Re-evaluation Decision RVD2020-01

Clodinafop-propargyl and Its Associated End-use Products

Final Decision

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Re-evaluation Decision

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

Clodinafop-propargyl is a registered herbicide for use in western Canada on spring and durum wheat. Currently registered products containing clodinafop-propargyl can be found in the Pesticide Label Search and in Appendix I.

The regulatory approach for the re-evaluation of clodinafop-propargyl was first presented in the Proposed Re-evaluation Decision PRVD2018-16, *Clodinafop-propargyl and Its Associated End-use Products*,[1] which underwent a 90-day consultation period ending on 26 December 2018. PRVD2018-16 proposed continued registration provided that proposed risk mitigation measures, to protect human health and the environment, are implemented.

Health Canada received comments and information relating to the health assessments. Respondents are listed in Appendix III. These comments are summarized in Appendix II along with the responses by Health Canada. The comments and new data/information did not result in revisions to the risk assessments (see Science Evaluation Update), and did not result in changes to the proposed regulatory decision as described in PRVD2018-16. A reference list of information used as the basis for the proposed re-evaluation decision is included in PRVD2018-16, and further information used in the re-evaluation decision is listed in Appendix VI of this document.

This document presents the final regulatory decision[2] for the re-evaluation of clodinafop-propargyl, including the required risk mitigation measures to protect human health and the environment. All products containing clodinafop-propargyl that are registered in Canada are subject to this re-evaluation decision.

Outcome of Science Evaluation

Clodinafop-propargyl is used in western Canada on spring and durum wheat. It provides effective control of wild oats, which is one of the major weed problems for wheat growers in western Canada.

With respect to human health, the health risks associated with the use of clodinafop-propargyl and associated end-use products are acceptable when these products are used according to the revised label directions.

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*.

Based on the available scientific information, risks to the environment were found to be acceptable when clodinafop-propargyl is used according to the revised label directions, which include advisory statements and spray buffer zones.

Regulatory Decision for Clodinafop-propargyl

Health Canada has completed the re-evaluation of clodinafop-propargyl. Under the authority of the *Pest Control Products Act*, Health Canada has determined that continued registration of products containing clodinafop-propargyl is acceptable. An evaluation of available scientific information found that uses of clodinafop-propargyl products meet current standards for protection of human health and the environment when used according to revised label directions, which include new mitigation measures. No additional data 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 revised label statements and/or mitigation measures required, as a result of the re-evaluation of clodinafop-propargyl, are summarized below. Refer to Appendix V for details.

Human Health

To protect workers, homeowners and those entering treated areas from occupational/residential exposure, the following risk-reduction measures are required:

- A spray drift statement standardized across all use product labels for label consistency.
- Additional personal protective equipment (PPE) for mixers/loaders and ground boom applicators.
- A closed mix/load system when handling more than 15 kilograms of active ingredient (kg a.i.) in a day.

To protect consumers from dietary exposure, the following risk-reduction measures are required:

- A plant-back interval of 30 days.
- Preharvest intervals of 60 days for grain and straw, 30 days for hay, and 7 days for forage.

Environment

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

- Standard hazard statements to inform users of the potential toxic effects on non-target terrestrial plants.
- A hazard statement to inform users of the presence of aromatic petroleum distillates and their toxicity to aquatic organisms.
- Advisory statement to inform users that residues of clodinafop-propargyl have the potential to leach to groundwater.

- To reduce the potential for runoff of clodinafop-propargyl to adjacent aquatic habitats, precautionary label statements for sites with characteristics that may be conducive to runoff and when heavy rain is forecasted.
- To mitigate the potential exposure of clodinafop-propargyl to non-target organisms, addition of spray buffer zones to protect sensitive terrestrial and aquatic habitats from spray drift.

Next Steps

To comply with this decision, the required mitigation measures must be implemented on all product labels sold by registrants no later than **24 months** after the publication date of this decision document. 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 clodinafop-propargyl 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 test data on which the decision is based (as referenced in PRVD2018-16 and this document) are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service.

