Intake by Individuals (CSFII) 1994-96/1998 consumption data, which was the most current information at the time. DEEM-FCID 4.02 with NHANES consumption data from 2005-2010 was used to conduct the updated dietary exposure and risk assessments.

Comment: use of the probabilistic method for the acute dietary assessment

The registrant indicated that the probabilistic method and PCT information should be used to refine the acute dietary exposure and risk assessment.

Health Canada response

The use of the probabilistic method and PCT information is not required to further refine the acute dietary assessment.

Comment: residue definition for livestock

The registrant recommended hydroxy-norlinuron be removed from the residue definition

Health Canada response

Health Canada agrees that the risk assessment residue definition for poultry should not include hydroxyl-norlinuron, as the poultry metabolism data available (PMRA# 1304307) did not indicate that hydroxy-norlinuron as a major metabolite (>10% of the total radioactive residue). However, there is insufficient data to conclusively exclude hydroxyl-norlinuron from the residue definition for ruminants.

Comment: livestock dietary burden estimates

The registrant proposed that the livestock dietary burden and residue estimates be revised to reflect modern husbandry practices. The registrant proposes to use different residue estimates for different milk fractions such as fat, non-fat solids, sugar, and water.

Health Canada response

The dietary burden estimates were re-calculated according to the new OECD feed classification system. The use of a single residue concentration estimate for milk inherently corrects the concentrations in the different fractions of milk in DEEM-FCID, since the program partitions dairy consumption (for example drinking a glass of whole milk) into different fractions.

Comment: linuron MRLs

The registrant noted that PRVD2012-02 did not address potential trade irritant issues associated with the cancellation of linuron, which will pose MRL issues and competitive disadvantage for Canadian growers.

Health Canada Response

Specific MRLs for linuron have not been established in Canada. As a result, residues in food are regulated by B.15.002(1) of the Food and Drug Regulations to not exceed 0.1 ppm. Parties interested in requesting commodity specific MRLs for linuron should contact Health Canada to discuss the submission of appropriate information.

1.3 Comments related to occupational exposure

Comment – dermal absorption:

The registrant requested that Health Canada revisit the dermal triple pack study to use the more appropriate dermal penetration value.

Health Canada response

The in vivo/vitro studies originally submitted in the triple pack for linuron did not meet the standards for use in a triple pack approach, since there were considerable limitations in the submitted rat in vivo study. One new study was submitted during the PRVD comment period; however due to the poor quality of the study it was not used. A new rat in vivo dermal absorption study was voluntarily submitted by the registrant to Health Canada in November 2019, after the data submission period had closed. While the study was received too late in the process to be considered quantitatively in this re-evaluation, a preliminary assessment indicated the new study results support the current dermal absorption value. This study when used in conjunction with the other dermal absorption data, may allow some activity specific refinements, but overall the body of evidence supports the continued use of 20% for dermal absorption. The current dermal absorption of 20% is not expected to underestimate exposure and was used in the updated risk assessment.

Comment – mitigation and refinement:

Comments were received from a number of stakeholders voicing concern that Health Canada did not consider all possible mitigation and refinement options. Concerns were also raised regarding the accuracy of the data that was used in occupational risk assessment, as well as the assessed application rates. Several mitigation and refinement options were suggested, however, no data was submitted to support these recommendations.

Health Canada response

Extensive consultation was conducted between Health Canada, the registrant and grower groups relating to application rates and use scenarios. This information was used to refine the risk assessment. All possible options were taken into consideration when revising the risk assessment, including consideration of higher levels of PPE, engineering controls, refined application rates and area treated per day estimates, limits to the amount of active ingredient handled per day, refined transfer coefficients for situations where lower exposure is expected, and chemical-specific DFR data. These refinements have changed the overall risk picture; however, some uses continue to show unacceptable risk. At this time, there are no other refinements available for the occupational risk assessment.

Comment – dislodgeable foliar residues (DFR):

Comments suggested that dislodgeable foliar residues would dissipate and rapid growth of the plant would decrease the contact potential to treated surfaces.

Health Canada response

A chemical-specific DFR study was received by Health Canada to support this information. A chemical-specific peak DFR value of 22% along with a chemical-specific daily dissipation of 16% was used in the updated risk assessment.

Comment – post application Exposure:

Comments were received that suggested there was no need to assess post application activities for various crops (for example, asparagus, carrots, orchards) due to the low frequency of those activities occurring in those crops. Comments were also received that suggested that post application exposure should not have been considered in the risk assessment for linuron since the product is applied pre-emergence or below trees and bushes without treatment of the plant foliage.

Health Canada response

Only activities with the potential for exposure were considered in the post application risk assessment for linuron. For example, activities where crops are at an early growth stage with minimal foliage present were not included. Refined transfer coefficients (TC) for situations where lower exposure is expected were also considered.

Pre-emergent applications have been considered to have negligible exposure in situations where there is a lack of foliage and thus minimal potential for dermal exposure from contact with foliar residues. However, this approach does not consider dermal exposure from other sources, such as soil and potentially dead vegetation. The post application assessment for linuron considered pre-emergent application exposures due to the high toxicity and relatively high application rates for linuron. This scenario was assessed using a TC of 70 cm^2/hr, the lowest available TC for agricultural crops, which was based on a central value from hand weeding in cotton and beans. In scenarios where crops were sprayed both pre-emergent and post-emergent, post-emergent applications were considered separately from pre-emergent applications in the post application assessment, as residues are not expected to accumulate between applications. Refined transfer coefficients for situations where lower exposure is expected were also considered.

Post-emergent applications for linuron are typically applied when the crop is in an early stage of growth where there is minimal foliage (for example, 2 to 4 leaf stage). Only those transfer coefficients that were applicable to low foliage and activities that would occur at this stage (in other words, hand weeding, scouting) were included in the updated risk assessment.

Linuron application to fruit trees is direct application to weeds on the ground (<10 cm high) and there is instruction to avoid contact with the foliage, bark or fruit. As fruit tree TCs are from contact with treated fruit tree foliage, they were not considered to be appropriate for this risk assessment.

Instead, the same TC that was selected for pre-emergent applications of linuron was used, as it was considered to be more representative of scouting activities in this situation. This was also considered to be the case for Saskatoon berries and shelterbelts, as directions are to apply linuron to the soil and under trees, respectively, and to avoid contact with foliage.

Handset irrigation may occur in some crops, but this transfer coefficient was not considered to be appropriate for those crops that are at an early stage of development when linuron is applied, as the level of foliage present would be minimal.

In terms of the occupational exposure assessment, PRVD2012-02 identified chemical specific dislodgeable foliar residue studies as information that could refine the risk assessment. This study was submitted and has been used to refined the post application risk assessment for linuron. Worker biomonitoring data representative of the Canadian use pattern may also be of value. For the orchard uses specifically, post application exposure was assumed to occur from hand weeding activities only, as the potential exposure from overhead branches was considered negligible. Additional use pattern information for the use of linuron in orchard settings may have assisted in more accurate characterization of this exposure. However, this data was not provided by the registrant to refine worker exposure.

Comment – post application cancer risk:

Comments on mitigation options for the cancer risk assessment were received.

Health Canada response

Cancer risk was addressed by a threshold approach in the updated risk assessment.

Comment – restricted-entry intervals:

There were many comments received as to the agronomic feasibility of the proposed restricted-entry intervals (REIs).

Health Canada response

Extensive consultation between Health Canada, the registrant, and growers was conducted. This information was used to refine the risk assessment and determine agronomically feasible REIs.

Comment - aerial application:

There were many comments stating that aerial application is rarely used and should not be included in the risk assessment.

Health Canada response

Aerial application was voluntarily discontinued by the registrant and was not included in the updated risk assessment.

Comment – cereal crops:

Although labelled for use in spring cereals, it was noted that linuron is not applied on any cereal acres in Ontario and was not identified as being used on cereals in the 2008 Ontario Pesticide Use Survey.

Health Canada response

Cereal crop application is assessed separately from other crops and the results of the risk assessment for cereals do not impact the results for other crops for occupational exposure.

2.0 Comments related to the environmental risk assessment

2.1 Comments relating to the environmental fate of linuron

Comment

Two fate studies were submitted by the registrant related the biotransformation of linuron in aerobic soil and in aerobic water/sediment systems.

Health Canada response

The additional studies submitted were reviewed and they were both found to be acceptable.

For the soil biotransformation study (PMRA# 2917856), the extraction method was considered appropriate and the unextracted radioactivity was considered to be bound/unextractable residues.

Health Canada calculated half-lives for each soil. Representative half-lives ranged from 28.5 and 856 days and the corresponding DT_{50} for linuron ranged from 23.6 to 158 days at 20°C (Table 3). During the calculation of aquatic EECs via water modelling the SP (sand) soil half-life was excluded because addition of nutrients to this soil indicated the degradation rate was nutrient-limited. Because more nutrients would be available in a natural environment, it was determined that the half-life from the Sand SP soil should not be considered accurate (PMRA# 2964113, PMRA# 2934717). Linuron would be considered slightly persistent to moderately persistent according to the classification scheme of Goring *et al.* (1975).

Table 3 Representative half-lives, DT_{50} and DT_{90}s for linuron in soils without nutrient amendment

Soil test system	Model	DT_{50} (days)	DT_{90} (days)	$t_{1/2\text{-}rep}$
Sandy loam (DU)	IORE	29.9	300	90.3
Loamy sand (CA)	DFOP	129	614	209
Sandy clay loam (SW)	IORE	23.6	94.6	28.5
Sand (SP)[1]	DFOP	158	1979	856

[1]Half-life from this soil was ultimately excluded because of nutrient limitation (PMRA# 2964113)

For the aerobic water/sediment study (PMRA# 2431768), Health Canada calculated half-lives. In whole systems, the $t_{1/2\text{-}rep}$ was 40.6 and 15.4 days and the DT_{50} was 14 and 11 days in the Taunton and Weweantic systems, respectively (Table 4).

According to the classification scheme of McEwen and Stephenson (1979), linuron is considered to be non-persistent in whole systems (DT_{50} = 11-14 d) under aerobic aquatic conditions. The results from both studies were considered in the revised environmental risk assessment.

Table 4 Representative half-lives and DT_{50} for linuron in aerobic soil/water whole systems

Soil type	Best fit model	$t_{1/2\text{-}rep}$	DT_{50} (days)
Linuron Only			
Taunton Total System	IORE	40.6	14.1
Weweantic Total System	IORE	15.4	11.0

Comment

Several comments were received from the registrant questioning the accuracy of environmental fate properties reported for linuron as well as the acceptability of the studies from which the data was extracted. A study submitted by the registrant (AMR 1348-88; PMRA# 1685617) reports the aerobic soil half-life as 48.9 days, where as Health Canada had used 161 days in the risk assessment reported in PRVD2012-02.

Health Canada response

Health Canada typically compiles a range of values for the various chemical properties of a pesticide. Variation in results is expected because the studies are conducted on different soils or under different experimental conditions. A range of results allows Health Canada to consider how the fate of the pesticide will differ among the various environmental conditions experienced throughout Canada.

Health Canada evaluates the acceptability of each study and recalculates endpoints. As a result, in some cases, the endpoints reported by the study authors are different from those recalculated by Health Canada.

In PMRA# 1685617, the study authors reported a half-life of 48.9 days. However, for the purposes of the RVD, Health Canada recalculated the dissipation rate for this study using current standard fate tools and found the DT_{50} to be 50 days at 25°C and 71 days when adjusted to 20°C.

The DT_{50} value of 161 days was from another submitted study (AMR-19-80; PMRA# 1685590) and at the time of the PRVD2012-02 was considered valid. Further consideration found recoveries were low and as a result the study in now found to be not acceptable and it was not considered in the current revised risk assessment.

Comment

The registrant commented that the highest peak transformation rate to 3,4-DCA was ~2% AR, not 11.8% AR as reported in the registrant submitted study HLO 515-91 (PMRA# 1304360) that was reported in PRVD2012-02.

Health Canada response

The registrant submitted study HLO 515-91 (PMRA# 1304360) is an acute toxicity study on mysids and no transformation products were determined in the study. The value reported as 11.8% is from an aerobic aquatic biotransformation study (PMRA# 1695376) that was reported in PRVD2012-02.

Comment

The registrant suggested that the photodegredation half-life of linuron in water was 49 days, not 54 days (AMR 616-86; PMRA# 1685610) as reported in PRVD2012-02.

Health Canada response

Although the registrant submitted study AMR 616-86 (PMRA# 1685610) does report a half-life of 49 days for linuron in water, the Health Canada found that there was significant biotransformation in the dark control. As a result, the half-life value in the light-treated water was corrected for the loss in the dark control, resulting in a DT_{50} of 54 days.

Comment

The registrant indicated that the half-life of linuron in anaerobic aquatic systems was 7-22 days, not 15.8 days (PMRA# 1685611).

Health Canada response

The study authors reported half-lives of 7.4 – 22 days in PMRA# 1685611. Health Canada recalculated the DT_{50} values using the raw data to determine a range of 7.4 to 15.8 days.

Comment

The conclusion that linuron has the potential to leach was questioned by the registrant. The registrant had concerns that some field studies used exaggerated application rates, there was cross-contamination during sampling, and some studies were considered obsolete, deficient or were conducted outside of Canadian-equivalent ecozones.

Health Canada response

Based on the comments received, Health Canada reconsidered the leaching potential of linuron.

Considering the weight of evidence, it is the opinion of Health Canada that the residues observed in the 30-90 cm layer of the one soil dissipation study (PMRA# 1685614) was a result of sample contamination from upper layers and should not be used to conclude linuron has the potential to leach.

K_{oc} values range from 166-2600, classifying linuron as being slightly to moderately mobile according to McCall et al. (1981). The USEPA also indicates that linuron is slightly to moderately mobile.

Considering maximum application rates are being reduced as a result of the re-evaluation and the lack of leaching observed in terrestrial field dissipation studies, Health Canada agrees with the registrant that linuron is unlikely to leach in appreciable amounts.

Comment

The use of terrestrial field dissipation (TFD) studies from ecozones in California that do not extend into Canada and do not represent the registered uses of linuron in Canada, is not acceptable according to the registrant.

Health Canada response

Although field dissipation studies from California were reported in PRVD2012-02 to describe field persistence, the data from California (DT_{50} values of 92 and 100 days, in other words, moderately persistent) were not used in the Canadian risk assessment. It should be noted that in their recent re-registration review of linuron, EFSA (PMRA# 3038895) included TFD studies from Canadian-equivalent ecozones and the results from these studies have been incorporated into the final re-evaluation decision and risk assessment where applicable. These studies reported DT_{50} values of 10.1-168.4 days, corroborating very well with the DT_{50} values observed in aerobic soil laboratory studies (DT_{50}: 24-129 days) and also with the values from studies previously reported in PRVD2012-02 from California.

Comment

A comment was received from the registrant that the following statement is inaccurate: “As for the climate, if temperatures are cooler, residues may break down more slowly.” The registrant indicated that “above freezing, the rate of metabolism depends on temperature within an ecosystem. Only cold temperature microorganisms are active up to approximately 5°C. Above this temperature, metabolism increases by a factor Q10 for every ten degrees. Above 35°C warm-adapted organisms are more active, but metabolism may slow down.”

When comparing between ecosystems in warmer and colder climates, it is necessary to consider that cold-adapted micro-organism may be able to carry on metabolism faster at low temperatures.

Health Canada response

There was no data provided to substantiate the claims. As additional TFD studies conducted in Canadian-equivalent ecozones were available from the recent EFSA review (PMRA# 3038895), sufficient information was available to determine the fate of linuron under typical Canadian conditions.

2.2 Comments relating to water modelling

Degradation rates in soil and water were revisited for water modelling. Revisions to the soil degradation rates were necessary because a new aerobic soil biotransformation study was submitted. A detailed description of the revisions to the water modelling are presented in Appendix VIII.

Comment

The registrant questioned the half-lives used in drinking water modelling (aerobic soil, aerobic aquatic and anaerobic aquatic) because they were based on combined residues of linuron and three transformation products of human health concern. They stated that this is a very conservative assumption because it assumes that all peak EECs will occur at the same time. Some of these compounds are not major transformation products in soil and water, therefore, they should not be lumped together for water modelling purposes and only the half-life for the parent compound (linuron) should be used for the calculation of drinking water EECs.

Health Canada response

Combining linuron and the transformation products of human health concern has the effect of slowing the overall disappearance, but this does not mean that all peak EECs occur at the same time. For pesticides modelled this way, the EEC would consist mostly of the parent compound shortly after application and slowly shift to the daughter compound(s) over the course of the model run. This is the same as what would occur if the two compounds were modelled separately, except that only the sum of their concentrations is determined.

The residue definition for the drinking water assessment includes linuron transformation products that were found at more than 10% of the applied in environmental fate studies and are known to be or were assumed to be toxic to humans.

Comment

The registrant suggested corrections to water modelling: 1) The use of aerobic soil half-life for parent linuron alone for calculation of the drinking water EEC, 2) Revise the K_d value used, 3) Eliminate aerial applications, 4) Change the soil dissipation half-life and reduce drift from ground boom applications to 1.3%.

Health Canada response

1) Although some of the residues are not major transformation products, they share a common moiety that is a concern for human health. Therefore, Health Canada is compelled to include these transformation products in the water modelling exercise. Modelling EEC values for drinking water have been revised taking into consideration lower proposed application rates, reduced use-pattern and results from new fate studies that resulted in faster dissipation half-lives. This has resulted in lower modelled drinking water EEC values, with a maximum of 74 and 13 µg a.i./L for acute and chronic exposures, respectively

2) The K_d used for modelling was 5.8 indicating low mobility. The USEPA (PMRA# 3038898) also reports that linuron has low mobility and uses a K_{oc} of 833. There are differences between how the EPA and Health Canada select K_{oc} values for modelling. Health Canada is confident in the calculation and selection of the 20th percentile value of K_d (5.8). This follows standard Health Canada procedures for the use of the K_d in water modelling. Modelling of linuron reported in the final re-evaluation decision used a K_d rather than a K_{oc}. Only one soil in the two studies (Sassafras) had less than 1% organic matter, and it had a relatively high K_d. Removing that soil from the calculations

would slightly lower the 20th percentile K_d value from 5.8 to 5.5, but this slight reduction would not make a noticeable difference in the calculations of the EEC values.

3) As suggested by the registrant, aerial applications were not considered in the updated modelling.

4) There was no information provided by the registrant on the rationale for reducing drift to 1.3% for ground boom applications. Current Health Canada data show that drift 1 m away from the ground boom application equipment is 3, 6 and 11% for coarse, medium and fine sprays, respectively (according to Wolf and Caldwell 2001). Without data to substantiate the reduction to 1.3%, validation of this refinement is not possible.

Comment

The registrant commented that the drinking water scenarios are very conservative in that it is assumed that the watershed is 100% cropped and the percent treated is 100%.

Health Canada response

Health Canada did not consider the percent crop treated in estimating environmental concentrations of pesticides because doing so would require field or small catchment-scale percent crop treated data, which is unavailable. Percent cropped area has been considered by Health Canada in the past for certain chemicals, but in the case of linuron, which is registered for use on several major crops, it is not expected to have a significant impact on EEC values. The percent crop treated varies from season to season and reliable information that would allow refinement is not available.