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

Science Evaluation Update

1.0 Health Risk Assessment

1.1 Toxicology Assessment for Clodinafop-propargyl

Comments received during the consultation period covered a range of issues pertaining to the toxicology assessment, including: 1) the vascular tumour analysis; 2) the NOAEL/LOAEL (no/lowest observed adverse effects levels) values for several studies; and 3) the choice of point of departure (POD) endpoint, and study selected for the toxicological reference value for the occupational exposure scenarios in PRVD2018-16. Newly submitted data for clodinafop-propargyl included detailed histopathology for the two-generation dietary reproductive toxicity study, as well as historical control (HC) and individual animal data analysis for several key findings in the two-generation dietary reproductive toxicity study, the gavage developmental toxicity study in rats, the 18-month dietary oncogenicity study in mice, and the 90-day dietary study in dogs. In addition, the most recent United States Environmental Protection Agency (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 PRVD2018-16 were revisited. However, this did not result in a change to the assessment in PRVD2018-16, and, therefore, all Health Canada's conclusions remain unchanged.

Detailed responses to the comments received are provided in Appendix II. Toxicological reference values are provided in Appendix IV, Table 1.

1.2 Dietary, Occupational and Non-Occupational and Environmental Exposure and Risk Assessments

The dietary, occupational and non-occupational and environmental assessments for clodinafop-propargyl were previously conducted and published in PRVD2018-16. All risks were shown to be acceptable when additional mitigation measures are followed. No comments specific to these assessments were received, therefore, Health Canada's risk assessments remain unchanged.

2.0 Conclusion of Science Evaluation

Clodinafop-propargyl is a widely used grass herbicide in spring and durum wheat. It provides effective control of wild oats, which is one of the major weed problems for wheat growers across Canada. It can be tank mixed with a wide range of broadleaf herbicides to broaden weed control spectrum and reduce application passes.

With respect to human health and the environment, risks associated with the use of clodinafop-propargyl and associated end-use products are considered to be acceptable when these products are used according to revised label directions.

List of Abbreviations

ADI	acceptable daily intake
a.i.	active ingredient
ASAE	American Society of Agricultural Engineers
AST	aspartate aminotransferase
ARfD	acute reference dose
bw	bodyweight
CAF	composite assessment factor
CARC	Cancer Assessment Review Committee
EFSA	European Food Safety Authority
F_1	first generation
F_2	second generation
HC	historical control
IPCS	International programme on chemical safety
kg	kilogram
LDT	lowest dose tested
LOAEL	lowest observed adverse effect level
mg	milligram
MOE	margin of exposure
NOAEL	no observed adverse effect level
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPE	personal protective equipment
PRVD	proposed re-evaluation decision
POD	point of departure
REI	restricted-entry interval
USEPA	United States Environmental Protection Agency

Appendix I Registered Clodinafop-propargyl Products in Canada[1]

Table 1 Products Requiring Label Amendments

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Active ingredient (%, g/L)
29495	Commercial	Adama Agricultural Solutions Canada LTD	Mana Ladder 240 EC	Emulsifiable Concentrate or Emulsion	240 g/L
30428	Commercial		Cadillac		240 g/L
32497	Commercial		Ladder All In		80 g/L
32539	Commercial		Cadillac One		80 g/L
30137	Commercial	Albaugh LLC	Slam'r Clodinafop Herbicide		240 g/L
31053	Commercial		Slam'r Herbicide		240 g/L
29614	Commercial	Arysta Lifescience North America, LLC	Nextstep NG Herbicide		60 g/L
29299	Commercial	Production Agriscience Canada Company	Harmony Grass		128 g/L
31689	Commercial		Harmony Grass 240 EC Herbicide		240 g/L
29526	Commercial	Interprovincial Cooperative Limited	Legend A		240 g/L
29711	Commercial	Newagco Inc.	MPower Aurora® Clodinafop Herbicide		240 g/L
30949	Commercial		MPower Aurora-I Clodinafop Herbicide		240 g/L
29172	Commercial	Nufarm Agriculture Inc.	Signal Herbicide		240 g/L
29962	Commercial		Nufarm Clodinafop Herbicide		240 g/L
30168	Commercial		Nufarm Signal Herbicide		240 g/L
31434	Commercial		Signal F Herbicide		112 g/L (+ fluoxypyr 217 g/L)
31261	Commercial	Farmers Business Network Canada Inc.	Foax Herbicide		240 g/L
33323	Commercial		FBN Clodinafop		240 g/L
24067	Commercial	Syngenta Canada Inc.	Horizon 240EC Herbicide		240 g/L
24076	Commercial		Horizon 240EC Herbicide (component of horizon herbicide tank mix)		240 g/L
29089	Commercial		Horizon NG Herbicide		60 g/L
29855	Commercial		Traxos Herbicide		25 g/L (+ pinoxaden 25 g/L)
30341	Commercial		Foothills NG Herbicide		60 g/L
31674	Commercial		Traxos®two Grass Component		25 g/L (+ pinoxaden 25 g/L)
33133	Commercial	Agrogill Chemicals PTY LTD	Agrogill Clodinafop 240EC		239 g/L
30743	Commercial	UPL NA Inc.	Current 240 EC Herbicide		240 g/L