Comment

The Conseil québécois de l'horticulture (CQH) commented that the choice of crops by area of production used by Health Canada for water modelling does not reflect reality. For example, they stated that according to the modelling done by Health Canada, it appears carrots are mostly grown in the Prairies; however, carrots are grown mainly in Quebec and Ontario. The Canadian Horticultural Council also commented that accurate use-pattern information is required.

Health Canada response

PRVD2012-02 did not intend to suggest Canadian carrots are mostly grown on the prairies. Health Canada recognizes that the majority of carrot production is in Ontario and Quebec. Water modelling was conducted for carrots in the prairies because more carrots are grown there than apples, and this was chosen to represent a crop receiving the highest labeled application rate in the Prairies.

Water modeling EEC values were determined for a number of different scenarios and crops for each region of Canada. The carrot scenario was just one of the crop scenarios modeled. The use on potatoes, at a rate of 1.78 kg a.i./ha and the use on carrots (1 × 1.08 kg a.i./ha) were selected for drinking water modelling.

Ecological EEC values were determined using 1 × 0.72 kg a.i./ha (as used on corn), 1 × 0.6 kg a.i./ha followed by 1 × 1.08 kg a.i./ha after 14 days (as used on carrots), and 2.16 kg a.i./ha (as used on shelterbelts). The revised modelling also takes into account reduced application rates.

2.3 Comments relating to water monitoring

Comment

A study on the presence of linuron in surface water in PEI was submitted by the registrant during the PRVD comment period.

Health Canada response

Health Canada reviewed this study and found that it had a number of deficiencies that limit the usefulness of the data.

In PEI, linuron is used as a pre-emergent herbicide on soybean, potato, carrots, sweet corn and sweet white lupins and as a post-emergent herbicide on carrots (2+ leaf stage). The study analyzed twelve water samples from PEI for the presence of linuron and the transformation products, with samples collected on 22 July, 8 August, 3 September and 18 September, 2013. Given the application timing for linuron in PEI and the timing of the water sampling, the first samples would have been taken 2 months after linuron had been applied. As a result, peak concentrations would likely have been missed. The study does not provide details on sampling locations, does not provide evidence that linuron was used in the vicinity of the sampling site and does not provide details on sampling methodology.

Despite the limitations described above, the results of this study were added to the available water monitoring database for linuron.

Comment

A groundwater monitoring study was submitted by the registrant. Purdy, J. Linuron: Well Water Monitoring, Canada 2017. FINAL REPORT TKI PROJECT NUMBER: TKI-CR-LIN-10. 217 pp. (PMRA# 2849050).

Health Canada response

This study collected water samples in the summer of 2017 from four wells (2 in PEI and 2 in Ontario) and analyzed the samples for linuron and transformation products. Wells were selected to represent worst-case groundwater exposure from agricultural fields.

The two fields in PEI had a recent history of linuron use, with one field having had linuron applied in 2016 and the other having had linuron applied in the season the samples were taken (2017). The authors assumed these fields had a history of linuron use based on crop rotation records; however, at one Ontario site, linuron was applied seven times between 1998 and 2009. but the site was subsequently converted into an orchard in 2012. The second Ontario site was planted with potato and linuron had been applied in 2017.

At the Ontario sites, linuron was not detected, however desmethyl linuron was detected in one sample. Linuron was detected at both sites in PEI (peak concentrations of linuron of 0.108 and 0.075 µg a.i./L). Linuron transformation products were also detected, with the peak concentration of linuron + transformation products detected at 0.112 µg/L.

The study was reviewed and found to be acceptable with limitations. Sampling was limited to four sites (which is too few to draw broad conclusions), with linuron use being difficult to characterize at the sites and one site having gone a decade without any linuron being applied. For the study to provide definitive information for a risk assessment, additional work would be needed to demonstrate water from the field would flow towards the well and information on transit time from field to groundwater at each location would be needed. This study does indicate that linuron and at least one transformation product can be found in groundwater. The data from this study has been added to the database of water monitoring information that Health Canada collects; however, based on the above limitations, the results of the study alone cannot be used to establish the appropriate drinking water EEC values.

Comment

The Conseil québécois de l'horticulture commented that the statistical data of the water samples that Health Canada used for the re-evaluation of linuron came from various sources. In addition, no information was provided on the sampling parameters, choice of sites, history of the discharges and/or the data concerning use of linuron in drainage basins. Other comments on the statistical analysis of the water monitoring data were received from the registrant.

Health Canada Response

Water monitoring data from various sources is analyzed and used by Health Canada in risk assessments. The available data can have many limitations, including lack of information on linuron use in the vicinity of the sampling site, peak values may be missed and limits of detection may be too high to identify concentrations that would pose a risk of concern. New data that has become available since the publication of PRVD2012-02 has been included in an update to the monitoring analysis. In addition, Health Canada has revised their statistical methodology for analyzing water monitoring data, and no longer calculates 90^{th} or 95^{th} percentiles of concentrations. The current methodology employs peak concentrations from the available dataset and when datasets are rich enough, average concentrations over time may be calculated. The risks associated with the use of linuron were determined using EEC values generated through water modelling. Water monitoring data was used to confirm concentrations predicted by modelling are not exceeded when used under real-world conditions.

Comment

The registrant commented that Health Canada did not make use of water monitoring data for estimating drinking water concentrations and did not follow previous precedents where even limited water monitoring information was included for other actives.

Health Canada response

As is standard practice for re-evaluations, Health Canada considered available water monitoring data in the assessment of linuron. This included analysis of data collected in Canada and the United States.

As the drinking water residue definition included the parent linuron and a number of transformation products, water monitoring data for the transformation products is also required. Unfortunately, the availability of water monitoring data on transformation products was very limited. Water monitoring data was discussed in PRVD2012-02, but the proposed regulatory decision relied on EEC values derived from water modelling. Some additional water monitoring data generated since PRVD2012-02 provided information on transformation products, but this data was limited and not considered to be robust. The final regulatory decision uses EEC values generated from water modelling in the risk assessment and provides an update on available water monitoring information.

2.4 Comments relating to ecotoxicology

Comment

A dietary acute toxicity study conducted on canaries was submitted by the registrant (PMRA# 2431769).

Health Canada response

The submitted study was reviewed by Health Canada and found to be acceptable. The results (LC_{50} was 1386 mg a.i./kg diet (92.6 mg a.i./kg bw/d)) were considered in the updated avian dietary risk assessment.

Comment

The registrant requested that the avian, mammalian and terrestrial plant risk assessments be redone considering lower proposed application rates and mitigation measures.

Health Canada response

In addition to considering new study data, the terrestrial environmental risk assessment was revised to take into consideration new application rates (Appendix IX) and limiting applications to ground boom only.

Comment

A new study (PMRA# 2185692) on the effects of linuron to fathead minnow during a short-term reproductive assay was submitted by the registrant.

Health Canada response

The submitted study was reviewed and found to be acceptable. The NOEL and LOEL from this study were determined to be 0.099 mg a.i./L and 0.92 mg a.i./L, respectively for significant effects on fathead minnow fecundity, fertility success and male body weight. The study shows potential effects in fish due to interactions with the endocrine system.

Comment

The registrant reported that toxicity endpoints for linuron to some aquatic species were inaccurate or that Health Canada used toxicity endpoints from "outdated" studies (for example, EC_{50} of 1.9 mg a.i./L in *Daphnia* or the acute toxicity in rainbow trout is 3.3 mg/L).

Health Canada response

A study on toxicity to *Daphnia* (PMRA# 1304356, EC_{50} = 1.9 mg a.i./L) described by the registrant was reviewed for the re-evaluation but was not used in the risk assessment because a more sensitive endpoint for aquatic invertebrates (0.12 mg a.i./L) was available. The more sensitive endpoint (0.12 mg a.i./L) was also used by the USEPA in the risk assessment for the California red-legged frog (EPA 2008).

Health Canada did not have access to the toxicity study on rainbow trout with a LC_{50} of 3.3 mg/L, therefore, this value was not used in the risk assessment. The risk assessment used a similar endpoint (3.15 mg a.i./L) from a study with rainbow trout (PMRA# 3038896).

3.0 Comments related to the value assessment

3.1 Comment: linuron is an essential and critical herbicide for certain crops in Canada. It has a unique fit in many crops due to its efficacy, weed spectrum, crop safety, crop rotation characteristics, and use as an herbicide resistance management tool.

Many comments received expressed the important contribution of linuron to the production of each of the labelled crops. Justification for the importance of linuron in the production of all labelled crops includes:

- primary herbicide for weed management, especially for minor specialty crops;
- high level of efficacy (that is, weed control spectrum and duration of control);
- limitation of alternative herbicides (application method, application timing, variety sensitivity, regional use restrictions, soil texture variations, etc.);
- lack of suitable alternatives;
- tool for weed resistance management;
- cost effectiveness; and
- improved crop quality and yield.

Health Canada response

As stated in the PRVD2012-02 *Linuron*, Health Canada acknowledges the importance of linuron for weed management in many important Canadian agricultural corps. As a result of additional information received from stakeholders during the consultation period, Health Canada refined the risk assessments of linuron, and risks were shown to be acceptable for certain uses. Therefore, some of the registered crops will be maintained on product labels by amending the use pattern. Risk mitigation measures are presented in Appendix X. Appendix IX, Table 1: Comparison of the Supported Use Pattern versus the Labelled Use Pattern shows currently registered use patterns compared to the revised use patterns for the crops to be maintained on the linuron product labels. Growers will have the option of using linuron in rotation with other currently registered alternative herbicides for weed control and resistance management.

3.2 Comment: Linuron is important for resistance management. The proposed restriction on the use of linuron put Canadian growers at a competitive disadvantage.

With the exception of asparagus, linuron is the only Group 7 herbicide registered for use on all the listed crops. In addition to being an important tool for managing herbicide resistant weeds, thereby prolonging the efficacy of other herbicides, linuron provides broad spectrum weed control in key crops in Canada.

Most registered uses of linuron were eligible for reregistration in the European Union (EU) and the United States; there are, thus, potential trade irritant issues associated with the cancellation of linuron, which will pose competitive disadvantage for Canadian growers.

Health Canada response

Health Canada acknowledges the importance of linuron to agriculture for weed control, resistance management for higher quality and yield. During consultation with stakeholders, Health Canada received additional information, including those related to crop production practices and the use of linuron. This additional information was used to refine the assessment of linuron and risks were shown to be acceptable for certain uses. As a result, Health Canada will retain some of the uses for linuron, but with a lower rate of application and reduced number of applications to mitigate risk concerns. Growers will still have the option for weed control and resistance management.

Note that the European Union (EU) published a 2017 decision for non-renewal of linuron thus prohibiting all uses of linuron for health and environmental reasons. Health Canada is currently conducting a special review of linuron initiated under subsection 17(2) of the *Pest Control Products Act*. The aspects of concern identified in the EU decision will be considered in this special review.

Appendix IV Revised toxicology reference values for linuron

Table 1 Toxicology reference values for use in health risk assessment for linuron

Exposure scenario	Study	Point of departure and endpoint	CAF or target MOE
ARfD (population subgroups other than females 13-49 years of age)	Acute neurotoxicity study in rats	NOAEL = 20 mg/kg bw/day Decreased motor activity and increased incidences of FOB findings and clinical signs of toxicity	CAF =100 PCPA factor = 1-fold
	ARfD = 0.2 mg/kg bw		
ARfD (females of 13-49 years of age)	Non-guideline developmental mechanistic study (McIntyre et al., 2000)	NOAEL = Not determined LOAEL = 12.5 mg/kg bw/day Increased incidence of hypoplastic testes and epididymides, and seminiferous tubular degeneration	CAF = 1000 PCPA factor = 3-fold UF_L= 3-fold
	ARfD = 0.0125 mg/kg bw		
Repeated Dietary (all populations)	Two-generation reproductive toxicity study in rats	NOAEL = 0.74 mg/kg bw/day Decreased body weight in P and F_1 rats, and slight, but numerous, effects on the F_1 male reproductive syste	CAF = 300 PCPA factor = 1-fold UF_{DB}= 3-fold
	ADI = 0.0025 mg/kg bw/day		
Short-, intermediate-, and long-term dermal and inhalation	Two-generation reproductive toxicity study in rats	NOAEL = 0.74 mg/kg bw/day Decreased body weight in P and F_1 rats, and slight, but numerous, effects on the F_1 male reproductive system	MOE = 300 UF_{DB}= 3-fold
Cancer	The threshold approach is considered appropriate for assessing uterine adenocarcinomas and ovarian tumours. The ADI provides a margin of 640-fold to the low dose level showing equivocal evidence of uterine adenocarcinomas and ovarian tumours in female rats in 27 month combined chronic and carcinogenicity study in Wistar rats (PMRA# 1074302, 1074320, and 1074321)		

[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 assessments; UF_{DB} refers to database uncertainty factor; UF_L refers to LOAEL to NOAEL extrapolation factor

Appendix V Dietary exposure and risk estimates for linuron

1.0 Introduction

The updated dietary risk assessment incorporated comments from the technical registrant and the Canadian Horticulture Council (CHC). The updates include the use of PCT information provided by CHC, the use of the updated DEEM-FCID version 4.02, and changes to several food residue estimates and processing factors, as well as the updated drinking water EECs. Registrant-proposed lower use rates were also considered by Health Canada.

2.0 Toxicology

The toxicology reference values related to the dietary exposure and risk assessments have been updated since PRVD2012-02. These new reference values were incorporated into the updated dietary exposure and risk assessments. Refer to Appendix IV for details.

3.0 Processing factors

The processing factors used in the updated dietary exposure and risk assessment are indicated in Table 1. Revisions from the original assessment (PRVD2012-02) are in bold. This includes the application of revised boiling and washing factors for asparagus, washing and peeling factor for carrots, and a processing factor for cottonseed oil.

Table 1 Processing factors used in the updated linuron risk assessment

Commodity	Food form	Processing factor	Comment
Apples	Dried	8	DEEM default factor
	Juice	1.3	DEEM default factor
Asparagus	**Boiled**	**0.35**	**Boiling factor**
	All other forms	**0.61**	**Washing factor**
Beef	Dried	1.92	DEEM default factor
Carrots	Boiled	0.25	Boiling, washing, peeling factor
	Uncooked Fresh	0.88	Washing factor
	All other forms	**0.41**	**Washing and peeling factor**
Cherry	Juice	1.5	DEEM Default Factor
Corn (field)	Starch	0.75	Starch factor
	Flour	0.75	Flour factor
	Oil	1.25	Oil factor
	Syrup	1.5	DEEM default factor
Cotton	**Oil**	**0.14**	**Oil Factor**
Peach	Dried	7	DEEM default factor
Pear	Dried	6.25	DEEM default factor

Commodity	Food form	Processing factor	Comment
Plum, Prune	Dried	5	DEEM default factor
	Juice	1.4	DEEM default factor
Potato	Chips	2.05	Chip factor
	Dry granules	3.42	Dry Granule factor
	Without Peel	0.81	Peeling factor
	Baked	1.25	Baking factor
	Boiled	0.59	Boing factor
	Baked/boiled[1]	0.74	Baking × boiling factor (No longer used)
Soybean	Soy milk	0.15	Soy milk factor
	Oil	0.19	Oil factor

[1] The baked/boiled factor for potatoes is no longer used as there are no baked/boiled forms in DEEM-FCID version 4.02.

4.0 Percent crop treated

The Canadian PCT estimates have been updated using PCT information provided by the CHC for asparagus, tree fruits (apple, peach, cherry, and plum/prune), potatoes, and parsnip. PCT for carrots were also provided and were consistent with the previous assumptions made by Health Canada at 100%. PCT for Canadian registered crops, other than those crops with CHC information, were based on Health Canada use analysis information. When PCT data or food supply information were not available, 100% CT was assumed. PCT estimates were applied to the revised chronic assessment but not the deterministic acute assessment.

The US PCT information has been revised and now incorporates the more recent data from the USEPA Screening Level Usage Analysis (2015). The PCT estimates used are indicated in Table 2. Domestic and imported food supply information was also updated based on Statistics Canada data (2009-2013).

PCT is applied to residue data by assuming a percentage of the samples are not treated. A true zero value is assigned to this portion of “untreated” samples. For the remaining portion of the samples considered “treated”, a residue value is assigned based on the residues found in field trial data. PCT data is typically not applied for blended food forms because treated and untreated samples may be mixed together and there is a reasonable expectation of residues present in all blended commodities. An exception from this standard was made for the linuron assessment to reduce the impact of exposure from imports in the dietary assessment. For example, linuron is registered for use on lentils and dry peas in the US but not in Canada, and the commodities were included in the dietary assessment in consideration of potential exposure from imports. The use of PCT and food supply information for these blended commodities significantly reduced the chronic residue estimates as more than 95% of lentils and dry peas are produced domestically.

When available, PCT was applied not only to non-blended or partially blended commodities as per standard practice, but also to blended **commodities** to refine the residue estimates. However, this also increased the level of uncertainty in the overall assessment.

Table 2 Percent crop treated estimates for the updated linuron risk assessment

Commodity	Form	Weighted chronic PCT[1]
Apple	Forms except dried, juice, and sauce	20%
	Dried	21%
	Juice	69%
	Sauce	84%
Asparagus	All forms	91%
Barley	Pearled barley	1%
	Bran2	100%
	Flour2	100%
Caraway	All forms2	100%
Carrot	Forms except juice	97%
	Juice2	100%
Celeriac	All forms2	100%
Celery	Forms except juice	25%
	Juice2	100%
Cherry	Forms except juice	14%
	Juice2	100%
Choke Cherries	All forms2	100%
Coriander	All forms2	100%
Corn Field	Bran	1%
	Flour	1%
	Meal2	100%
	Starch2	100%
	Syrup2	100%
	Oil	1%
Corn Sweet	All forms	81%
Cotton	All forms	3%
Dill/Dillweed	All forms2	100%
Oats	Groats or rolled oats	3%
	Bran2	100%
	Flour2	100%
Parsley	Forms except dried	80%
	Dried2	100%
Parsnip	All forms2	100%
Pear	Forms except dried and juice	43%
	Dried2	100%
	Juice2	100%
Peach	Forms except dried and juice	26%
	Dried2	100%
	Juice2	100%
Plume/Prune	All Forms	32%
	Dried2	100%
	Juice2	100%

Commodity	Form	Weighted chronic PCT[1]
Potato	Forms except chips, dry granule, flour	35%
	Chips	45%
	Dry granules2	100%
	Flour	24%
Rhubarb	All forms2	100%
Saskatoon berry	All forms3	100%
Sorghum	All forms2	100%
Soybean	Oil	2%
	Seed	5%
	Vegetable	5%
	Flour2	100%
	Milk2	100%
Wheat	Grain	1%
	Flour	1%
	Germ2	100%
	Bran	1%
Lupin	All forms3	100%
Cilantro	All forms2	100%
Horseradish	All forms2	100%
Lentils	All forms	1%
Chickpea	Forms except flour	4%
	Flour2	100%
Guar	All forms2	100%
Dry Pea	All forms	1%

PCT = percent crop treated

[1] Weight PCT = (% Domestic Supply × Canadian PCT) + (% US Supply × US PCT) + (Others Supply × 100% CT)

[2] 100% CT was assumed as Food Supply and/or PCT information was not available for the commodity form

[3] Choke cherries, sweet white lupin, and Saskatoon berries were not included in the dietary assessment as these commodities are not in DEEM-FCID.