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Active ingredient (%, g/L)
31157	Manufacturing Concentrate		Current 240 EC MUP Herbicide		240 g/L
29373	Technical Active	Adama Agricultural Solutions Canada LTD	Mana Clodinafop-Propargyl Technical	Dust	97.1%
29425	Technical Active	Agrogill Chemicals PTY LTD	Clodinafop-propargyl Agrogill Technical Grade Active Ingredient	Solid	98.0%
29424	Technical Active	Newagco Inc.	Newagco Clodinafop-Propargyl Herbicide Technical		95.2%
33168	Technical Active		Newagco Clodinafop Herbicide Technical		96.8%
30762	Technical Active	Farmers Business Network Canada Inc.	Technical Clodinafop Herbicide		96.75%
30218	Technical Active	Sinon USA Inc.	Clodinafop-propargyl Sinon Technical Active Ingredient		98.0%
27430	Technical Active	Syngenta Canada Inc.	Clodinafop-propargyl Technical Active Ingredient	Dust or Powder	98%
29432	Technical Active	UPL NA Inc.	UPI Clodinafop-propargyl Technical Herbicide		97.7%

[1] as of 11 October 2019, excluding discontinued products or products with a submission for discontinuation

Appendix II Comments and Responses

In response to the consultation for the clodinafop-propargyl proposed re-evaluation decision, Health Canada received written comments (respondents' affiliations listed in Appendix III). These comments were considered during the final decision phase of this re-evaluation. Summarized comments and Health Canada's responses, are provided below.

1.0 Comments Related to the Health Risk Assessment

1.1 Toxicology

1.1.1a Comment – Vascular Tumours

The registrant provided comments stating that the increased incidence of vascular tumours noted in the high dose female group of the 18-month dietary oncogenicity study in mice was not treatment-related. Their rationale included the following: 1) the tumours were noted in one sex only and at a very low incidence rate; 2) the incidences fell within the HC range, and 3) combining benign (hemangiomas) and malignant (angiosarcoma) incidences across all tissue types is not appropriate from a cancer biology perspective. It was further suggested that Health Canada use the USEPA assessments, particularly the 2006 USEPA cancer assessment review committee (CARC) report, along with numerous cited or submitted (PMRA# 2947056) published articles from the scientific literature to reconsider these tumours as incidental and unrelated to exposure to clodinafop-propargyl.

1.1.1b Response

Health Canada revisited the incidences of vascular tumours observed in the 18-month dietary oncogenicity study in mice in light of comments, scientific rationales, and HC data. The following reflects the conclusions from the weight of evidence review:

- The submitted or cited scientific rationales and articles discussed a lack of progression, site concordance, and similarity in gene expression profile of hemangiomas and angiosarcomas in humans. The USEPA CARC (2006) report, which was previously considered and included in the reference list of the PRVD2018-16, addressed the scientific basis of these rationales concluding that combining incidences of vascular tumours from all tissues sites was appropriate.
- The sum of the incidences of murine vascular tumours from all tissue sites should be considered in the evaluation of the carcinogenic potential of clodinafop-propargyl. The comments did not adequately support a rationale for not combining these tumour incidences in mice. The USEPA CARC report concurs. A scientific rationale written in accordance with the IPCS framework to consider the relevance of these tumours to humans was also not submitted or available.
- The newly submitted HC data was relevant to the incidence rate of vascular tumours in the liver only, which was previously available and considered in PRVD2018-16. Due to a lack of HC data to address the incidence rate of murine vascular tumours from all tissue sites, the tumour data could not be assessed against appropriate HC background rates.