5.0 Crop residue estimates

Asparagus

Residues estimates were based on four field trials conducted in California. Only the data from the samples treated at the lowest field trial rate were taken as it was more reflective of the proposed use rate provided during the comment period (PRVD2012-02). A washing factor (0.61) was applied to all forms of asparagus except boiled forms, where a boiling/washing factor (0.35) was applied (PMRA# 1404346). The processing factor was incorporated under adjustment factor 1 in DEEM-FCID. 91% CT was used for the chronic assessment.

The highest average field trial residue at 4.2 ppm (HAFT) was used for the acute assessment and the median at 4.05 ppm was used for the chronic assessment. The PCT information was incorporated under adjustment factor 2 in DEEM-FCID for the chronic assessment.

Tree fruits (apple, cherry, peach, pear, and plum/prune)

Residue estimates for tree fruits were based on the general MRL at 0.1 ppm as there are no residue data and MRL/Tolerances to support linuron use on tree fruits. PCT information was determined for the different fruits and fruit forms based on PCT information from CHC and food supply information from Stats Canada. DEEM default processing factors were applied to dried forms of apples (8), pears (6.25), and plums (5). In addition, a DEEM default processing factor was applied to apple juice (1.3), cherry juice (1.5) and plum juice (1.4). The processing factors were applied under adjustment factor 1 in DEEM-FCID.

The general MRL of 0.1 ppm was used for the acute and chronic assessment. The PCT information was incorporated under adjustment factor 2 in DEEM-FCID for the chronic assessment. There is a high level of uncertainty in this estimate due to a lack of data.

Barley, oats, wheat

Residues estimates for barley, oats, and wheat were based on two field trials conducted for wheat in Oregon (PMRA# 1404336). Residues could not be detected in any wheat samples treated at 2.8 and 5.6 kg a.i./ha. The residue estimate for wheat, barley, and oats is set at the LOD (0.03 ppm). The PCT information was determined for each individual crop based on PCT information and food supply information.

The estimate of 0.03 ppm was used for the acute and chronic assessment. The PCT information was incorporated under adjustment factor 2 in DEEM-FCID for the chronic assessment.

Carrot

Residues estimates were based on five field trials conducted in the Florida, New Jersey, Wisconsin, and California (2 trials) (PMRA# 1404326). A washing factor was applied to uncooked fresh carrot forms (0.88), a boiling factor was applied to boiled forms (0.25), and a washing and peeling factor (0.41) was applied to all other forms (PMRA# 1404347). The processing factors were incorporated under adjustment factor 1 in DEEM-FCID. 97% PCT was assumed for most forms except juice the chronic assessment. 100% CT was used for juice as there were no food supply information for juice.

The HAFT (0.5 ppm) was used for the acute assessment and the median (0.38 ppm) was used for the chronic assessment. The PCT information was incorporated under adjustment factor 2 in DEEM-FCID for the chronic assessment.

Celeriac

Celeriac is not a registered use in Canada but is registered in the US and may potentially be imported to Canada. The residue estimate for celeriac is based on the US tolerance at 1 ppm. 100% CT was assumed are there were no PCT or food supply data available.

Celery

Residue estimates were based on one field trial conducted in Ontario (PMRA# 1147021). 25% CT was used for most forms except juice for the chronic assessment. 100% CT was used for juice as there were no food supply information for juice.

The HAFT (0.11175 ppm) was used for the acute assessment and the median estimate (0.072 ppm) was used for the chronic assessment. The PCT information was incorporated under adjustment factor 2 in DEEM-FCID for the chronic assessment

Herbs and spices

Caraway

Residue estimates for caraway were based on the general MRL at 0.1 ppm as there are no residue data and MRLs/Tolerances available. 100% CT was assumed as there were no PCT or food supply data available. The “herbs, other” commodity in DEEM-FCID was as used as a surrogate commodity for caraway, as this commodity is not included in DEEM-FCID.

Cilantro

Cilantro is not a registered use in Canada but is registered in the US and may potentially be imported to Canada. Residues estimates for cilantro were based on the US tolerance for cilantro, dried leaves (10 ppm) and cilantro, fresh leaves (3 ppm). The tolerance for dried leaves was applied to dried forms while the tolerance for fresh leaves was applied to other forms. 100% CT was assumed as there were not PCT or food supply data available. This commodity was included in the updated assessment as new US tolerances were identified.

Coriander

The residue estimates for coriander were based on the US tolerance for coriander seed at 0.01 ppm. 100% CT was assumed as there were no PCT or food supply data available. The residue estimate for coriander has been updated from the general MRL used in the previous assessment to the US tolerance, as new Tolerances were identified for the commodity.

Dill/dill weed

Residues estimates for dill were based on the US tolerance for dill, seed (0.5 ppm) and dillweed fresh leaves (1.5 ppm). The tolerance for dillweed dried leaves and dill oil were not used as there were no dried forms in DEEM. 100% CT was assumed as there were no PCT or food supply data available. The residue estimate for dill has been updated from the general MRL used in the previous assessment to the US tolerance, as new Tolerances were identified for the commodity.

Horse radish

Horse Radish is not a registered use in Canada but is registered in the US and may potentially be imported to Canada. The residues estimate for horseradish was based on the US tolerance at 0.05 ppm. 100% CT was assumed as there were no PCT or food supply data available. The PCT information was incorporated under adjustment factor 2 in DEEM-FCID for the chronic assessment. This commodity was added in the updated assessment, as new US tolerances were identified.

Parsley (leaves)

Parsley is not a registered use in Canada but is registered in the US and may potentially be imported to Canada. The residue estimate for parsley is based on the US tolerance at 0.25 ppm. 80% CT was used for the chronic assessment for fresh parsley. 100% CT was used for dried parsley as there are no food supply data available for the form. The PCT information was incorporated under adjustment factor 2 in DEEM-FCID for the chronic assessment.

Corn (field)

Residue estimates for field corn were based on one field trial conducted in California (PMRA# 1404335). Only the sample treated at the lowest field trial rate (1.68 kg a.i./ha) was included, as it was more reflective of the proposed use pattern. In the trial, the treated samples had residue levels below the limit of quantitation. Thus, the residue estimate was set at the limit of quantitation (LOQ) at 0.01 ppm. Chemical specific processing factors were used for corn starch (0.75), flour (0.75), and oil (1.25) (PMRA# 1404349). The DEEM default value was used for syrup (1.5). 1% CT was used for field corn bran, flour, and oil. 100% CT was used for meal, starch, and syrup as food supply data was not available for these forms.

The processing factors are incorporated under adjustment factor 1 in DEEM-FCID. The PCT information was incorporated under adjustment factor 2 in DEEM-FCID for the chronic assessment.

Corn (sweet)

Residue estimates for sweet corn were based on field trials conducted in California, Florida, Illinois, Minnesota, North Carolina, Ohio, Oregon (two trials), and Pennsylvania (PMRA# 1404338). 81% CT was used for the chronic assessment based on PCT and food supply data. LOQ was assumed at 0.01 ppm for censored data. Only the trial in California had detectable residues.

The highest average field trial (HAFT) (0.044 ppm) was used for the acute assessment and the median (0.01 ppm) was used for the chronic assessment. The PCT information was incorporated under adjustment factor 2 in DEEM-FCID for the chronic assessment.

Cotton

The residue estimate for cottonseed was based on field trials conducted in the US. The trial data was provided by TKI during the comment period. 3% (round from 2.5%) CT was used for the chronic assessment, based on US PCT data. The LOQ level was assumed at 0.05 ppm for samples with non-detectable residues. A processing factor was applied to cotton seed oil (0.14). The processing factor was incorporated under adjustment factor 1 in DEEM-FCID.

The HAFT (0.29 ppm) was used for the acute assessment and the median (0.05 ppm) was used for the chronic assessment. The PCT information was incorporated under adjustment factor 2 in DEEM-FCID for the chronic assessment.

Parsnip

The residue estimates for parsnip was based on the tolerance at 0.05 ppm as there are no Canadian data available. 100% CT was assumed based on PCT information provided by the Canadian Horticulture Council. The tolerance was used for both the acute and chronic assessment. There were data deficiencies identified for parsnip in the PRVD. However, there are residue data available for carrots and the data for carrots may be able to support parsnip given the similar use pattern and crop physiology.

Pea dry commodities

Chickpea

Chickpea is not a registered use in Canada but is registered in the US and may potentially be imported to Canada. The residues estimate was based on the US tolerance at 0.09 ppm. 4% CT was used for chickpea seed based on US PCT and food supply information. 100% CT was used for chickpea flour as food supply data was not available for the form. The PCT was on applied to the chronic assessment under adjustment factor 2. This commodity was included in the updated assessment as new US tolerances were identified.

Guar

Guar is not a registered use in Canada but is registered in the US and may potentially be imported to Canada. The residue estimate is based on the US tolerance at 0.09 ppm. 100% CT was assumed as there were no PCT or food supply data available. This commodity was included in the updated assessment as new US tolerances were identified.

Lentil

Lentil is not a registered use in Canada but is registered in the US and may potentially be imported to Canada. The residues estimate was based on the US tolerance at 0.09 ppm. 1% CT was assumed based on US PCT and food supply information. The PCT was only applied to the chronic assessment under adjustment factor 2. This commodity was included in the updated assessment as new US tolerances were identified.

Pea dry

Dry pea is not a registered use in Canada but is registered in the US and may potentially be imported to Canada. The residue estimate was based on the US tolerance at 0.09 ppm. 1% CT was assumed based on US PCT and food supply information. The PCT was applied to the chronic assessment under adjustment factor 2. This commodity was included in the updated assessment as new US tolerances were identified.

Potato

The residue estimate for potatoes was based on one field trial conducted in North Carolina, Florida, New York, Maine, and Wisconsin (PMRA# 1404327). In the trial, treated samples had residues below the limit of quantitation. Thus, the LOQ was assumed at 0.01 ppm for both the acute and chronic assessment. Processing factors were applied to chips (2.05), dry granule (3.42), peeled (0.81), baked (1.25), and boiled forms (0.59) (PMRA# 1404343). The processing factors were applied under adjustment factor 1 in DEEM-FCID. The PCT information was incorporated under adjustment factor 2 in DEEM-FCID for the chronic assessment. 35% CT was used for tuber forms in the chronic assessment. 45% CT was used for chip forms and 24% CT was used for flour forms. 100% CT was used for dry granules as food supply information was not available for the form.

Rhubarb

Rhubarb is not a registered use in Canada but is registered in the US and may potentially be imported to Canada. The residue estimate for rhubarb is based on the US tolerance at 0.5 ppm. 100% CT was assumed, as there were no PCT or food supply data available.

Sorghum

Sorghum is not a registered use in Canada but is registered in the US and may potentially be imported to Canada. The residue estimate for sorghum is based on the US tolerance at 0.25 ppm. 100% CT was assumed as there were no food supply data available.

Soybean

The residue estimate for soybeans was based on field trials conducted in Delaware (two trials), Arkansas, Illinois (two trials), Indiana, Ohio, Iowa (two trials), Montana (two trials), and Minnesota (PMRA# 1404333). Only data from samples treated at the lowest rate in the trials (1x application at 2.8 kg a.i./ha) was used as it is more reflective of the proposed use pattern. Chemical specific processing factors were applied to soy milk (0.15) and oil (0.19) (PMRA# 1404341). The processing factors were applied to adjustment factor 1 under DEEM-FCID. 5% CT was used for soybean seed and vegetable and 2% CT was used for oil forms. 100% CT was assumed for soy milk and soybean flour as food supply data was not available for these forms.

The HAFT (0.18 ppm) was used for the acute assessment and the median (0.0435 ppm) was used for the chronic assessment. The PCT information was incorporated under adjustment factor 2 in DEEM-FCID for the chronic assessment.

6.0 Animal residue estimates

The residue estimates for animal commodities are based on poultry and goat feeding studies on file (PMRA# 1414020). The estimate is set at the LOD at 0.05 ppm for all commodities except for ruminant liver and kidney, and swine kidney. The residue estimates for animal commodities are indicated in Table 3. A DEEM-FCID default processing factor was applied to dried beef (1.92) under adjustment factor 2.

Table 3 Residue estimates for animal commodities

Animal commodity	Matrix	Residue estimate (ppm)
Beef, Sheep, Goat	Muscle	0.05
	Fat	0.05
	Liver	0.5
	Kidney	0.67
	Meat byproducts	0.05
	Milk	0.05
	Skin	0.05
Pork	Muscle	0.05
	Fat	0.05
	Liver	0.05
	Kidney	0.07
	Meat byproducts	0.05
	Skin	0.05
Chicken, Poultry, Turkey	All (including eggs)	0.05

7.0 Drinking water modelling estimates

Drinking water estimates have been updated since PRVD2012-02. The new estimated environmental concentrations were incorporated into the updated dietary exposure and risk assessments. Refer to Appendix VIII for details.

8.0 DEEM-FCID program and consumption information

Acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model – Food Commodity Intake Database™ (DEEM-FCID™; Version 4.02) program which incorporates food consumption data from the National Health and Nutrition Examination Survey (NHANES) 2005-2010.

An updated version of DEEM-FCID was used for the current assessment, whereas the assessment conducted in PRVD2012-02 used DEEM-FCID version 2.03 and consumption data from the Continuing Survey of Food Intake by Individuals (CSFII) 1994-96/1998. The updated DEEM-FCID 4.02 does not have a significant impact on the dietary exposure and risk estimates.

9.0 Acute dietary assessment

The results for the acute dietary assessment are listed in Table 4.

The acute exposure from food alone accounted for less than 38% of the ARfD for all population groups and is shown to be acceptable.

Table 4 Acute food and drinking water exposure and risk estimates

Population Group	Food only		Food and drinking water	
	mg/kg bw	% ARfD[1]	mg/kg bw	%ARfD[1]
General Population[2]	-	-	-	-
All Infants (<1 years)	0.0057	3	0.0153	8
Children 1-2 years	0.0083	4	0.0115	6
Children 3-5 years	0.0053	3	0.0081	4
Children 6-12 year	0.0030	1	0.0056	3
Male 13-19 years	0.0016	<1	0.0039	2
Male 20-49 years	0.0012	<1	0.0039	2
Adults 50-99 years	0.0010	<1	0.0040	2
Females 13-49 years	0.0011	9	0.0046	37

[1] ARfD = 0.2 mg/kg bw for the general population except female 13-49 years. The ARfD for Female 13-49 years = 0.0125 mg/kg bw. Exposure and risk estimates reported at the 95th percentile.

[2] The risk estimate could not be determined for the general population as separate ARfDs were selected for females age 13-49 years and the other population groups.

10.0 Chronic dietary assessment

The results for the chronic dietary assessment are listed in Tables 5 and 6.

The chronic exposure from food alone accounted for 135% of the ADI for children 1-2 years and is of concern. The major risk contributors were milk, pome fruits, and root vegetables. The chronic exposure was below the ADI for all other population groups.

Cereals (sweet and field corn, barley, oats, wheat), soybean, tree fruit (apple, cherry, peach, pear, plum and prune), and animal commodities were removed to mitigate the dietary risk concerns. Cereals and soybeans were removed because the crops are major feed items. With the removal of these uses, the only feed uses left are potatoes and carrots, which are alternative feed items that do not contribute significantly to the dietary burden. As such, animal commodities could be removed from the assessment with the removal of cereal and soybean uses. With the incorporation of mitigation measures, the chronic exposure from food accounted for less than 8% of the ADI for all population groups. Soybean and tree fruit uses were also removed to reduce drinking water estimates, as these uses have application rates that exceeded the drinking water modelling rate of 1.78 kg a.i./ha.

The mitigated food assessment was subsequently aggregated with drinking water estimates. The estimated exposure from food and drinking water was less than 71% of the ADI for all population groups and therefore, was shown to be acceptable.

Table 5 Chronic food only exposure and risk estimates

Population group	Food only		Food only with mitigation[1]	
	mg/kg bw/day	% ADI[2]	mg/kg bw/day	% ADI[2]
General Population	0.00059	23	0.00004	2
All Infants (<1 years)	0.00136	55	0.00016	7
Children 1-2 years	0.00337	135	0.00012	5
Children 3-5 years	0.00194	78	0.00010	4
Children 6-12 years	0.00100	40	0.00006	2
Youth 13-19 years	0.00047	19	0.00002	<1
Adults 20-49 years	0.00036	14	0.00003	1
Adults 50-99 years	0.00033	13	0.00004	2
Females 13-49 years	0.00035	14	0.00003	1

[1] Mitigation includes the removal of cereals (sweet and field corn, barley, oats, wheat), soybean, tree fruit (apple, cherry, peach, pear, plum and prune), and animal commodities

[2] ADI = 0.0025 mg/kg bw/day

Table 6 Chronic food and drinking water exposure and risk estimates

Population group	Food with mitigation[1] and drinking water	
	mg/kg bw/day	% ADI[2]
General Population	0.00047	19
All Infants (<1 years)	0.00175	70
Children 1-2 years	0.00071	28
Children 3-5 years	0.00057	23
Children 6-12 years	0.00041	17
Youth 13-19 years	0.00032	13
Adults 20-49 years	0.00045	18
Adults 50-99 years	0.00045	18
Females 13-49 years	0.00045	18

[1] Mitigation includes the removal of cereals (sweet and field corn, barley, oats, wheat), soybean, tree fruit (apple, cherry, peach, pear, plum and prune), and animal commodities

[2] ADI = 0.0025 mg/kg bw/day

11.0 Cancer dietary assessment

Based on additional information obtained during the PRVD2012-02 comment period, a threshold approach was considered appropriate for uterine adenocarcinomas and ovarian tumour risk assessment, rather than the non-threshold approach used in PRVD2012-02. Thus, a separate non-threshold dietary cancer risk assessment is no longer required. The ADI used in the chronic dietary assessment provides a margin of 640-fold to the low dose where there was equivocal evidence of uterine carcinomas and ovarian tumours in female rats.

12.0 Conclusions

The following uses will be cancelled due to dietary risk concerns:

Apple, cherry, peach, pear, plum/prune, soybean, corn (sweet and field), barley, oats, and wheat.

The following uses will be cancelled due to data deficiencies in the residue chemistry database:

Saskatoon berries, choke cherries, caraway, coriander, dill, and sweet white lupin.

These data deficiencies were identified in PRVD2012-02 and were not addressed during the comment period. There is also a lack of data to support tree fruit uses. The tree fruit uses will be cancelled due to health risk concerns.

For the remaining uses, the maximum annual application rate is to be reduced to mitigate risk concerns from food and drinking water:

- 1.68 kg a.i./ha for carrot (pre and post-emergent application)
- 1.50 kg a.i./ha for parsnip (pre and post-emergent application)
- 1.78 kg a.i./ha for potato (pre-emergent application)
- 1.63 kg a.i./ha for asparagus (pre-emergent or post-harvest application)
- 2.16 kg a.i./ha for shelterbelts (post-emergent application)

Celery is also shown to be acceptable in the dietary assessment but the use is to be cancelled due to occupation risk concerns.