Furthermore, the concurrent control group, unless aberrant, is the most relevant comparator for determining treatment-related effects within a study.

- When the incidences of hemangiomas and angiosarcomas were combined and analyzed across all tissue sites, a statistically significantly increase (trend and pairwise) and dose-related trend was observed in the high dose female mice group compared to concurrent controls. However, it should also be noted that a revision to Health Canada's interpretation of the hemangiomas and angiosarcomas data would have no impact on the cancer risk assessment, as this was based on the linear, low-dose extrapolation method using the prostate tumour data.

In summary, Health Canada's conclusion regarding vascular tumours as noted in PRVD2018-16 remains unchanged.

1.1.2a Comment – Toxicological reference value selected for the short- and intermediate-term dermal and inhalation exposure scenarios

The registrant contested the selection of the offspring NOAEL at the dose level of 0.4 mg/kg bw/day in the two-generation dietary reproductive toxicity study. This dose level was used as the POD for deriving the toxicological reference value for the occupational exposure scenarios in the PRVD2018-16. The registrant requested that Health Canada select the offspring NOAEL and the POD at the next higher dose level of 3.8 mg/kg bw/day for this study, in agreement with the latest USEPA and EFSA assessments.

The registrant also requested that the NOAELs for the 90-day dietary toxicity study in dogs and the gavage developmental toxicity study in rats be revised to higher dose levels and not be used as the POD for deriving the toxicological reference value. To further support their comments, relevant histopathology data, HC data, as well as individual animal data analysis, and other scientific rationales were provided or cited.

1.1.2b Response

Health Canada revisited the NOAELs selected for each of the three toxicity studies identified by the registrant, and subsequently, the selection of the appropriate study for the short- and intermediate-term dermal and inhalation risk assessments. Each study is discussed separately below.

A. 90-day dietary toxicity study in dogs

In PRVD2018-16, a NOAEL of 0.4 and 1.9 mg/kg bw/day for males and females respectively, was selected for this study. The LOAEL of 8 and 7 mg/kg bw/day in males and females, respectively, was based on decreased cholesterol levels, increased AST activity, and increased incidence of skin lesions noted during the routine examination of the animals.

Based on a review of laboratory-specific HC data submitted following publication of PRVD2018-16, cholesterol and AST activity levels in test animals were judged to be within the HC range at the LOAEL. However, a treatment-related effect in these clinical chemistry parameters was not excluded at the high dose level due to a dose-related trend and a large difference compared to the concurrent control values. A re-examination of the individual animal

data in this study and in the 12-month dietary toxicity study in dogs indicated that these lesions were transient in nature, did not persist until necropsy, and were not corroborated by the histopathology results, except at dose levels of approximately 16 mg/kg bw/day in both studies.

Therefore, the NOAEL for the 90-day dietary toxicity study in dogs was revised to 8 and 7 mg/kg bw/day in males and females, respectively. However, this did not change the reference values selected in PRVD2018-16.

B. Developmental toxicity study in rats

A developmental toxicity NOAEL was not established for this study in PRVD2018-16. Instead, a LOAEL was established at the lowest dose tested (LDT) of 5 mg/kg bw/day, based on increased incidences of incomplete or absent ossification and bilateral ureter torsion and distension. The registrant requested that Health Canada revise the developmental toxicity NOAEL to the mid-dose level of 40 mg/kg bw/day because the above-noted developmental findings fell within their respective HC ranges. This supporting HC data were not available for PRVD2018-16. Additional comments, along with additional cited or submitted scientific rationales and journal articles, suggested that the incomplete or absent ossification findings, as well as bilateral ureter torsion and distension findings, did not constitute serious developmental effects.

Following a weight of evidence review of comments and data submitted, including the recent evaluations from EFSA and the USEPA, as well as published scientific rationales, Health Canada reached the following conclusions:

- Incomplete or absent ossification and bilateral torsion or distension of the ureters do not constitute serious developmental effects and are categorized as developmental variations rather than malformations in the scientific literature (Solecki et al. 2003).
- Fetal incidences of incomplete or absent ossification and bilateral torsion and distension of the ureters fell within their respective HC ranges, except for the incidence of bilateral incomplete ossification of the metacarpals at the high dose level.
- Given that HC data for litter incidences of these findings were not available; the dose-related trend and the statistical significance for a number of these findings, beginning at the mid-dose level, could not be dismissed.
- A dose-related increase in the litter and fetal incidences of bilateral distension and torsion of ureters was observed beginning at the LDT, while the fetal incidence of bilateral torsion of the ureters, but not distension, was also statistically significantly increased beginning at the LDT.
- Dilated renal pelvis, which is often associated with distended ureters (Makris et al, 2009), was also noted as a treatment-related effect in the pups in the dietary two-generation reproduction study in the same dose range as that tested in the developmental toxicity study. See next section for discussion of these findings.