Plant back interval (PBI) updates were identified in PRVD20102-02 based on confined crop rotation data on file. The updates resulted in an increase of the PBI from 4 months on existing labels to 12 months. This update was not proposed for implementation in PRVD2012-02 as all uses were proposed for cancellation at that time. Since some uses will be retained, the PBI is now required specifically for carrot, parsnip, and potato uses. The PBI is not applicable to asparagus and shelterbelts.

Appendix VI Occupational mixer/loader/applicator (MLA) and post application exposure and risk estimates for linuron

Details for the revised risk assessment are included in this appendix and in PRVD2012-02. Please refer to PRVD2012-02 for additional information.

Toxicology reference values

The toxicology reference values have been revised since PRVD2012-02 (Appendix IV). All scenarios were updated and the q_1* value was removed. All human health risk assessments have been updated as necessary using the revised values.

Dermal absorption

The dermal absorption value of 20% described in PRVD2012-02 was used in the human health risk assessments. The additional data was considered and supported the continued use of 20%.

Use pattern

The full use pattern was revised for the updated occupational exposure assessment, except for uses voluntarily cancelled by the registrant. Application rates were reduced from those presented in PRVD2012-02; however, the number of applications and timing of applications are consistent with PRVD2012-02.

Dislodgeable foliar residues (DFR)

The registrant submitted a new chemical-specific DFR study to Health Canada. The DFR calculated based on this study was used in the post application risk assessment for all crops (peak DFR of 22% of the application rate, with a 16% dissipation rate per day) and is a refinement from the default values used in PRVD2012-02.

Transfer coefficients (TC)

The TCs have been revised since PRVD2012-02. All scenarios were updated using the values provided by the Agricultural Re-entry Task Force (ARTF).

Applicator exposure

The unit exposure values have been revised since PRVD2012-02. The open cab groundboom and closed cab airblast scenarios were updated using the values provided by Agricultural Handlers Exposure Task Force (AHETF).

Area treated per day (ATPD)

Some of the ATPD values have been revised since PRVD2012-02. Relevant scenarios were updated based on information provided by the registrant and updated information available to Health Canada.

Table 1 Occupational exposure risk assessment summary

Crop	Application rate (kg a.i./ha)	Timing of application	Occupational risk assessment/mitigation required
Field Corn*	0.72	Post-emergence	Voluntary discontinuation by registrant
Soybeans*	2.16	Pre-emergence	Mixer, loader, applicator risk cannot be mitigated
Celery	1.68	Post-emergence	Post application risk cannot be mitigated: scouting REI not feasible
Fruit Trees*	4.32	Post-emergence	Post application risk cannot be mitigated: REIs not feasible
Field Corn*	0.72	Pre-emergence	Limited kg a.i./day, increased REI, increased PPE and engineering controls
Wheat*, Spring wheat*, Barley*, Oats*	0.28	Post-emergence	Limited kg a.i./day, increased REI, increased PPE and engineering controls
Potatoes	1.78	Pre-emergence	Limited kg a.i./day, increased REI, increased PPE and engineering controls
Asparagus	1.63	Pre-emergence & Post-harvest*	Increased REI, increased PPE and engineering controls
Carrots	1.08	Pre-emergence & Post-emergence	Increased REI, increased PPE and engineering controls
Parsnip, Dill*	1.2	Pre-emergence & Post-emergence	Increased REI, increased PPE and engineering controls
Coriander & Caraway*	0.8	Post-emergence	Increased REI
Sweet Corn*	0.78	Pre-emergence	Limited kg a.i./day, increased REI, increased PPE and engineering controls
Sweet White Lupins*	1.49	Pre-emergence	Increased REI, increased PPE and engineering controls
Chokecherries*	1.70	Pre-emergence	Increased REI , increased PPE and engineering controls
Saskatoon Berries*	2.16	Post-emergence	Limited kg a.i./day, increased REI, increased PPE and engineering controls
Shelterbelts	2.16	Post-emergence	Limited kg a.i./day, increased REI, increased PPE and engineering controls

REI = restricted-entry interval, PPE = personal protective equipment
REIs range from 12 hours to 9 days for crops with acceptable occupational risk.
Increased PPE includes chemical-resistant coveralls over a single layer with chemical-resistant gloves for mixer, loaders and cotton coveralls over a single layer with chemical-resistant gloves for applicators.
Engineering controls include closed mixing and loading systems and closed cab applications.
*Crops that have dietary and or drinking water concerns

Table 2 Short-, intermediate-term M/L/A exposure estimates and MOEs with refined application rates

Crop	Application equipment [a]	Activity scenario [b]	Refined application rate (kg a.i./ha)	Area treated per day (ha/day) [c]	Dermal dose [d] (µg/kg bw/day)	Inhalation dose [e] (µg/kg bw/day)	MOEs (Target – 300)		
							Dermal [f]	Inhalation [f]	Combined [g]
Closed Mixing/Loading wearing Maximum PPE, unless otherwise noted. Closed Cab wearing Mid-level PPE for Groundboom and Airblast application, unless otherwise noted. Maximum PPE for Right-of-Way Sprayers.									
Field Corn	Groundboom	MLA – Farmer [i]	0.72	80	2.02	0.122	370	6000	340
		MLA - Custom		140	3.06	0.214	240	3400	230
Soybeans	Groundboom	MLA – Farmer	2.16	75	4.92	0.344	150	2200	140
		MLA – Custom		360	23.6	1.65	31	450	29
Wheat, Spring Wheat, Barley, Oats	Groundboom	MLA – Farmer [h, i]	0.28	107	1.78	0.670	420	1100	300
		MLA - Custom		360	3.06	0.214	240	3400	230
Potatoes	Groundboom	MLA - Farmer	1.78	58	3.14	0.219	240	3400	220
		MLA - Custom		360	19.5	1.36	38	540	36
Asparagus	Groundboom	MLA – Farmer [i]	1.63	26	1.49	0.090	500	8200	470
Carrots	Groundboom [h]	MLA – Farmer [i]	1.08	26	1.67	0.628	440	1200	320
Celery	Groundboom	MLA – Farmer [i]	1.68	26	1.53	0.093	480	8000	460
Parsnip, Dill	Groundboom [h]	MLA – Farmer [i]	1.2	26	1.86	0.698	400	1100	290
Coriander, Caraway	Groundboom [h]	MLA – Farmer [i]	0.80	26	1.23	0.465	600	1600	440
Sweet Corn	Groundboom	MLA – Farmer [i]	0.78	80	2.19	0.133	340	5600	320
		MLA - Custom		140	3.32	0.232	220	3200	210
Sweet White Lupins	Groundboom	MLA – Farmer [i]	1.49	26	1.36	0.082	540	9000	510
Fruit Trees (apple, cherry, pear, plum, prune)	Groundboom	MLA – Farmer [i]	4.32	10	1.52	0.092	490	8100	460
	Airblast	MLA		20	4.75	0.464	160	1600	140
Choke-cherries	Groundboom	MLA – Farmer [i]	1.70	26	1.55	0.094	480	7900	450
Saskatoon Berries	Groundboom	MLA – Farmer [i]	2.16	10	0.758	0.046	980	16000	920
Shelterbelts	Groundboom	MLA – Farmer [i]	2.16	10	0.758	0.046	980	16000	920
	Rights of Way Sprayer [j]	MLA		10	24.9	1.38	30	540	28

[a] Mid-level personal protection equipment (PPE) = cotton coveralls over a single layer (long pants and a long-sleeved shirt) with chemical resistant gloves. Gloves are not included in the closed cab scenarios. Maximum PPE = chemical resistant coveralls over single layer (long pants and long sleeved shirt) with chemical resistant gloves.
[b] ML = Mixer, Loader; A = Applicator
[c] Based on standard assumptions or refined values when available.
[d] Where dermal dose µg/kg bw/day = (unit exposure × area treated per day × application rate × dermal absorption)/80 kg. Dermal absorption value = 20%.
[e] Where inhalation dose µg/kg bw/day = (unit exposure × area treated per day × application rate)/80 kg.
[f] Based on a short-, intermediate-term oral NOAEL of 0.74 mg/kg bw/day and a target MOE of 300
[g] Combined MOE = $1/(1/MOE_{dermal} + 1/MOE_{inhalation})$; Shaded cells indicate MOEs that are less than the target MOE.
[h] Open cab application.
[i] Mid-level PPE for mixer/loaders.
[j] Maximum PPE for mixer, loader, applicators.

Table 3 Restricted-entry intervals for commercial post application activities

Crop [a]	Application		Activity	Transfer coefficient (cm^2/hr) [d]	DFR [e] (µg/cm^2)	Dermal exposure [f] (µg/kg bw/day)	Day 0 MOE [g]	REI [h] (days)	PHI [i] (days)
	per year [b]	Rate [c] kg a.i./ha							
Field Corn	1	0.72	Pre-emergent	70	1.58	2.22	330	0.5	60
Soybeans	1	2.16	Pre-emergent	70	4.75	6.65	110	6	NS
Wheat, spring wheat, barley, oats	1	0.28	Hand weeding	70	0.62	0.86	860	0.5	NS
			Scouting	210		2.59	290	0.5	
Potatoes	1	1.78	Pre-emergent	70	3.92	5.48	140	4	NS
Asparagus	1-2	1.02	Pre-emergent, Post-harvest	70	2.24	3.14	240	1	NS
		1.63	Pre-emergent, Post-harvest	70	3.59	5.02	150	4	
Carrots	1-2	1.08	Pre-emergent, Hand weeding	70	2.38	3.33	220	2	NS
			Scouting	210		9.98	74	8	
Parsnip, Dill	1-2	1.2	Pre-emergent	70	2.64	3.70	200	2	60
		0.9	Hand weeding	70	1.98	2.77	270	1	
			Scouting	210		8.32	89	7	
		1.2	Hand weeding	70	2.64	3.70	200	2	
			Scouting	210		11.09	67	9	
Celery	1	1.68	Hand weeding	70	3.70	5.17	140	4	NS
			Scouting	210		15.52	48	10	
Chokecherries	1	1.70	Pre-emergent	70	3.74	5.24	140	4	NS
Coriander, Caraway	1	0.80	Hand weeding	70	1.76	2.46	300	0.5	60
			Scouting	210		7.39	100	6	
Sweet corn	1	0.78	Pre-emergent	70	1.72	2.40	310	0.5	50
Sweet White Lupins	1	1.49	Pre-emergent	70	3.28	4.59	160	3	80
Fruit Trees	1	4.32	Scouting, Hand weeding	70	9.50	13.31	56	10	NS
Saskatoon berries	1	2.16	Scouting, Hand weeding	70	4.75	6.65	110	6	50
Shelterbelts									NS

NS = not stated

[a] For crops where there is a pre- and post-emergent application, the applications were assessed separately as no accumulation of exposures is expected. For pre-emergent applications, a quantitative assessment was conducted due to the high toxicity and application rates of linuron.

[b] The label listed number of pre- and/or post-emergence applications per year.

[c] The refined label rates expressed in kilograms a.i./hectare.

[d] Transfer coefficients (TC) are from the ARTF (ARTF, 2008). Carrot TCs were used as surrogate data for parsnips and parsley TCs were used as surrogate data for dill and coriander and caraway. The smooth foliage hand weeding TC was used as a surrogate for pre-emergent applications and for scenarios where minimal dermal exposure from contact with foliar residues would be expected.

[e] DFR = Dislodgeable foliar residue. Based on DFR data, at × days after application, where × is the day when an MOE > 300 is determined for the proposed REI. Based on the chemical-specific peak DFR value of 22% and daily dissipation rate of 16%.

[f] Dermal exposure = DFR × TC × 8 hr × DA / 80 kg. Dermal absorption value = 20%.

[g] The resulting MOE on the recommended REI day. Based on the short-, intermediate-term oral NOAEL of 0.74 mg/kg bw/day and a target MOE of 300. MOEs in the range of the target MOE were considered to be acceptable due to conservatisms in the risk assessment.

[h] REI = Restricted-entry interval = Day at which the dermal exposure results in an MOE close to or greater than 300. Shaded cells indicate REIs not considered to be agronomically feasible.

[i] PHI = Pre-harvest interval

Appendix VII Revised environmental risk assessment

Table 1 Summary of the fate and behaviour of linuron in the terrestrial environment.

Property	Test substance	Value	Transformation products	Comments	Reference
Abiotic transformation					
Phototransformation on soil	Technical grade active ingredient	Half-live: >15 d continuous radiation	Major: None Minor: Norlinuron, desmethyl linuron, 3,4-DCA	Not an important route of transformation	1224455=16856 12 1304334 1304335 1685593
Phototransformation in air	N/A	$t_{1/2}$ = 1 day		Not susceptible to LRT	EPISuite (v.4.11)
Biotransformation					
Biotransformation in aerobic soil	Technical grade active ingredient	DT_{50}: 23.6-129 d $t_{1/2rep}$: 28.5 – 209 d 90th percentile upper bound of mean: 163 d	Major: none Minor: desmethoxy linuron, desmethyl linuron, norlinuron, desmethoxy monolinuron and 3,4-DCA	Slightly persistent to moderately persistent	1685617 2917856
Biotransformation in anaerobic soil	Technical grade active ingredient	DT_{50}: 32 d	Major: desmethoxy linuron Minor: 3,4-DCA, norlinuron	Slightly persistent	1695375
Mobility					
Adsorption / desorption in soil	Technical grade active ingredient	Kad OC: 166-2600 K_d: 20th percentile = 5.8	NA	Moderate to slight mobility	1685594 1304353 1304354 1304347
	desmethoxy monolinuron	Kad OC: 520-1100	NA	Low mobility	1304347
	desmethoxy-linuron	Kad OC: 3900-8100	NA	Slightly mobile to immobile	1304347
	norlinuron	Kad OC: 2400-10000	NA	Slightly mobile to immobile	1304347
Soil leaching	Technical grade active ingredient	TLC Rf: 0-0.11	NA	Low mobility to immobile	1685594
	Technical grade active ingredient	Soil column: Up to 0.4% in percolate	NA		1685592

Property	Test substance	Value	Transformation products	Comments	Reference
	EP: Afalon WP 50	Lysometer: 0.1 µg/L in percolate	desmethyl linuron		1695373
Volatilization	No Studies				
Field studies					
Field dissipation	Linuron EP	DT_{50}: 10.1-168.4 d Carry over: 1.4-25%	NA	Non-persistent to moderately persistent	3038895
Field leaching	Linuron EP	Detected in 30-90 cm deep sandy clay loam soil most likely due to sample contamination.		Not expected to leach	1685614 1685596

NA = Not available

Table 2 Summary of the fate and behaviour of linuron in the aquatic environment.

Study type	Test material	Value	Transformation products	Comments	Reference
Abiotic transformation					
Hydrolysis	Technical grade active ingredient	DT_{50}: 945 d	Major: None Minor: 3,4-dichloroaniline (DCA)	Not an important route of transformation	1304331= 1685615
Phototransformation in water	Technical grade active ingredient	DT_{50}: 54 d	Major: 3-(3-chloro-4-hydroxyphenyl)-1-methoxy-1-methylurea Minor: norlinuron, desmethoxy linuron	Not an important route of transformation	1685610, 1315093 1304340
Biotransformation					
Biotransformation in aerobic water systems	Technical grade active ingredient	DT_{50}: 11.0-28.3 d	Major: desmethoxy linuron, norlinuron and 3,4-DCA. Minor: desmethyl linuron, and unidentified products	Non-persistent to slightly persistent	1695376 2431768
Biotransformation in anaerobic water systems	Technical grade active ingredient	DT_{50}: 7.4 -15.8 d	Major: desmethoxy linuron, desmethoxy monolinuron, and norlinuron. Minor: desmethyl linuron, 3,4-DCA	Non-persistent to slightly persistent	1685611= 1224456, 1304351
BCF		49	Not applicable	Not expected to bioaccumulate	

Table 3 Summary of effects of linuron on terrestrial organisms.

Organism	Exposure	Test substance	Endpoint value (bold values used in the risk assessment)	Degree of toxicity[a]/comment	Reference
Invertebrates					
Earthworm (*Eisenia foetida*)	Acute	95.8% linuron	LC_{50}: >1000 mg a.i./kg; NOEC: 1000 mg a.i./kg	NA	1281899
		End-use product (47.5% w/w)	LC_{50}: >1000 mg a.i./kg; NOEC: 560 mg a.i./kg	NA	1281899
		No information	14-D LC_{50}: **>500 mg a.i./kg soil**	NA	3038896
	Chronic	End-use product (46.1%)	**28- and 56-d NOEC = 13.55 mg a.i./kg soil dw**	NA	
Earthworm (*Allolobophora caliginosa*)	Acute	End-use product	LC_{50}: invalid	Study is no longer acceptable. No indication in study if endpoint was corrected for percent active ingredient of the EP	1304355
Bee (*Apis mellifera*)	Acute oral LD_{50}	Technical grade active ingredient	**> 112.1 µg a.i./bee**	Relatively non-toxic	3038896
	Acute contact LD_{50}	Technical grade active ingredient	**> 97.8 µg a.i./bee**		
	Acute oral LD_{50}	End-use product	> 145 µg a.i./bee		
	Acute contact LD_{50}	End-use product	>150 µg a.i./bee		
	10-d chronic adult NOED	End-use product	**≤10.97 µg a.i./bee/day**		
	Acute larval study LD_{50}	End-use product	**31.1 µg a.i./larva**	NA	
Beneficial Arthropods					
Carabid beetles (*Poecilus cupreus*)	Contact	48.6% WP formulation	Invalid endpoints	Study is no longer acceptable. No indication in study if endpoint was corrected for percent active ingredient of the EP.	1281899 3038896
Staphylinid beetles (*Aleochara bilineata*)	Contact	48.6% WP formulation			
Lycosid spiders (*Araneae lycosidae*)	Contact	48.6% WP formulation			
Predatory mites *T. pyri*	7-d Laboratory (glass plate)	45% EP	**LR_{50} = 38 g a.i./ha**	Used in risk assessment as both glass-plate and higher tier leaf disk studies are in good agreement.	3038896
	7-d Leaf disks	45.5% EP	**LR_{50} = 42.7 g a.i./ha**	NA	
Parasitoids *A. rhopalosiphi*	48-h Laboratory (glass plate)	45% EP	**LR_{50}= ~100 g a.i./ha**	NA	

Organism	Exposure	Test substance	Endpoint value (bold values used in the risk assessment)	Degree of toxicity[a]/comment	Reference
	48-h leaf exposure	45% EP	**LR_{50} > 950 g a.i./ha**	NA	
Carabid beetles (*Poecilus cupreus*)	14-d; application to quartz	44.4% SC EP	LR_{50} > 950 g a.i./ha	NA	
Birds					
Bobwhite quail *(Colinus virginianus)*	Acute	Technical grade active ingredient	LD_{50}: 940 mg a.i./kg bw; NOEC: <292 mg/kg bw	Moderately toxic	1304383 1685599 3038898
	Acute	Technical grade active ingredient	**LD_{50}: 314 mg a.i./kg; NOEC: 100 mg a.i./kg bw**	**Highly toxic**	1700200 3038896
	Dietary	Technical grade active ingredient	LC_{50}: 1838 mg a.i./kg diet; NOEC: <178 mg a.i./kg diet	Slightly toxic	1304384
	Dietary	Technical grade active ingredient	LC_{50}: > 1250 mg a.i./kg diet 113 mg a.i./kg bw/day; NOEC: <312.5 mg a.i./kg diet	Slightly toxic	1700202 3038896
	Reproduction	Technical grade active ingredient	NOEC: 100 mg a.i./kg diet **NOEC = 14.4 mg a.i./kg bw/d**	**Used in risk assessment**	1304386 3038898 3038896
Mallard duck *(Anas platyrhynchos)*	Acute	Technical grade active ingredient	LD_{50} not calculated due to emesis; NOEC: <250 mg a.i./kg	NA	1700201
	Acute	EP	LD_{50}: 1173 mg/kg	Slightly toxic	1685598
	Dietary	Technical grade active ingredient	LC_{50}: 5224 mg a.i./kg; NOEC : <178 mg a.i./kg diet	Practically non-toxic	1304385
	Dietary	Technical grade active ingredient	LC_{50}: >5000 mg a.i./kg; NOEC : <312.5 mg a.i./kg diet	Practically non-toxic	1700203
	Reproduction	Technical grade active ingredient	NOEC: 100 mg a.i./kg diet		1304387 3038898
Canary	Dietary	Technical grade active ingredient	**LC_{50} = 1386 mg a.i./kg diet (92.6 mg a.i./kg bw/d)**	**Used in risk assessment**	2431769
			LC_{50} of 973 mg a.i./kg diet	No details available	3038898
Mammals					
Rat	Acute	Technical grade active ingredient	LD_{50}: 1146-6500 mg a.i./kg bw **LD_{50} = 1146 mg a.i./kg bw**	Slightly to practically non-toxic	2424253 3038896
		Technical grade active ingredient	LD_{50}= 2600 mg a.i./kg bw	Practically non-toxic	
Rat	Reproduction	Technical grade active ingredient	**NOAEL: 0.74 mg a.i./kg bw/day**		2556332
		Technical grade active ingredient	NOAEL = 5.8 mg/kg-bw	NA	3038898
		Technical grade active ingredient	NOAEL = 10 mg a.i./kg bw/d	NA	3038896
Rat	Inhalation	Technical grade active ingredient	LC_{50} = 5.08 mg/L	NA	3038898

Organism	Exposure	Test substance	Endpoint value (bold values used in the risk assessment)	Degree of toxicity[a]/comment	Reference
Vascular plants					
Vascular plant	Seedling emergence Onion (*Allium cepa*)	Technical grade active ingredient	EC_{50} (Shoot dry weight): 125 g a.i./ha	NA	1304390 1304391 1304392
	Vegetative vigour Cucumber (*Cucumis sativus*)	Technical grade active ingredient	**EC_{50} (shoot height): 6 g a.i./ha**	NA	1304390 1304391 1304392
	Vegetative vigour Sugar beet	46% EP	ER_{50} = 0.17 L/ha or 78.4 g a.i./ha	NA	3038896
	Seedling emergence rape	46% EP	**ER_{50} = 0.07 L/ha or 32.3 g a.i./ha**	NA	
	Seedling emergence (monocots)	49.3% EP	EC_{25}= 62.6 g a.i./ha (0.0558 lbs/A)	NA	3038898
	Seedling emergence (dicots)		EC_{25}= 139 g a.i./ha (0.124 lb/A)	NA	
	Vegetative vigour (monocots)		EC_{25}= 37.7 g a.i./ha (0.0336 lb/A)	NA	
	Vegetative vigour (dicot)		EC_{25}= 15.9 g a.i./ha (0.0142 lbs/A)	NA	
	HC_{05} (11 species)		HC_{05} = 20 g a.i./ha	NA	

[a] Atkins et al. (1981) for bees and USEPA classification for others, where applicable.
BOLD values indicate endpoints used in the risk assessment
NA = Not available

Table 4 Summary of effects of linuron on aquatic organisms.

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	Reference
Freshwater species					
Daphnia magna	Acute	Technical grade active ingredient	**EC_{50}: 0.12 mg a.i./L**	Highly toxic	1685603 3038898
	Acute	Technical grade active ingredient	EC_{50}: 1.9 mg a.i./L NOEC: 1.58 mg a.i./L		1304356
	Acute	Technical grade active ingredient	EC_{50}: 5.4 mg a.i./L NOEC: 1.29 mg ai /L		1695384
	Acute	Technical grade active ingredient	EC_{50}: 0.75 mg ai /L NOEC: 0.32 mg ai /L		1281899
	Acute	EP	EC_{50}: 1.1 mg a.i./L		1685602
	Acute	Technical grade active ingredient	EC_{50}: 0.31 mg a.i./L		3038896
	Acute	EP	EC_{50}: 5.81 mg a.i./L	Moderately toxic	
	Acute	Desmethoxy-linuron	EC_{50}: 5.40 mg a.i./L	Moderately toxic	3038896

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	Reference
	Chronic	Technical grade active ingredient	**NOEC: 0.13 mg ai /L**	NA	1304359 3038898
	Chronic	Technical grade active ingredient	NOEC : 0.18 mg a.i./L		3038896
	Chronic	3,4-dichloroaniline	NOEC: <0.025 mg ai /L		1404379
Hyalella azteca	Chronic sediment exposure	Technical grade active ingredient	Sediment: NOAEC <0.42 mg a.i./kg Pore Water: **NOAEC <0.012 mg a.i./L**	NA	3038898
Chironomus riparius	Spiked sediment (28-d)	End-use product (45% a.i.)	**NOEC: 9.5 mg a.i./kg sed dw**	NA	3038896
	Spike water (28-d)	Desmethoxy-linuron	NOEC: 2.0 mg/L	NA	3038896
Rainbow trout	Acute	Technical grade active ingredient	LC_{50}: 4.2 mg a.i./L NOEC: 1.0 mg ai /L	Moderately toxic	1695380
	Acute	Technical grade active ingredient	LC_{50}: 16.4 mg a.i./L		1685597
	Acute	Technical grade active ingredient	**LC_{50}: 3.15 mg a.i./L**		3038896
	Acute	Desmethoxy-linuron	LC_{50}: 4.2 mg a.i./L		3038896
	Acute	Technical grade active ingredient	LC_{50}: 3.085 mg a.i./L		3038898
	Chronic	**Technical grade active ingredient**	**NOEC: 0.042 mg a.i./L**	NA	1304378 1304379 3038898
	Chronic	Technical grade active ingredient	NOEC: 0.1 mg a.i./L	NA	PRVD2012-02
Bluegill sunfish	Acute	Technical grade active ingredient	LC_{50}: 9.6 mg/L LC_{50}: 16.2 mg/L	Moderately toxic	1685609 1685597
	Acute	EP	LC50: 9.2 mg/L		1685601
Fathead minnow	ELS (264 days)	Technical grade active ingredient	NOEC: 0.097 mg a.i./L (highest dose tested)	NA	3038896
	21-d acute	Technical grade active ingredient	NOEC 0.099 mg a.i./L	NA	2185692
Amphibian Perez's frog embryo	192-h (8 days)	Technical grade active ingredient	LC_{50}: 21 mg a.i./L	Can not be used in RA	3032998
Amphibian	Chronic – Effects to the endocrine system	Technical grade active ingredient	**NOEC <0.009 mg a.i./L**	NA	3033298
Freshwater algae (*Navicula pelliculosa*)	Acute	Technical grade active ingredient	**EC_{50}: 0.014 mg a.i./L**	NA	1304388 1304389 1695388 1695389 3038898
Green algae (*Desmodesmus subspicatus*)	Acute	Technical grade active ingredient	EC_{50}:0.016 mg a.i./L	NA	3038896
Green algae (*Pseudokirchneriella subcapitata*)	Acute	Desmethoxy linuron	EC_{50}: 0.0226 mg a.i./L	NA	3038896

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	Reference
Vascular plant duckweed (*Lemna gibba)*	Dissolved	Technical grade active ingredient	**EC_{50}(biomass): 0.021 mg a.i./L** EC_{50} (frond number): 0.055 mg a.i./L NOEC: 0.01 mg a.i./L	NA	1695390 3038896
Vascular plant (*Lemna gibba*)	Acute	Technical grade active ingredient	EC_{50}(biomass): 0.0273 mg a.i./L	NA	3038898
Microcosm – Community Structure Effects	Chronic	EP	**NOAEC: 0.015 mg a.i./L**	NA	3038896
Marine species					
Crustacean Mysid, *Mysidopiss bahia*	Acute	Technical grade active ingredient	**LC_{50}: 3.4 mg a.i./L** NOEC: 2.1 mg a.i./L.	Moderately toxic	1304360 3038898
	Chronic	Technical grade active ingredient	**NOEC: 0.297 mg a.i./L**	NA	1304362 1304363 1304364 1304365 3038898
Mollusk eastern oyster, (*Crassostrea virginica)*	Acute	Technical grade active ingredient	LC_{50}: 5.5 mg a.i./L	Moderately toxic	1304361
Fish Sheepshead minnow *(Cyprinodon variegates)*	Acute	Technical grade active ingredient	**LC_{50}: 0.89 mg a.i./L** NOEC: 0.49 mg a.i./L	Highly toxic	1685620 3038898
	Acute	EP	LC_{50}: 1.27 mg a.i./L NOEC: 0.942 mg a.i./L		1404380
	Chronic	Technical grade active ingredient	**NOEC: 0.357 mg a.i./L**	NA	1304373 1304374 1304375 1304376 1304377 3038898
Marine alga *Skeletonema costatum*	Acute	Technical grade active ingredient	**EC_{50}: 0.036 mg/L**	Very highly toxic	1304388

[a] USEPA classification, where applicable
BOLD values indicate endpoints used in the risk assessment
NA = Not available

Table 5 Risk of linuron to earthworms.

Exposure	Endpoint (mg a.i./kg dw)	Uncertainty factor	Application rate (g a.i./ha)	EEC (mg a.i./kg dw)	RQ	LOC exceeded
Acute LC_{50}	>500	0.5	2160	0.96	<0.01	No
Chronic NOEC	13.55	1	2160	0.96	0.07	No

Table 6 Refined Tier I pollinator risk assessment for linuron uses.

Crop	Application method	Application timing	Exposure scenario	Potential for exposure to level that may result in risks at tier I	Potential mitigation
Potatoes	Spray	Pre-emergence	**Exposure route:** Residue in pollen/nectar of plants resulting from translocation after pre-flowering applications. **Attractiveness to bees:** moderate **Harvest time:** after bloom	Negligible	Not required
Carrots, Parsnip	Spray	Pre- and post-emergence	**Exposure route:** Residue in pollen/nectar of plants resulting from translocation after pre-flowering applications. **Bee attractiveness:** moderate **Harvest time:** typically before bloom and not grown for seed in Canada.	Negligible	Not required
Asparagus	Spray	Pre-emergence	**Exposure route:** Residue in pollen/nectar of plants resulting from translocation after pre-flowering applications. **Bee attractiveness:** moderate **Harvest time:** typically before bloom and not grown for seed in Canada.	Negligible	Not required
Shelterbelts	Spray	Before or immediately after weeds emerge, or before buds open in spring for new and established plants. Spray to keep chemical off the leaves	**Exposure route:** Residue in pollen/nectar of flowering plants in shelterbelts resulting from translocation after pre-flowering applications. **Bee attractiveness:** variable **Harvest time:** variable/not applicable.	Negligible	Not required

Table 7 Refined risk assessment for beneficial arthropods exposed to linuron.

Organism Endpoint (g a.i./ha)	In-Field EEC (g a.i./ha)	RQ / LOC exceeded	Off-field EEC (g a.i./ha)	RQ / LOC exceeded
T. pyri (42.7)	1780	41.7 / yes	106.8	2.5 / yes
A. rhophalosiphi (>950)	1780	<1.9 / yes	106.8	0.1 / no
T. pyri (42.7)	2160	50.6 / yes	129.6	3.1 / yes
A. rhophalosiphi (>950)	2160	<2.27 / yes	129.6	0.14 / no

Table 8 Risks to non-target terrestrial plants exposed to linuron after maximum single application rate of 1780 g a.i./ha.

Exposure	Endpoint	Endpoint value (g a.i./ha)	Uncertainty factor	Risk assessment for:	EEC (g a.i./ha)	RQ	LOC exceeded
Seedling emergence (onion)	ER_{50}	32.3	0.5	On-field	1780	110	Yes
	ER_{50}	32.3	0.5	Off-field (boom sprayer)	106.8	6.7	Yes
Vegetative vigour (cucumber)	EC_{50}	6	0.5	On-field	1780	593	Yes
	HC_5 of EC_{50} and ER_{50} values	20	1	On-field	1780	89	Yes
	EC_{50}	6	0.5	Off-field (boom sprayer)	106.8	35.6	Yes
	HC_5 of EC_{50} and ER_{50} values	20	1	Off-field (boom sprayer)	106.8	5.34	Yes

Table 9 Refined avian risk assessment for on-field and off-field exposure at 1.78 kg a.i./ha and off-field at 2.16 kg a.i./ha.

	Toxicity (mg a.i./kg bw/d)	Food guild (food item)	Mean nomogram residues (1.78 kg a.i./ha)				2.16 kg a.i./ha to shelterbelts.
			On field		Off field		Off field
			EDE (mg a.i./kg bw)	RQ[1]	EDE (mg a.i./kg bw)	RQ[1]	Drift RQ[1]
Small Birds (0.02 kg)							
Acute	31.40	Insectivore	100.04	**3.19**	6.00	0.19	0.23
	31.40	Granivore (grain and seeds)	10.69	0.34	0.64	0.02	0.02
	31.40	Frugivore (fruit)	21.39	0.68	1.28	0.04	0.05
Dietary	9.26	Insectivore	100.04	**10.80**	6.00	0.65	0.79
	9.26	Granivore (grain and seeds)	10.69	**1.15**	0.64	0.07	0.08
	9.26	Frugivore (fruit)	21.39	**2.31**	1.28	0.14	0.17
Reproduction	14.40	Insectivore	100.04	**6.95**	6.00	0.42	0.51
	14.40	Granivore (grain and seeds)	10.69	0.74	0.64	0.04	0.05
	14.40	Frugivore (fruit)	21.39	**1.49**	1.28	0.09	0.11
Medium Sized Bird (0.1 kg)							
Acute	31.40	Insectivore	78.07	**2.49**	4.68	0.15	0.18
	31.40	Granivore (grain and seeds)	8.35	0.27	0.50	0.02	0.02
	31.40	Frugivore (fruit)	16.69	0.53	1.00	0.03	0.04

	Toxicity (mg a.i./kg bw/d)	Food guild (food item)	Mean nomogram residues (1.78 kg a.i./ha)				2.16 kg a.i./ha to shelterbelts.
			On field		Off field		Off field
			EDE (mg a.i./kg bw)	RQ[1]	EDE (mg a.i./kg bw)	RQ[1]	Drift RQ[1]
Dietary	9.26	Insectivore	78.07	**8.43**	4.68	0.51	0.61
	9.26	Granivore (grain and seeds)	8.35	0.90	0.50	0.05	0.07
	9.26	Frugivore (fruit)	16.69	**1.80**	1.00	0.11	0.13
Reproduction	14.40	Insectivore	78.07	**5.42**	4.68	0.33	0.39
	14.40	Granivore (grain and seeds)	8.35	0.58	0.50	0.03	0.04
	14.40	Frugivore (fruit)	16.69	**1.16**	1.00	0.07	0.08
Large Sized Bird (1 kg)							
Acute	31.40	Insectivore	22.79	0.73	1.37	0.04	0.05
	31.40	Granivore (grain and seeds)	2.44	0.08	0.15	0.00	0.01
	31.40	Frugivore (fruit)	4.87	0.16	0.29	0.01	0.01
	31.40	Herbivore (short grass)	25.94	0.83	1.56	0.05	0.06
	31.40	Herbivore (long grass)	14.56	0.46	0.87	0.03	0.03
	31.40	Herbivore (Broadleaf plants)	22.34	0.71	1.34	0.04	0.05
Dietary	9.26	Insectivore	22.79	**2.46**	1.37	0.15	0.18
	9.26	Granivore (grain and seeds)	2.44	0.26	0.15	0.02	0.02
	9.26	Frugivore (fruit)	4.87	0.53	0.29	0.03	0.04
	9.26	Herbivore (short grass)	25.94	**2.80**	1.56	0.17	0.20
	9.26	Herbivore (long grass)	14.56	**1.57**	0.87	0.09	0.11
	9.26	Herbivore (Broadleaf plants)	22.34	**2.41**	1.34	0.14	0.18
Reproduction	14.40	Insectivore	22.79	**1.58**	1.37	0.09	0.12
	14.40	Granivore (grain and seeds)	2.44	0.17	0.15	0.01	0.01
	14.40	Frugivore (fruit)	4.87	0.34	0.29	0.02	0.02
	14.40	Herbivore (short grass)	25.94	**1.80**	1.56	0.11	0.13
	14.40	Herbivore (long grass)	14.56	**1.01**	0.87	0.06	0.07
	14.40	Herbivore (Broadleaf plants)	22.34	**1.55**	1.34	0.09	0.11

[1] Bolded values exceed the level of concern

Table 10 Refined avian risk assessment for on-field and off-field exposure at 1.08 kg a.i./ha.