Based on the considerations noted above, the LOAEL determined for this study in PRVD2018-16 remains unchanged.

C. Two-generation reproductive toxicity study in rats

An offspring NOAEL of 0.4 mg/kg bw/day was selected for this study in PRVD2018-16. The LOAEL of 3.8 mg/kg bw/day was based on decreased body weight in the F_1 pups and increased incidence of unilateral and/or bilateral renal pelvis dilatation in the F_2 pups. The registrant stated that, at the dose level of 3.8 mg/kg bw/day, the decrease in body weight was slight and the incidence of dilated renal pelvis fell within the newly submitted HC range. Further comments and the associated individual animal data analysis conducted by the registrant suggested that data from a single litter at the dose level of 3.8 mg/kg bw/day was a statistically significant outlier and should be excluded from the pup body weight data analysis. Significant mortality and reduction in the body weight of pups in this single litter, as well as body weight loss in the maternal animal, provided further justification for this exclusion.

Following a weight of evidence review of comments and data submitted, including the recent evaluations from EFSA and USEPA, Health Canada reached the following conclusions:

- At the dose level of 3.8 mg/kg bw/day, the incidences of dilated renal pelvis in the F_2 pups were increased and, while the incidences of bilateral and total dilated renal pelvis in the F_2 pups were within their respective HC range, the incidence of unilateral renal pelvis in the F_2 pups was above the HC range.
- At higher dose levels, the decrease in body weight in pups and increase in the incidence of bilateral or unilateral dilated renal pelvis, which fell outside of the newly submitted HC range, were observed across the pups of both generations.
- Excluding the single litter outlier from the analysis of litter body weight data based on significantly increased pup mortality and decreased pup body weight was confounded by treatment-related effects on the same parameters (mortality, body weight) noted at higher dose levels in this study. Thus, the rationale for excluding this litter from analysis was not supported.
- When pup body weight data were analyzed without the single litter outlier, the mean pup body weight at the dose level of 3.8 mg/kg bw/day was lower compared to their control counterparts throughout the postnatal days of 4 to 21.

Based on the considerations noted above, the LOAEL determined for this study in PRVD2018-16 remains unchanged. Thus, as indicated in PRVD2018-16, the LOAEL is 3.8 mg/kg bw/day based on decreased pup body weight in F1 and increased incidence of dilated unilateral renal pelvis in the F_2 pups.

Conclusion

The toxicological reference value of 0.4 mg/kg bw/day, with a target MOE of 100, which was selected for the short- and intermediate-term occupational exposure scenario in PRVD2018-16, was re-confirmed.

Appendix III List of Respondents to PRVD2018-16

List of respondents' affiliations in terms of comments submitted in response to PRVD2018-16

Category	Respondent
Registrant	Syngenta Canada Inc.

Appendix IV Toxicological Reference Values

Table 1 Toxicological Reference Values for Use in Health Risk Assessment for Clodinafop-propargyl

Exposure Scenario	Study	Point of Departure and Endpoint	CAF or target MOE[1]
ARfD (all populations)	Developmental neurotoxicity study in rats	NOAEL = 9 mg/kg bw/day Decreased auditory startle reflex and changes in brain morphometrics	300 PCPA factor = threefold
--	--	**ARfD = 0.03 mg/kg bw**	--
Repeated Dietary (all populations)	Two-year dietary chronic toxicity/ carcinogenicity study in rats	NOAEL = 0.3 mg/kg bw/day Liver toxicity (elevated enzyme activities, increased weight and histopathological findings) and kidney toxicity (chronic progressive nephropathy, and tubular pigmentation)	100
--	--	**ADI = 0.003 mg/kg bw/day**	--
Short- and Intermediate-term dermal and inhalation	Two-generation reproductive toxicity study in rats	NOAEL = 0.4 mg/kg bw/day Increased incidence of unilateral dilatation of the renal pelvis in F2 pups and decreased pup (and litter) body weight on PND 4–21 in F_1	100
Cancer	--	q_1* value = 0.0302 (mg/kg bw/day)$^{-1}$ for rat prostate adenomas and carcinomas (combined) which is also protective of vascular tumours	--