	Toxicity (mg a.i./kg bw/d)	Food guild (food item)	Mean nomogram residues (1.08 kg a.i./ha)			
			On field		Off field	
			EDE (mg a.i./kg bw)	RQ[1]	EDE (mg a.i./kg bw)	RQ[1]
Small Birds (0.02 kg)						
Acute	31.40	Insectivore	60.70	**1.93**	3.64	0.12
	31.40	Granivore (grain and seeds)	6.49	0.21	0.39	0.01
	31.40	Frugivore (fruit)	12.98	0.41	0.78	0.02
Dietary	9.26	Insectivore	60.70	**6.55**	3.64	0.39
	9.26	Granivore (grain and seeds)	6.49	0.70	0.39	0.04
	9.26	Frugivore (fruit)	12.98	**1.40**	0.78	0.08
Reproduction	14.40	Insectivore	60.70	**4.22**	3.64	0.25
	14.40	Granivore (grain and seeds)	6.49	0.45	0.39	0.03
	14.40	Frugivore (fruit)	12.98	0.90	0.78	0.05
Medium Sized Bird (0.1 kg)						
Acute	31.40	Insectivore	47.37	**1.51**	2.84	0.09
	31.40	Granivore (grain and seeds)	5.06	0.16	0.30	0.01
	31.40	Frugivore (fruit)	10.13	0.32	0.61	0.02
Dietary	9.26	Insectivore	47.37	**5.12**	2.84	0.31
	9.26	Granivore (grain and seeds)	5.06	0.55	0.30	0.03
	9.26	Frugivore (fruit)	10.13	**1.09**	0.61	0.07
Reproduction	14.40	Insectivore	47.37	**3.29**	2.84	0.20
	14.40	Granivore (grain and seeds)	5.06	0.35	0.30	0.02
	14.40	Frugivore (fruit)	10.13	0.70	0.61	0.04
Large Sized Bird (1 kg)						
Acute	31.40	Insectivore	13.83	0.44	0.83	0.03
	31.40	Granivore (grain and seeds)	1.48	0.05	0.09	0.00
	31.40	Frugivore (fruit)	2.96	0.09	0.18	0.01
	31.40	Herbivore (short grass)	15.74	0.50	0.94	0.03
	31.40	Herbivore (long grass)	8.83	0.28	0.53	0.02
	31.40	Herbivore (Broadleaf plants)	13.55	0.43	0.81	0.03
Dietary	9.26	Insectivore	13.83	**1.49**	0.83	0.09
	9.26	Granivore (grain and seeds)	1.48	0.16	0.09	0.01
	9.26	Frugivore (fruit)	2.96	0.32	0.18	0.02
	9.26	Herbivore (short grass)	15.74	**1.70**	0.94	0.10
	9.26	Herbivore (long grass)	8.83	0.95	0.53	0.06

	Toxicity (mg a.i./kg bw/d)	Food guild (food item)	Mean nomogram residues (1.08 kg a.i./ha)			
			On field		Off field	
			EDE (mg a.i./kg bw)	RQ[1]	EDE (mg a.i./kg bw)	RQ[1]
	9.26	Herbivore (Broadleaf plants)	13.55	**1.46**	0.81	0.09
Reproduction	14.40	Insectivore	13.83	0.96	0.83	0.06
	14.40	Granivore (grain and seeds)	1.48	0.10	0.09	0.01
	14.40	Frugivore (fruit)	2.96	0.21	0.18	0.01
	14.40	Herbivore (short grass)	15.74	**1.09**	0.94	0.07
	14.40	Herbivore (long grass)	8.83	0.61	0.53	0.04
	14.40	Herbivore (Broadleaf plants)	13.55	0.94	0.81	0.06

[1] Bolded values exceed the level of concern

Table 11 Refined risk assessment of mammals exposed to linuron at most sensitive NOEL (0.74 mg a.i./kg bw/d) and LOEL (5.8 mg a.i./kg bw/d) at 1.78 kg a.i./ha using mean nomogram food residue values.

	Food guild (food item)	Mean nomogram residues and NOEL of 0.74 mg a.i./kg bw/d				Mean nomogram residues and NOEL of 5.8 mg a.i./kg bw/d	
		On field		Off field		On field	
		EDE (mg a.i./kg bw)	RQ[1]	EDE (mg a.i./kg bw)	RQ[1]	EDE (mg a.i./kg bw)	RQ[1]
Small Mammal (0.015 kg)							
Reproduction	Insectivore	57.54	**77.8**	3.45	**4.7**	57.54	**9.92**
	Granivore (grain and seeds)	6.15	**8.3**	0.37	0.50	6.15	**1.06**
	Frugivore (fruit)	12.30	**16.6**	0.74	**1.00**	12.30	**2.12**
Medium Sized Mammal (0.035 kg)							
Reproduction	Insectivore	50.44	**68.2**	3.03	**4.1**	50.44	**8.70**
	Granivore (grain and seeds)	5.39	**7.3**	0.32	0.44	5.39	0.93
	Frugivore (fruit)	10.78	**14.6**	0.65	0.87	10.78	**1.86**
	Herbivore (short grass)	57.40	**77.6**	3.44	**4.7**	57.40	**9.90**
	Herbivore (long grass)	32.22	**43.5**	1.93	**2.6**	32.22	**5.56**
	Herbivore (Broadleaf plants)	49.43	**66.8**	2.97	**4.0**	49.43	**8.52**
Large Sized Mammal (1 kg)							
Reproduction	Insectivore	26.95	**36.4**	1.62	**2.2**	26.95	**4.65**
	Granivore (grain and seeds)	2.88	**3.9**	0.17	0.23	2.88	0.50
	Frugivore (fruit)	5.76	**7.8**	0.35	0.47	5.76	**0.99**
	Herbivore (short grass)	30.67	**41.4**	1.84	**2.5**	30.67	**5.29**
	Herbivore (long grass)	17.22	**23.3**	1.03	**1.4**	17.22	**2.97**
	Herbivore (Broadleaf plants)	26.41	**35.7**	1.58	**2.1**	26.41	**4.55**

[1] Bolded values exceed the level of concern

Table 12 Refined risk assessment for small mammals exposed to linuron at an application rate of 1.08 kg a.i./ha using most sensitive NOEC (0.74 mg a.i./kg bw/d) and LOEC (5.8 mg a.i./kg bw/d) and mean nomogram food residue values.

	Food guild (food item)	Mean nomogram residues NOEC of 0.74 mg a.i./kg bw/d				Mean nomogram residues and NOEC of 5.8 mg a.i./kg bw/d	
		On field		Off field		On field	
		EDE (mg a.i./kg bw)	RQ[1]	EDE (mg a.i./kg bw)	RQ[1]	EDE (mg a.i./kg bw)	RQ[1]
Small Mammal (0.015 kg)							
Reproduction	Insectivore	34.91	**47.2**	2.09	**2.8**	34.91	**6.02**
	Granivore (grain and seeds)	3.73	**5.0**	0.22	0.30	3.73	0.64
	Frugivore (fruit)	7.46	**10.1**	0.45	0.61	7.46	**1.29**
Medium Sized Mammal (0.035 kg)							
Reproduction	Insectivore	30.60	**41.4**	1.84	**2.5**	30.60	**5.28**
	Granivore (grain and seeds)	3.27	**4.4**	0.20	0.27	3.27	0.56
	Frugivore (fruit)	6.54	**8.8**	0.39	0.53	6.54	**1.13**
	Herbivore (short grass)	34.83	**47.1**	2.09	**2.8**	34.83	**6.00**
	Herbivore (long grass)	19.55	**26.4**	1.17	**1.6**	19.55	**3.37**
	Herbivore (Broadleaf plants)	29.99	**40.5**	1.80	**2.4**	29.99	**5.17**
Large Sized Mammal (1 kg)							
Reproduction	Insectivore	16.35	**22.1**	0.98	**1.3**	16.35	**2.82**
	Granivore (grain and seeds)	1.75	**2.4**	0.10	0.14	1.75	0.30
	Frugivore (fruit)	3.50	**4.7**	0.21	0.28	3.50	0.60
	Herbivore (short grass)	18.61	**25.1**	1.12	**1.5**	18.61	**3.21**
	Herbivore (long grass)	10.45	**14.1**	0.63	0.8	10.45	**1.80**
	Herbivore (Broadleaf plants)	16.03	**21.7**	0.96	**1.3**	16.03	**2.76**

[1] Bolded values exceed the level of concern

Table 13 Screening level risk of linuron to aquatic organisms.

Organism	Study type	Original toxicity values (mg a.i./L)	Values for RA (mg a.i./L)	Screening level EEC from 2.16 kg a.i./ha (mg a.i./L)	RQ[1]
Daphnia magna	Acute	0.12	0.06	0.27	**4.50**
	Chronic	0.13	0.13	0.27	**2.08**
Rainbow Trout	Acute	3.15	0.315	0.27	0.86
	ELS	0.042	0.042	0.27	**6.43**
Amphibian	Acute (fish)	3.15	0.315	1.44	**4.57**
	Chronic (ED)	<0.009	0.009	1.44	**>160**
Freshwater algae	Acute	0.014	0.007	0.27	**38.6**
Vascular plant (duckweed)	Acute	0.021	0.0105	0.27	**24.6**
Saltwater mysid	Acute	3.4	1.7	0.27	0.16
	Chronic	0.297	0.297	0.27	0.91
Marine fish sheepshead minnow	Acute	0.89	0.089	0.27	**3.03**
	Chronic	0.357	0.357	0.27	0.76
Marine algae	Acute	0.036	0.018	0.27	**15.0**
Higher Tier Microcosm	chronic	0.015	0.015	0.27	**18.0**

1 Bolded values exceed the level of concern

Table 14 Refined risk assessment of aquatic organisms exposed to parent linuron due to runoff and drift at application rates of 1.08, 1.78 and 2.16 kg a.i./ha.

Organism	Study type	Endpoint for risk assessment (mg a.i./L)	Application rate (2160 g a.i./ha)				Application rate (1780 g a.i./ha)				Application rate (1.08 kg a.i./ha)			
			Runoff EEC (mg a.i./L)[1]	RQ[2]	Drift EEC (mg a.i./L)	Drift RQ[2]	Runoff EEC (mg a.i./L)	RQ[2]	Drift EEC (mg a.i./L)	Drift RQ[2]	Runoff EEC (mg a.i./L)	RQ[2]	Drift EEC (mg a.i./L)	Drift RQ[2]
Daphnia magna	Acute	0.06	0.039	0.65	0.016	0.27	0.089	**1.48**	0.013	0.22	0.0535	0.89	0.008	0.13
	Chronic	0.13	0.037	0.28	0.016	0.12	0.082	0.63	0.013	0.10	0.0499	0.38	0.008	0.06
Hyalella azteca	Chronic (Porewater)	<0.012	0.013	**>1.08**	-	-	0.0276	**>2.30**	-	-	0.019	**>1.58**	-	-
Rainbow Trout	ELS	0.042	0.037	0.88	0.016	0.38	0.082	**1.95**	0.013	0.31	0.0499	**1.19**	0.008	0.19
Amphibian	Acute (fish)	0.315	0.191	0.61	0.086	0.27	0.360	**1.14**	0.071	0.23	0.224	0.71	0.043	0.14

Organism	Study type	Endpoint for risk assessment (mg a.i./L)	Application rate (2160 g a.i./ha)				Application rate (1780 g a.i./ha)				Application rate (1.08 kg a.i./ha)			
			Runoff EEC (mg a.i./L)[1]	RQ[2]	Drift EEC (mg a.i./L)	Drift RQ[2]	Runoff EEC (mg a.i./L)	RQ[2]	Drift EEC (mg a.i./L)	Drift RQ[2]	Runoff EEC (mg a.i./L)	RQ[2]	Drift EEC (mg a.i./L)	Drift RQ[2]
	Chronic (endocrine disruption)	<0.009	0.142	**>15.8**	0.086	**>9.56**	0.303	**>33.7**	0.071	**>7.9**	0.188	**>20.9**	0.043	**>4.78**
Freshwater algae	Acute	0.007	0.039	**5.6**	0.016	**2.29**	0.089	**12.6**	0.013	**1.86**	0.0535	**7.64**	0.008	**1.14**
Vascular plant (duckweed)	Acute	0.0105	0.039	**3.71**	0.016	**1.52**	0.089	**8.4**	0.013	**1.24**	0.0535	**5.1**	0.008	0.76
Marine fish sheepshead minnow	Acute	0.089	0.039	0.43	0.016	0.18	0.089	0.99	0.013	0.15	0.0535	0.60	0.008	0.09
Marine algae	Acute	0.018	0.039	**2.17**	0.016	0.89	0.089	**4.92**	0.013	0.72	0.0535	**2.97**	0.008	0.44
Higher Tier Microcosm	Chronic	0.015	0.037	**2.47**	0.016	**1.07**	0.082	**5.47**	0.013	0.87	0.0535	**3.57**	0.008	0.53

[1] EECs for shelterbelts were lower compared to the potato application rate because the model used for shelterbelt was an orchard scenario and was a row crop scenario for potato.

[2] Bolded values exceed the level of concern

Table 15 Refined risk assessment of aquatic organisms exposed to linuron and the aquatic residues of concern from runoff at application rates of 1.08, 1.78 and 2.16 kg a.i./ha.

Organism	Study type	Values for risk assessment (mg a.i./L)	Application rate (shelterbelts 2.16 kg a.i./ha)[1]		Application rate (potato 1.78 kg a.i./ha)		Application rate (carrots 1.08 kg a.i./ha)	
			Runoff EEC (mg a.i./L)	RQ[2]	Runoff EEC (mg a.i./L)	RQ[2]	Runoff EEC (mg a.i./L)	RQ[2]
Daphnia magna	Acute	0.06	0.0698	**1.2**	0.163	**2.7**	0.0624	**1.04**
	Chronic	0.13	0.0672	0.5	0.16	**1.2**	0.0612	0.47
Hyalella azteca	Chronic (Porewater)	<0.012	0.0512	**>4.3**	0.123	**>10.3**	0.0473	**>3.94**
Rainbow Trout	ELS	0.042	0.0672	**1.6**	0.16	**3.8**	0.0612	**1.46**
Amphibian	Acute (fish)	0.315	0.25	0.79	0.552	**1.8**	0.213	0.68
	Chronic (endocrine	<0.009	0.20	**>22.2**	0.488	**>54.2**	0.19	**>21.1**

Organism	Study type	Values for risk assessment (mg a.i./L)	Application rate (shelterbelts 2.16 kg a.i./ha)[1]		Application rate (potato 1.78 kg a.i./ha)		Application rate (carrots 1.08 kg a.i./ha)	
			Runoff EEC (mg a.i./L)	RQ[2]	Runoff EEC (mg a.i./L)	RQ[2]	Runoff EEC (mg a.i./L)	RQ[2]
	disruption)							
Freshwater algae	Acute	0.007	0.0698	**28.6**	0.163	**23.3**	0.0624	**8.91**
Vascular plant (duckweed)	Acute	0.0105	0.0698	**6.6**	0.163	**15.5**	0.0624	**5.94**
Marine fish sheepshead minnow	Acute	0.089	0.0698	0.8	0.163	**1.8**	0.0624	0.70
Marine algae	Acute	0.018	0.0698	**3.9**	0.163	**9.1**	0.0624	**3.47**
Higher Tier Microcosm	Chronic	0.015	0.0672	**4.5**	0.16	**10.7**	0.0612	**4.08**

[1] EECs for shelterbelts were lower compared to the potato application rate because the model used for shelterbelt was an orchard scenario and was a row crop scenarios for potato.
[2] Bolded values exceed the level of concern

Table 16 Comparison of refined risk assessment due to runoff for aquatic organisms at application rates of 1.08, 1.78 and 2.16 kg a.i./ha for linuron, norlinuron and desmethoxy linuron as combined residues and linuron alone.

Organism	Study type	Application rate (shelterbelts 2.16 kg a.i./ha)[1]		Application rate (potato 1.78 kg a.i./ha)		Application rate (carrots 1.08 kg a.i./ha)	
		RQ linuron only[2]	RQ combined residues[2]	RQ linuron only[2]	RQ combined residues[2]	RQ linuron only[2]	RQ combined residues[2]
Daphnia magna	Acute	0.65	**1.2**	**1.48**	**2.7**	0.89	**1.04**
	Chronic	0.28	0.5	0.63	**1.2**	0.38	0.47
Hyalella azteca	Chronic (Porewater)	**>1.08**	**>4.3**	**>2.30**	**>10.3**	**>1.58**	**>3.94**
Rainbow Trout	ELS	0.88	**1.6**	**1.95**	**3.8**	**1.19**	**1.46**
Amphibian	Acute (fish)	0.61	0.79	**1.14**	**1.8**	0.71	0.68
	Chronic (endocrine disruption)	**>15.8**	**>22.2**	**>33.7**	**>54.2**	**>20.9**	**>21.1**
Freshwater algae	Acute	**5.6**	**28.6**	**12.6**	**23.3**	**7.64**	**8.91**
Vascular plant (duckweed)	Acute	**3.71**	**6.6**	**8.4**	**15.5**	**5.1**	**5.94**
Marine fish	Acute	0.43	0.8	0.99	**1.8**	0.60	0.70
Marine algae	Acute	**2.17**	**3.9**	**4.92**	**9.1**	**2.97**	**3.47**
Higher Tier Microcosm	Chronic	**2.47**	**4.5**	**5.47**	**10.7**	**3.57**	**4.08**

[1] EECs for shelterbelts were lower compared to the potato application rate because the models used for the shelterbelt and potatoes were orchard and row crop, respectively.
[2] Bold values exceed the level of concern. Shaded cells indicate LOC was exceeded for risk assessment conducted using combined residues but not for risk assessment conducted using linuron only.

Table 17 Toxic substances management policy considerations – comparison of linuron to TSMP track 1 criteria

TSMP track 1 criteria	TSMP track 1 criterion value		Linuron	Norlinuron and desmethoxylinuron
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes
Persistence[3]	Soil	Half-life ≥ 182 days	DT_{50} <129 days No	Not major TPs in soils
	Water	Half-life ≥ 182 days	DT_{50} <16 days No	DT_{50} <288 Yes
	Sediment	Half-life ≥ 365 days	DT_{50} <87 days No	DT_{50} <507 Yes
	Air	Half-life ≥ 2 days or evidence of long range transport	EPISuite $t_{1/2}$: 1 day No	No information
Bioaccumulation[4]	Log K_{ow} ≥ 5		Log K_{ow} = 3.0 No	Given similar structure of TPs to parent, the Log K_{ow} is expected to be within range of parent linuron: No
	BCF ≥ 5000		49 for whole fish No	Not available
	BAF ≥ 5000		Not available	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			**No, does not meet all TSMP Track 1 criteria**	**No, does not meet all TSMP Track 1 criteria**

[1]All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (in other words, all other TSMP criteria are met).
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4]Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{ow}).

Appendix VIII Revised water modelling

Degradation rates in soil and water were revisited for the current modelling. Revisions to the soil degradation rates were necessary because a new aerobic soil biotransformation study was submitted. The new study used adequate extraction methods that support the exclusion of the unextracted residues from rate calculations. While revised degradation rates in water were similar to previous modelling, revised rates in soil were considerably faster and resulted in lower EEC values than previously reported.

Revised drinking water modelling was conducted on a combined residue of linuron with the transformation products norlinuron, desmethoxy linuron, desmethyl linuron and 3,4-dichloroaniline (3,4-DCA). This is the same residue definition as previous modelling reported in the PRVD, with the addition of 3,4-DCA which was not previously included. The latter compound was included in the current modelling because it was flagged for potential toxicological concerns.

The ecological water modelling was conducted on linuron alone, and also linuron combined with norlinuron and desmethoxy linuron given the environmental relevance of these transformation products. For simplicity, the half-lives used for the ecological modelling on the combined residue were the same as those used for drinking water modelling, despite the ecological residue definition not including desmethyl linuron or 3,4-DCA as compounds of concern. This decision was made mainly for convenience, as excluding these additional transformation products was not expected to have a major effect on the dissipation rates and, consequently, the ecological water EEC values.

The major fate inputs used for the drinking water and ecological modelling are listed in Table 1.

Table 1 Chemical parameters used for modelling. Where two values are given, the first was used for degradation of combined residues and the second for linuron alone.

Parameter	Value (linuron+ROC/linuron only)[1]	Units
K_d	5.8	
Water $t_{1/2}$	375/33	days at 20°C
Sediment $t_{1/2}$	507/16	days at 24°C
Aqueous Phototransformation $t_{1/2}$	54	days, 38° latitude
Hydrolysis $t_{1/2}$	945	days
Soil $t_{1/2}$	225/163	days at 20°C
Molecular Weight	249	g/mol
Vapour Pressure	1.5×10^{-6}	torr
Solubility	63.8	mg/L
Henry's law Constant	3.15×10^{-7}	unitless
Air Diff	4.42×10^{3}	cm^2/day
Heat of Henry	5.4×10^{4}	J/mol

[1] Where two values are given, the first was used for degradation of combined residues and the second for linuron alone.