[1] CAF (composite assessment factor) refers to a total of uncertainty and Pest Control Product Act factor (PCPA factor) for dietary assessments; MOE refers to a target MOE for occupational assessments

Appendix V Label Amendments for Products Containing Clodinafop propargyl

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

1. **Label statements for Technical Products**

On the primary panel, **remove** "GUARANTEE" and **replace** with "ACTIVE INGREDIENT".

Before STORAGE section, add "ENVIRONMENTAL HAZARDS" and the following statements:

- TOXIC to non-target terrestrial plants
- TOXIC to aquatic organisms

2. **Label statements for Commercial and Agricultural class products**

Precautions

The following label statements are to be added to the **PRECAUTIONS** section of all commercial end-use products, unless already present:

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

Personal Protective Equipment

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

a. **Add** the following text:
"If mixing and loading more than 15 kg a.i. in a day, workers must use a closed mixing/loading system."

b. **Remove**:
"Wear coveralls or long sleeved shirt and long pants, chemical resistant gloves, and goggles when mixing loading or during equipment clean up or repair."

Replace with:
"During mixing, loading, clean-up, repair and when applying by groundboom, workers must wear coveralls over long-sleeved shirt and long pants, shoes and socks, goggles, and chemical-resistant gloves. When applying by aerial application, pilots must wear long-sleeved shirt and long pants"

c. **Remove**:
"During mixing, loading, application, spill clean-up, and sprayer clean-up, maintenance or repair, wear a long-sleeved shirt, long pants and chemical resistant gloves."

Replace with:
"During mixing, loading, clean-up, repair and when applying by groundboom, workers must wear coveralls over long-sleeved shirt and long pants, shoes and socks, and chemical-resistant gloves. When applying by aerial application, pilots must wear long-sleeved shirt and long pants."

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

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

Directions For Use

- Add, "A 30-day plant-back interval must be observed for all unlabelled crops."

Current label restrictions for grazing of livestock on treated crops must be amended for the appropriate labels as follows:

a. **Remove**:
"Observe a minimum of three (3) days before grazing livestock on treated crops"

Replace with:
"Observe a minimum pre-harvest interval of 60 days after treatment for grain and straw and of 30 days after treatment for hay. Observe a minimum of seven (7) days before grazing livestock on treated crops".

Add the following to **ENVIRONMENTAL HAZARDS**:

- **TOXIC** to non-target terrestrial plants. Observe buffer zones specified under DIRECTIONS FOR USE.
- **TOXIC** to aquatic organisms. Observe buffer zones specified under DIRECTIONS FOR USE.
- The residues of this product demonstrate the properties and characteristics associated with chemicals detected in ground water. The use of clodinafop-propargyl products in areas where soils are permeable, particularly where the water table is shallow, may result in ground water contamination.
- To reduce runoff from treated areas into aquatic habitats, avoid application to areas with a moderate to steep slope, compacted soil or clay.
- Avoid application when heavy rain is forecast.

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

Add to DIRECTIONS FOR USE

The following statements are required for all agricultural and commercial pesticide products:

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

Remove the following statement under the **STORAGE** section of the labels for the end-use products:

> "Store the product in closed original container in a well-ventilated room. Keep out of reach of children, unauthorized persons and animals. To prevent contamination store this product away from food, feed, and fertilizer."

And **replace** it with the following statement:

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

The following statement is required under the **ENVIRONMENTAL PRECAUTIONS** section of the label for all clodinafop-propargyl end-use products that contain aromatic petroleum distillates (Products that do not contain petroleum distillates are Reg. Nos. 29089, 29614, 30341 and 30426):

> "This product contains an active ingredient and aromatic petroleum distillates which are toxic to aquatic organisms."