Soil degradation was taken as the 90% confidence bound on the mean of the representative half-lives calculated from three of the four soils from the submitted aerobic soil study, PMRA# 2917856. The water half-life was taken as the 80th percentile of the representative half-lives of

four water/sediment systems reported in two studies (PMRA# 1695376 and 2431768). The sediment half-life was calculated as the larger of the representative half-lives from two anaerobic water/sediment systems reported in PMRA# 1685611.

The calculated ecological and drinking water EECs and are reported in Tables 2 and 3:

Table 2 EECs (in µg a.i./L) for the ecological risk assessment of linuron.

	Use pattern	Water depth	Water column				Pore water	
			Peak	24 hour	96 hour	21 day	Peak	21 day
Linuron alone	0.72 kg a.i./ha	0.15	159.0	155.0	146.0	119.0	35.3	34.6
		0.80	35.7	35.5	35.0	32.0	12.0	11.8
	1.08 kg a.i./ha	0.15	242.0	236.0	224.0	188.0	57.4	56.4
		0.80	55.0	54.6	53.5	49.9	19.2	19.0
	0.6 + 1.08 kg a.i/ha	0.15	135.0	131.0	124.0	105.0	31.9	31.4
		0.80	30.6	30.3	29.7	27.7	10.7	10.6
	1.78 kg a.i./ha	0.15	396.0	386.0	360.0	303.0	88.0	85.8
		0.80	91.4	90.7	88.5	82.1	28.1	27.6
	2.16 kg a.i./ha	0.15	213.0	207.0	191.0	142.0	41.0	40.0
		0.80	40.7	40.4	39.4	36.6	13.1	12.8
Combined residues	0.72 kg a.i./ha	0.15	219.0	215.0	213.0	190.0	127.0	127.0
		0.80	62.8	62.6	62.4	61.2	47.4	47.3
	1.08 kg a.i./ha	0.15	359.0	353.0	337.0	295.0	197.0	197.0
		0.80	95.3	95.1	94.6	91.9	75.1	75.1
	0.6 + 1.08 kg a.i/ha	0.15	199.0	196.0	187.0	164.0	110.0	109.0
		0.80	53.1	52.9	52.6	51.1	41.8	41.8
	1.78 kg a.i./ha	0.15	567.0	560.0	552.0	488.0	330.0	329.0
		0.80	164.0	164.0	163.0	160.0	123.0	123.0
	2.16 kg a.i./ha	0.15	265.0	260.0	250.0	200.0	134.0	134.0
		0.80	70.6	70.4	69.8	67.2	51.3	51.2

Table 3 Level 1 EECs of the combined residue of linuron in potential sources of drinking water, reported as parent equivalent.

Use pattern	Groundwater (µg a.i./L)		Surface water (µg a.i./L)	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]
Single application of 1.78 kg a.i./ha	21	21	74	13
Single application of 1.08 kg a.i./ha	13	13	45	8

[1] 90th percentile of daily concentrations
[2] 90th percentile of 365-day moving average concentrations
[3] 90th percentile of the peak concentrations from each year
[4] 90th percentile of yearly average concentrations

Appendix IX Linuron Acceptable Uses - Supported Use Pattern versus Labelled Use Pattern

Table 1 Comparison of the supported use pattern versus the labelled use pattern for retained uses

Site/crop	Labelled use pattern	Supported use pattern
Carrot	• One pre-emergence application at 0.52-1.63 kg a.i./ha with a 12-h REI for all activities; or • One post-emergence application at 0.90-2.16 kg a.i./ha with a 12-h REI or • One pre-emergence application at 0.52-1.08 kg a.i./ha plus a post-emergence application made 14 days later at 0.90-2.16 kg a.i./ha, with a 12-h REI	• One pre-emergence application at 1.08 kg a.i./ha with a 2-day REI for all activities; or • One post-emergence application at 1.08 kg a.i./ha with a 8-day REI for scouting and 2-day REI for all other activities; or • One pre-emergence application at 0.6 kg a.i./ha with a 12-hour REI, plus a post-emergence application made 14 days later at 1.08 kg a.i./ha, with a 8-day REI for scouting and a 2-day REI for all other activities.
Potato	• one pre-emergence application at 0.86-2.25 kg a.i./ha with a 12-h REI	• one pre-emergence application at 1.78 kg a.i./ha with a 4-day REI
Parsnip	• One pre-emergence application at 0.62-1.22 kg a.i./ha with a 12-h REI for all activities; or • One post-emergence application at 0.90-2.26 kg a.i./ha with a 12-h REI or • One pre-emergence application at 0.63-0.91 kg a.i./ha plus a post-emergence application made 14 days later at 0.90-1.22 kg a.i./ha, with a 12-h REI	• One pre-emergence application at 1.2 kg a.i./ha with a 2-day REI for all activities; or • One post-emergence application at 1.2 kg a.i./ha with a 9-day REI for scouting and 2-day REI for all other activities; or • One pre-emergence application at 0.6 kg a.i./ha with a 12-hour REI, plus a post-emergence application made 14 days later at 0.9 kg a.i./ha, with a 7-day REI for scouting and a 1-day REI for all other activities.
Asparagus	• One pre-emergence application (before cutting season immediately following pre-emergence discing, treatment may be repeated after the last cutting) at 1.63-2.25 kg a.i./ha with a 12-h REI • One pre-emergence application on seedling asparagus in the first season (dormant application) in Western Canada only at 1.63-2.25 kg a.i./ha with a 12-h REI	• One pre-emergence application (before cutting season immediately following pre-emergence discing) at 1.63 kg a.i./ha with a 4-day REI. OR • One pre-emergence application on seedling asparagus in the first season (dormant application) in Western Canada only at 1.0-1.63 kg a.i./ha with a 4-day REI. OR • One post-harvest application (after the last cutting) at 1.63 kg a.i./ha with a 4-day REI.
Shelterbelts	• Pre-emergence (before bud break, in other words, dormant life stage of shelterbelt vegetation) at 0.38-2.25 kg a.i./ha	• Pre-emergence (before bud break, in other words, dormant life stage of shelterbelt vegetation) at 2.16 kg a.i./ha with a 6-day REI for all activities

Appendix X Label amendments for products containing linuron

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

CANCELLED USES TO BE REMOVED FROM PRODUCT LABELS (No extended phase out schedule):

- Tree fruit (apple, peach, pear, plum/prune, cherry)
- Corn (sweet and field)
- Wheat, barley, oats
- Soybean
- Saskatoon berries
- Pre-emergent combined with post-harvest application to asparagus

CANCELLED USES WITH AN EXTENDED PHASE OUT SCHEDULE:

A subset of cancelled uses were found to lack suitable alternatives for the management of weeds. Therefore, the cancellation of the following uses will be delayed for an additional two years:

- Chokecherries
- Dill
- Coriander and caraway
- Celery
- Sweet white lupins

The following table must be added to the PRINCIPAL DISPLAY PANEL of the label:

Cancellation Date For Cancelled Uses with an Extended Phase Out Period

Crops	Last date of use
Chokecherries (fall seeded plantings), Dill, Coriander, Caraway, Celery, Sweet white lupins	5 November 2024

GENERAL LABEL IMPROVEMENTS:

1) **Update and/or revise the use directions for retained uses and users with an extended phase out period according to required risk mitigation measures.**

2) **On the PRINCIPAL DISPLAY PANEL of all linuron technical and end use product labels, replace 'guarantee' with 'active ingredient'.**

HEALTH

1.1 PRECAUTIONS

1.1.1 Spray Drift Statement

Under PRECAUTIONS, the following label statements are to be added to 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.

1.1.2 Engineering Controls and Personal Protective Equipment

Under PRECAUTIONS, the following label statements are to be added to end-use product labels:

> Wear chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks, and chemical-resistant footwear, during mixing/loading, clean-up and repair. Wear cotton coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks, and chemical-resistant footwear during application. Gloves are not required during application within a closed cab.
>
> 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.
>
> 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.
>
> Limit the amount of product handled per day to [77 kg a.i.] per person for groundboom application when mixing, loading and applying. These restrictions are in place to minimize exposure to individual applicators. Application may need to be performed over multiple days or using multiple applicators.

1.1.3 Restricted-Entry Intervals (REIs)

Under PRECAUTIONS, the following label statement and tables are to be added to end-use product labels:

> DO NOT enter or allow worker entry into treated areas during the restricted-entry interval REI(s) specified in the following tables.

For uses with continued registration (carrots, parsnip, potato, asparagus, shelterbelts), add the following table below:

Restricted-Entry Intervals for Uses with Continued Registration carrots, parsnip, potato, asparagus, shelterbelts)

Crop	Post application activity	REI and/or PHI
Potatoes	All tasks	4 days
Asparagus	All tasks	4 days
Carrots	Scouting	8 days
	All other tasks	2 days
Parsnip	Harvesting	60 days
	Scouting	9 days
	All other tasks	2 days
Shelterbelts	All tasks	6 days

For cancelled uses with an extended phase out period (chokecherries, dill, coriander, caraway, celery, sweet white lupins), add the following interim table below:

Interim Restricted-Entry Intervals Uses with an Extended Phase Out Period (chokecherries, dill, coriander, caraway, celery, sweet white lupins)

Crop	Crop/stage	REI
Celery	Post-emergence	Scouting: 7 days All other activities: 4 days
Dill	Pre-emergence only	2 days
	Post-emergence only	Scouting: 9 days All other activities: 2 days
	Pre- and Post- emergence	Pre-emergent: 12 hrs Scouting: 7 days All other activities: 1 day
Coriander and Caraway	Post-emergence	Scouting: 6 days All other activities: 12 hrs
Sweet White Lupins	Pre-emergence	3 days
Chokecherries (fall seeded plantings)	Pre-emergence of seedlings	4 days

1.2 USE INSTRUCTIONS

1.2.1 Revised Maximum Application Rates and Use Scenarios

a) For uses with continued registration (carrots, parsnip, potato, asparagus, shelterbelts), update use directions with the required information provided in the table below:

Maximum Application Rates and Use Scenarios for Uses with Continued Registration (carrots, parsnip, potato, asparagus, shelterbelts)

Site/crop	Maximum rate (kg a.i./ha)	Application timing	Number of applications per year	Interval between applications
Potatoes	1.78	Pre-emergence	1	N/A
Asparagus	1.63	a. Pre-emergence only OR b. Post-harvest only	1	N/A
Carrots	1.08	a. Pre-emergence only OR b. Post-emergence only	1	N/A
				N/A
	0.6 (pre) 1.08 (post)	OR c. Pre- and Post-emergence	1 (pre) and 1 (post)	14 days
Parsnip	1.2	a. Pre-emergence only OR b. Post-emergence only	1	N/A
	0.6 (pre) 0.9 (post)	OR c. Pre- and Post-emergence	1 (pre) and 1 (post)	14 days
Shelterbelts	2.16	Pre-emergent (dormant stage) Apply as a directed spray under trees at least 1 year old, before weeds are 10 cm high, avoid contact with foliage	1	N/A

b) For cancelled uses with an extended phase out period (chokecherries, dill, coriander, caraway, celery, sweet white lupins), update use directions with the required interim information provided in the table below:

Interim Maximum Application Rates for Uses with an Extended Phase Out Period (chokecherries, dill, coriander, caraway, celery, sweet white lupins)

Site/Crop	Maximum rate (kg a.i./ha)	Application timing	Number of applications per year	Interval between applications
Celery	1.68	Post-emergence	1	N/A
Dill	1.20	a. Pre-emergence only OR b. Post-emergence only	1	N/A
	0.6 (pre) 0.9 (post)	c. Pre- and Post-emergence	1 (pre) and 1 (post)	14 days
Coriander and Caraway	0.80	Post-emergence	1	N/A

Site/Crop	Maximum rate (kg a.i./ha)	Application timing	Number of applications per year	Interval between applications
Sweet White Lupins	1.49	Pre-emergence	1	N/A
Chokecherries (fall seeded plantings)	1.70	Pre-emergence of seedlings	1	N/A

1.2.2 Equipment Limitations

The following label statement is to be added to end-use product labels:

Do not apply using right-of-way sprayers or handheld equipment.

1.2.3 Plant Back Interval

Revise the plant back interval restriction from 4 months to 12 months for carrots, potato, and parsnip.

ENVIRONMENT

2.0 LABEL AMENDMENTS FOR TECHNICAL CLASS PRODUCTS

The following statements are to be added to the "Environmental Hazards/Precautions" section of the linuron Technical Insecticide labels:

TOXIC to aquatic organisms.

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

The following statements are required under the "Disposal" Section of the linuron Technical Insecticide label:

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

2.1 LABEL AMENDMENTS FOR COMMERCIAL CLASS PRODUCTS CONTAINING LINURON

The following statements are to be added to the "Environmental Precautions" section of all product labels:

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

Toxic to birds.

Toxic to small wild mammals.

Toxic to certain beneficial arthropods (which may include predatory and parasitic insects, spiders, and mites). Minimize spray drift to reduce harmful effects on beneficial arthropods 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 of this product when heavy rain is forecast.

Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

The following statements are required under the “Directions for Use” section on all product labels:

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.

DO NOT apply by aerial application equipment.

BUFFER ZONES

Use of low-clearance hooded or shielded sprayers that prevent spray contact with crop, fruit or foliage 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, shelterbelts, woodlots, hedgerows, riparian areas and shrub lands), sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats.

Buffer zones for uses with continued registration (carrots, parsnip, potato, asparagus, shelterbelts)

Method of application	Crop	Buffer zones (metres) required for the protection of:				
		Freshwater habitat of depths:		Estuarine/marine habitat of depths:		Terrestrial habitat:
		Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m	
Field sprayer	Potatoes, shelterbelts	5	1	1	1	4
	Carrots, parsnips	4	1	1	1	3
	Asparagus	5	1	1	1	3

Buffer zones for cancelled uses with an Extended phase out period (chokecherries, dill, coriander, caraway, celery and sweet white lupins)

Method of application	Crop	Interim buffer zones (metres) required for the protection of:				
		Freshwater habitat of depths:		Estuarine/marine habitat of depths:		Terrestrial habitat:
		Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m	
Field sprayer	Celery, chokecherries	5	1	1	1	3
	Coriander and caraway	3	1	1	1	2
	Sweet white lupins, dill	4	1	1	1	3

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 spray 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.

2.2 STORAGE STATEMENTS

The following statement is to be added:

To prevent contamination, store this product away from food and feed.

2.3 UPDATE TO DISPOSAL STATEMENTS

Product manufacturers are required to update the disposal label statement as appropriate for their particular end use product.

VALUE

Label improvements:

1. On the PRINCIPAL DISPLAY PANEL of all end-use product labels, add the following statement outlining the purpose of the product:

   > For the control of labelled broadleaf and grassy weeds on carrots, potatoes, parsnip, asparagus, and shelterbelts.

2. Tank mix partners must be clearly indicated, by product name, on linuron product labels. Specific directions regarding use of the tank mix, or a reference to the tank mix partner label, must be included. A general reference that "this product can be tank mixed with other products" is not acceptable. Therefore, remove any vague or non-specific claims that the product can be tank mixed with another pesticide."

3. Update the resistance management statements on each end-use product label as per Regulatory Directive DIR2013-04, *Pesticide Resistance Management Labelling Based on Target Site / Mode of Action*.

Appendix XI References considered following publication of PRVD2012-02

Note that the following includes only references that were not previously considered in PRVD2012-02.

A. Information Considered in the Updated Toxicological Assessment

List of Studies/Information Submitted by Registrant

PMRA Document Number	Title
2203677	2012, a Pubertal Development and Thyroid Function Assay of Linuron Administered Orally in Intact Juvenile/Peripubertal Female Rats, DACO: 4.5
2431762	2011, a Uterotrophic Assay of Linuron Administered Orally in Ovariectomized Rats, DACO 4.8
2431754	2011, Linuron: Human Recombinant Aromatase Assay, DACO 4.8
2431761	2011, Linuron: Estrogen Receptor Binding (Rat Uterine Cytosol), DACO 4.8
2431764	2013, An Oral (Gavage) Acute Neurotoxicity Study in Rats, DACO 4.5.12
2431763	2012, A 28-Day Oral (Dietary) Immunotoxicity Study of Linuron in Male Wistar Han Rats, DACO 4.8
2249596	2012, Tessenderlo Kerley, Inc.'s Response to Health Canada's Pest Management Regulatory Agency Regarding its Proposed Re-evaluation Decision for Linuron (PRVD2012-02), DACO: NA
1430980	1980, preliminary report on chronic feeding study with linuron in rats, DACO: 4.4.1
1223427	1982, long-term feeding study with (lorox; linuron; Inz-326) in mice – includes batches 18-35, DACO: 4.4.1, DACO: 4.4.2
1146930	1994, carcinogenicity study with reg no.83258 – vinclozolin in Wistar rats, administration in diet for 24 months, DACO: 4.4.2

Additional Information Considered

Published Information

PMRA Document Number	Title
3081840	Ando-Lu J, Sasahara K, Nishiyama K, Takano S, Takahashi M, Yoshida M, Maekawa A. (1998). Strain-differences in proliferative activity of uterine endometrial cells in Donryu and Fischer 344 rats. Experimental and Toxicologic Pathology, 50 (3): 185-190, DACO: 4.8
3081841	Australian Pesticides and Veterinary Medicines Authority. (2011). Diuron Human Health Assessment, DACO: 12.5

3081846	Bloom JC, Brandt JT. (2001). Toxic Responses of the Blood. In Klaassen CD, ed. Casarett & Doull's Toxicology: the Basic Science of Poisons, 6th ed. McGraw-Hill, NY, 389-417. DACO: 4.8
3081849	California Environmental Protection Agency, Reproductive and Cancer Hazard Assessment Section, Office of Environmental Health Hazard Assessment. (2002). Evidence on the Developmental and Reproductive Toxicity of Diuron.
3081850	Creasy D, Bube A, Rijk ED, Kandori H, Kuwahara M, Masson R, Nolte T, Reams R, Regan K, Rehm S, Rogerson P, Whitney K. (2012). Proliferative and Nonproliferative Lesions of the Rat and Mouse Male Reproductive System. Toxicologic Pathology, 40: 40S-121S. DACO: 4.8
3081851	2016, EFSA (European food safety authority). Conclusion on pesticides peer review. Peer review of the pesticide risk assessment of the active substance linuron, DACO: 12.5
2947064	Harris, SB. DeSesso JM (1994). Practical guidance for evaluating and interpreting developmental toxicity tests. Journal of Hazardous Materials, 39:245-266. DACO: 4.8
3081852	Gregory Cope W, (2004). Exposure Classes, Toxicants in Air, Water, Soil, Domestic and Occupational Settings. In Hodgson E, ed. A Textbook of Modern Toxicology, 3rd ed. Wiley-Interscience, NJ, 33-49 DACO: 4.8
3081853	JMPR (2004). Pesticide residues in food – 2004, Joint FAO/WHO Meeting on Pesticides Residues. DACO: 12.5
3081854	Muller A, Jacobson H, Healy E, McMickan S, Istace F, Blaude MN, Howden P, Fleig H, Schulte A, and (EU Working Group on Haemolytic Anaemia) (2006). Hazard Classification of Chemicals Inducing Haemolytic Anaemia: An EU Regulatory Perspective. Regulatory Toxicology and Pharmacology, 45 (3):229-241, DACO: 4.8
3081855	OECD Series on testing and assessment number 43 (2008): Guidance document on mammalian reproductive toxicity testing and assessment, DACO: 4.8
3098139	OECD Series on testing and assessment number 116 (2012): Guidance document 116 on the conduct and design of chronic toxicity and carcinogenicity studies, supporting test guidelines 451, 452, and 453 2nd edition, DACO: 4.8
3081856	Plataniotis G, Castiglione M. (2010). Endometrial Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. Annals of Oncology, 21 (Supplement 5): v41-45. DACO: 4.8
3081857	Solecki R, Davies L, Dellarco Vicki, Dewhurst I, Raaij MV, Tritscher A (2005). Guidance on setting acute reference dose (ARfD) for pesticides. Food and Chemical Toxicology 43: 1569-1593, DACO: 4.8
3081858	USEPA (2013). Linuron: Section 3 Human Health Risk Assessment for Proposed Use on Coriander, Dill, Horseradish, Parsley, Celeriac, Rhubarb, and Pea (Dry). DACO: 12.5
3081859	USEPA (2008). Linuron – Human Health Risk Assessment to Support a Section 18 Emergency Exemption for Use on Lentils in Washington and Idaho. DACO: 12.5
3038901	USEPA (2015). Linuron – EDSP Weight of Evidence Conclusions on the Tier 1 Screening Assays for the List 1 Chemicals. DACO: 12.5
3081860	USEPA (2016). Linuron human health draft risk assessment for registration review. DACO: 12.5

3081861	USEPA (2019). Linuron Revised human health draft risk assessment for registration review. DACO: 12.5
3081862	USEPA (2019). Linuron. Response to Comments Regarding HED's human health assessment in support of registration review, DACO: 12.5
3081863	Wilson VS, Lambright CR, Furr JR, Howdeshell KL, Gray Jr. E. (2009). The herbicide linuron reduces testosterone production from the fetal rat testis during both in utero and in vitro exposures. Toxicology Letters, 186:73-77. DACO: 4.8
3081864	Woolf AD, Wright, RO. (2004). Chapter 21: Methemoglobinemia. In Medical Toxicology, ed. 3rd ed. Lippincott Williams & Wilkins, 92-98, DACO: 4.8

B. Information Considered in the Updated Dietary Assessment

Additional Information Considered

Published Information

PMRA Document Number	Title
	Organization for Economic Co-operation and Development (OECD). 2013. Guidance Document on Residues in Livestock. Series on Pesticides. No. 73. Published.
	United States Environmental Protection Agency (USEPA). 2013. Linuron: Acute and Chronic Dietary (Food and Drinking Water) Exposure and Risk Assessment for the Section (3) Registration Action on Coriander, Dill, Horseradish, Parsley, Rhubarb, and Dry Pea. Published.
	United States Environmental Protection Agency (USEPA). 2013. Linuron: Section 3 Human Health Risk Assessment for Proposed Use on Coriander, Dill, Horseradish, Parsley, Celeriac, Rhubarb, and Pea (Dry). Published
	United States Environmental Protection Agency (USEPA). 2010. Linuron (035506). Screening Level Usage Analysis (SLUA). Published.

Unpublished Information

PMRA Document Number	Title
2249596	2012. Tessenderlo Kerley, Inc.’s Response to Health Canada’s Pest Management Regulatory Agency Regarding Its Proposed Re-evaluation Decision for Linuron (PRVD2012-02).
3004362	2012. Canadian Horticultural Council Response to Linuron Consultation – PRVD 2012-02.

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

List of Studies/Information Submitted by Registrant

PMRA Document Number	Title
2851865 2887226	Wyatt, D. R., 2018. Dissipation of Dislodgeable Foliar Residues from Celery Foliage Following Treatment with One Foliar Application of Lorox® DF (2017). NovaSource/Tessenderlo Kerley, Inc. Golden Pacific Laboratories (Fresno, CA). February 14, 2018 and May 2, 2018.
2531618	Hutton, E. 2015. The In Vivo Percutaneous Absorption of Radiolabelled Linuron in the Concentrate Formulation, a 1:300 and a 1:600 In-Use Spray Dilution in the Rat. Charles River, UK. Tessenderlo Kerley Inc. Jan.15, 2015.
2531617	Blackstock, C. and J. Vinall. 2015. The In Vitro Percutaneous Absorption of Radiolabelled Linuron in the Concentrate Formulation and Two In-Use Spray Dilutions through Human and Rat Skin. Charles River, UK. Tessenderlo Kerley Inc. Jan.15, 2015.
2249596	Tessenderlo Kerley, Inc. 2012. Tessenderlo Kerley, Inc's Response to Health Canada's Pest Management Regulatory Agency Regarding its Proposed Re-evaluation Decision for Linuron (PRVD2012-02). Nov.8, 2012.
1612300	E.I du Pont Canada Company, 2008. DACO 5.2 Use-Site Description and Exposure Scenario: Linuron. E.I du Pont Canada Company, Ontario. Unpublished. June 2008.
1613477	Makhteshim Agan of North America Inc., 2008. Use Description Scenario for Afolan F 450. Makhteshim Agan of North America Inc., North Carolina. Unpublished. June 2008.
1738207	Hardwick, T., 2000. (14C)-Linuron: In vivo dermal absorption in the rat. E.I. du Pont de Nemours & Co., Inc., Delaware. Unpublished. July 2000.
3004362	Canadian Horticultural Council, 2012. Canadian Horticultural Council Response to LINURON CONSULTATION - PRVD 2012-02. Sept. 24, 2012.
3006825	Tessenderlo Kerley, 2016. Letter to PMRA RE: Linuron Reevaluation in Canada and Registration Review in the United States. December, 8, 2016. Unpublished.
3054080	Kern, 2019. In Vivo Percutaneous Absorption of [14C]-Linuron in the Rat. Charles River Laboratories Ashland, LLC. Tessenderlo Kerley, Inc. Phoenix, AZ. Unpublished. November 8, 2019.

Additional Information Considered

Published Information

PMRA Document Number	Title
1109755	U.S. EPA. 1995. Reregistration Eligibility Decision (RED) for Linuron. March 1995.
1281899	European Commission, 1996. Linuron Volume 1. October 1996.

Unpublished Information

PMRA Document Number	Title
2115788	Agricultural Re-entry Task Force (ARTF). 2008. Data Submitted by the ARTF to Support Revision of Agricultural Transfer Coefficients. Submission# 2006-0257.
1913109	AHETF, 2009. Agricultural Handler Exposure Scenario Monograph: Open Cab Groundboom Application of Liquid Sprays. Report Number AHE1004. December 23, 2009.
2572746	AHETF, 2015. Agricultural Handler Exposure Scenario Monograph: Closed Cab Airblast Application of Liquid Sprays. Report Number AHE1005-1. March 31, 2015.

E. Information Considered in the Updated Environmental Assessment

List of Studies/Information Submitted by Registrant

PMRA Document Number	Title
2431768	2014, 14C Linuron-Aerobic Aquatic Metabolism in Two Aerobic Water/Sediment Systems, DACO: 8.2.3.5
2849050	2017, Linuron: Well Water Monitoring, Canada 2017, DACO: 8.6.1
2917856	2018, AEROBIC SOIL METABOLISM OF [14C]LINURON IN FOUR SOILS, DACO: 8.2.3.4.2
2431769	2014, Linuron: Canary (Serinus canaria) Dietary Acute Toxicity Test, DACO: 9.6.2.3,9.9
2185692	2012, Linuron - Fish Short-Term Reproduction Assay with Fathead Minnow (Pimephales promelas), DACO: 9.5.4

Additional Information Considered

Published Information

PMRA Document Number	Title
1957282	United States Department of Agriculture (USDA), 2008, Pesticide Data Program Annual Summary, Calendar Year 2007. Science and Technology Programs, Agricultural Marketing Service, www.ams.usda.gov/pdp, DACO: 8.6.
2042915	Kurt-Karakus, P.B., C. Teixeira, J. Small, D. Muir, and T.F. Bidleman, 2011, Current-Use Pesticides In Ontario, Canada, Inland Lakes, Precipitation, Air and Zooplankton Samples, Env. Toxicol. Chem., DOI: 10.1002/etc.545, DACO: 8.6.
2101142	Struger, J., J. Grabuski, S. Cagampan, M. Rondeau, E. Sverko, and C. Marvin, 2011, Occurrence and Distribution of Sulfonylurea and Related Herbicides in Central Canadian Surface Waters 2006-2008, Bull. Environ. Contam. Toxicol., 87: 420-425, DACO: 8.6.
2102603	Giroux, I. and B. Sarrasin, 2011, Pesticides et nitrates dans l'eau souterraine près de cultures de pommes de terre - Échantillonnage dans quelques régions du Québec en 2008 et 2009. Ministère du Développement durable, de l'Environnement et des Parcs, Direction du suivi de l'état de l'environnement, Centre d'expertise en analyse environnementale du Québec, DACO: 8.6.
2149078	Elliott, J. et al., 2010, Groundwater vulnerability to pesticide contamination in the Assiniboine Delta Aquifer. Environment Canada Pesticide Science Fund, DACO: 8.6.
2170903	Prince Edward Island (PEI) Department of Environment, Energy and Forestry, 2010, Summary of Statistics from the PEI Groundwater Monitoring Program (2004 - 2009), notes from 2008, and the analyte list from 2009, DACO: 8.6.
2170936	Giroux, I., N. Roy, and C. Lamontagne, 2010, Présence de Pesticides dans l'Eau Souterraine en Milieu Agricole : Étude Pilote du Bassin Versant de La Rivière Châteauguay. Canadian Water Resources Journal., 35(4): 527-542, DACO: 8.6.
2312776	United States Department of Agriculture (USDA), 2011, Pesticide Data Program Annual Summary, Calendar Year 2009. Science and Technology Programs, Agricultural Marketing Service, www.ams.usda.gov/pdp, DACO: 8.6.
2312778	United States Department of Agriculture (USDA), 2013, Pesticide Data Program Annual Summary, Calendar Year 2010. Science and Technology Programs, Agricultural Marketing Service, www.ams.usda.gov/pdp, DACO: 8.6.
2312780	United States Department of Agriculture (USDA), 2012, Pesticide Data Program Annual Summary, Calendar Year 2011. Science and Technology Programs, Agricultural Marketing Service, www.ams.usda.gov/pdp, DACO: 8.6.
2424839	Environment Canada. 2007. Surveillance of Pesticide Residues in Surface Water in an Intensive Agricultural Region of Northwestern New Brunswick – 2006, Part 1. Internal Monitoring Project Report. A Cooperative Project by Environment Canada, Agriculture and Agri-Food Canada and the New Brunswick Department of Environment and Local Governments. A Pesticides Science Fund Project. December 2007, DACO: 8.6.
2424841	Environment Canada. 2007. Surveillance of Pesticide Residues in Surface Water in an Intensive Agricultural Region of Northwestern New Brunswick – 2006, Part 2. Internal Monitoring Project Report. A Cooperative Project by Environment Canada, Agriculture and Agri-Food Canada and the New Brunswick Department of Environment and Local Governments. A Pesticides Science Fund Project. December 2007, DACO: 8.6.

2424842	Environment Canada. 2008. Surveillance of Pesticide Residues in Surface Water and Groundwater in an Intensive Agricultural Region of Northwestern New Brunswick - 2007. Internal Monitoring Project Report. A Cooperative Project by Environment Canada, Agriculture and Agri-Food Canada and the New Brunswick Department of Environment and Local Governments. A Pesticides Science Fund Project. December 2007, DACO: 8.6.
2468268	Government of Prince Edward Island. 2014. Summary of pesticide detections in groundwater, surface water and sediment from the PEI Pesticide Monitoring Program (2004-2014). Downloaded from www.gov.pe.ca/pesticidemonitoring on October 24, 2014, DACO: 8.6.
2505827	United States Department of Agriculture (USDA), 2014, Pesticide Data Program Annual Summary, Calendar Year 2014. Science and Technology Programs, Agricultural Marketing Service, www.ams.usda.gov/pdp, DACO: 8.6.
2505828	United States Department of Agriculture (USDA), 2015, Pesticide Data Program Annual Summary, Calendar Year 2015. Science and Technology Programs, Agricultural Marketing Service, www.ams.usda.gov/pdp, DACO: 8.6.
2525751	Environment Canada. 2011. Presence and levels of priority pesticides in selected Canadian aquatic ecosystems. Water Science and Technology Directorate, Environment Canada. ISBN 978-1-100-18386-2. 111 pages, DACO: 8.6.
2526162	Z. Xing, L. Chow, H. Rees, F. Meng, S. Li, B. Ernst, G. Benoy, T. Zha and L.M. Hewitt. 2013. Influences of sampling methodologies on pesticide-residue detection in stream water. Archives of Environmental Contamination and Toxicology 64: 208-218, DACO: 8.6.
2526164	A.F. Choquette and S.E. Kroening. 2009. Water quality and evaluation of pesticides in lakes in the Ridge citrus region of central Florida: U.S. Geological Survey Scientific Investigations Report 2008-5178, DACO 8.6.
2544468	I. Giroux. 2014. Présence de pesticides dans l'eau au Québec - Zones de vergers et de pommes de terre, 2010 à 2012. Québec, Ministère du Développement durable, de l'Environnement et de la Lutte contre les changements climatiques. Direction du suivi de l'état de l'environnement, ISBN 978-2-550-71747-8 (PDF), DACO: 8.6.
2561884	I. Giroux. 2015. Présence de pesticides dans l'eau au Québec: Portrait et tendances dans les zones de maïs et de soya - 2011 à 2014, Québec, Ministère du Développement durable, de l'Environnement et de la Lutte contre les changements climatiques, Direction du suivi de l'état de l'environnement, ISBN 978-2-550-73603-5, Available: http://www.mddelcc.gouv.qc.ca/eau/flrivlac/pesticides.htm, DACO: 8.6.
2634013	California Environmental Protection Agency, Department of Pesticide Regulation, 2014, Sampling for Pesticide Residues in California Well Water - 2013 Update. Twenty-eighth Annual Report. May 2014, DACO: 8.6.
2634021	California Environmental Protection Agency, Department of Pesticide Regulation, 2015, Sampling for Pesticide Residues in California Well Water - 2014 Update. Twenty-nineth Annual Report. January 2015, DACO: 8.6.
2678735	California Department of Pesticide Regulation, 2016, Sampling for pesticide residues in California well water. 2015 Annual Report, DACO: 8.6.
2678737	California Department of Pesticide Regulation, 2016, Sampling for pesticide residues in California well water. 2016 Annual Report, DACO: 8.6.
2679623	M. Larocque, S. Gagné, D. Barnetche, G. Meyzonnat, M.-H. Graveline and M.-A. Ouellet, 2015, Projet de connaissance des eaux souterraines de la zone Nicolet et de la partie basse de la zone Saint-François. Rapport Final, DACO: 8.6.
2745506	Prince Edward Island Department of Communities, Land and Environment, 2016, PEI Pesticide Monitoring Program - Stream Water Pesticide Analysis, 2009-2015, DACO: 8.6.

2839822	Alberta Agriculture and Forestry - Irrigation and Farm Water Branch (Water Quality Section), 2017, Unpublished water monitoring data for pesticides in Albert irrigation water, from 2006 to 2016. Daco: 8.6.
2849050	Purdy, J., 2017, Linuron: Well Water Monitoring, Canada 2017, Produced by Abacus Consulting Services Ltd. for Tessenderlo Kerley, Inc., Report No ABA 1706, DACO: 8.6.
2945668	Metcalfe, C.D., P. Helm, G. Paterson, G. Kaltenecker, C. Murray, M. Nowierski, and T. Sultana, 2019, Pesticides related to land use in watersheds of the Great Lakes basin, Sci. Tot. Env., 648: 681-692, DACO: 8.6.
3118442	Califonia Department of Pesticide Regulation (DPR), 2020, Surface Water Protection Program Database, accessed on February 27, 2020, URL: https://www.cdpr.ca.gov/docs/emon/surfwtr/surfcont.htm, DACO: 8.6.
3118444	US Geological Survey (USGS), 2020, National Stream Quality Accounting Network (NASQAN), accessed on February 27, 2020, URL: https://cida.usgs.gov/nawqa_www/nawqa_data_redirect.html, DACO: 8.6.
3120373	US Geological Survey (USGS), 2020, National Water Quality Assessment Program (NAWQA), https://cida.usgs.gov/quality/rivers/home, DACO: 8.6.
3033298	Orton, F. et al., 2018, Scientific Reports 8:9124, Exposure to an anti-androgenic herbicide negatively impacts reproductive physiology and fertility in Xenopus tropicalis, DACO: 12.5.9
3038894	European Commission, 2015, European Food Safety Agency Volume 3 (PPP) Annex B.8, Draft Renewal Assessment Report. Linuron, DACO: 12.5.8
3038895	European Commission, 2015, European Food Safety Agency Volume 3 (AS) Annex B.8, Draft Renewal Assessment Report. Linuron, DACO: 12.5.8
3038896	European Commission, 2015, European Food Safety Agency Volume 3 (PPP) Annex B.9, Draft Renewal Assessment Report. Linuron, DACO: 12.5.9
3038898	U.S. EPA, 2016, Environmental Fate and Effects Division, Office of Pesticide Programs., Ecological Risk Assessment for the Registration Review of Linuron, DACO: 12.5.8,12.5.9
3038899	U.S. EPA, 2019, Environmental Fate and Effects Division, Office of Pesticide Programs. Docket Number EPA-HQ-OPP-2010-0228, Linuron - Proposed Interim Registration Review Decision, DACO: 12.5.8,12.5.9
3038901	U.S. EPA, 2015, Health Effects Division and Environmental Fate and Effects Division, Office of Pesticide Programs., EDSP: Weight of evidence analysis of potential interaction with the estrogen androgen or thyroid pathways. Chemical: Linuron, DACO: 12.5.9

Unpublished Information

PMRA Document Number	Title
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2170892	Environment Canada, 2007, Unpublished groundwater monitoring data from New Brunswick. Received June 2011, DACO: 8.6.
2170899	Environment Canada. (2006). Unpublished groundwater monitoring data from PEI (2004 - 2006). Received June 2011, DACO: 8.6.
2171036	Ontario Provincial Groundwater Monitoring Network, 2010, Unpublished groundwater monitoring data from Ontario (2002 – 2010), Provincial Groundwater Monitoring Network (PGMN). Received March 2102, DACO: 8.6.

2424843	Environment Canada, 2014, Surveillance of Pesticide Residues in Surface water, sediment and groundwater in agricultural regions of Prince Edward Island, New Brunswick and Nova Scotia. 2008. Unpublished report, DACO: 8.6.
2548877	Pest Management Regulatory Agency, 2015, Pesticides detected in water and soil samples collected during Bee Mortality Incidents in 2013 and 2014, Health Canada. Unpublished, DACO: 8.6.
2681876	Environment Canada, 2016, Unpublished monitoring data for neonicotinoid insecticides, fungicides (strobins and conazoles), acid herbicides, neutral herbicides, op insecticides, sulfonyls herbicides and carbamate pesticides in Ontario surface water in 2015, DACO: 8.6.
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