Add to ENVIRONMENTAL PRECAUTIONS:

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

Add to DIRECTIONS FOR USE:

> **Field sprayer application**: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Boom height must be 60 cm or less above the crop or ground.
>
> **Aerial application**: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets

smaller than the American Society of Agricultural Engineers (ASAE S572.1) coarse classification. Reduce drift caused by turbulent wingtip vortices. The nozzle distribution along the spray boom length **MUST NOT** exceed 65% of the wing- or rotorspan.

Buffer zones:

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

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands) and sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands).

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:		
			Freshwater Habitat of Depths:		Terrestrial Habitat:
			Less than 1 m	Greater than 1 m	
Field sprayer	Spring and durum wheat		1	0	1
Aerial	Spring and durum wheat (55.2–70.2 g a.i./ha)	Fixed wing	1	0	20
		Rotary wing	1	0	20
	Spring and durum wheat (30 g a.i./ha) (PCP# 29855 and 31674)	Fixed wing	1	0	15
		Rotary wing	1	0	15

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

The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator in the Pesticides portion of Canada.ca.

Appendix VI References Considered Following Publication of RVD2018-16

Note that the following includes only references that were not previously considered in PRVD2018-16.

A. Information Considered in the Updated Toxicological Assessment

List of Studies/Information Submitted by Registrant

PMRA Document Number	Title
2947054	2018, Correspondence – Re-evaluation of Clodinafop-propargyl (Ref No. 2012-1629), Proposed Re-evaluation Decision for Clodinafop-propargyl (PRVD2018-16).
2947055	2018, Response PMRA Sub. No. 2012-1629: Re-evaluation of Clodinafop-propargyl – Comments related to PMRA# 1123424, 1123353, 1158474, DACO: 4.4.3
2947056	2013, Pathogenesis of human hemangiosarcomas and hemangiomas, DACO: 4.4.3
2947057	2018, Clodinafop-propargyl, Evaluation of the NOAEL for Offspring toxicity in the rat two-generation reproduction study – Response to PMRA PRVD2018-16, DACO: 4.5.1
2947058	1994, Addendum histopathology – two-generation oral reproduction toxicity study in rat, DACO: 4.5.1
2947059	2018, Clodinafop-propargyl, Evaluation of the observed effect level for developmental toxicity in the rat prenatal developmental study – Response to PMRA PRVD2018-16, DACO: 4.5.2
2947060	2011, Significance, reliability, and interpretation of developmental and reproductive toxicity study findings. In: Developmental and reproductive toxicology: a practical approach, DACO: 4.5.2
2947061	2007, Review article: Interpretation of Skeletal variations for human risk assessment: delayed ossification and wavy ribs, DACO: 4.5.2
2947062	2010, Altered health outcomes in adult offspring of Sprague Dawley and Wistar rats undernourished during early or late pregnancy, DACO: 4.5.2
2947063	2017, Review article: species differences in renal development and associated developmental nephrotoxicity, DACO: 4.5.2
2947064	1994, Practical guidance for evaluating and interpreting developmental toxicity tests, DACO: 4.5.2
2947065	2014, Review article: relationship between bent long bones, bent scapulae, and wavy ribs: malformations or variations, DACO: 4.5.2
2947066	1998, Upper urinary tract obstruction: experimental and clinical aspects, DACO: 4.5.2

2947067	2001, Harmonisation of rat fetal skeletal terminology and classification. Report of the third workshop on the terminology in developmental toxicology Berlin, DACO: 4.5.2
2947068	2011, Comparative gestational milestones in vertebrate development, DACO: 4.5.2
2947069	2018, Clodinafop-propargyl – Assessment of NOAEL values for intermediate-term toxicology studies assessment, DACO: 4.8
2947070	2002, Recognition of adverse and nonadverse effects in toxicity studies, DACO: 4.8

Additional Information Considered

Published Information

PMRA Document Number	Title
3019737	2018, EFSA (European food safety authority). Conclusion on pesticides peer review. Peer review of the pesticide risk assessment of the active substance clodinafop-propargyl, DACO: 12.5
3019738	2017, USEPA (United States Environmental Protection Agency). Human health draft risk assessment for registration review, DACO: 12.5
3019739	R. Solecki et al. Harmonization of rat fetal external and visceral terminology and classification. Report of the fourth workshop on the terminology in developmental toxicology, Berlin 18-20 April 2002. Reproductive toxicology 17 (2003) 625-637.
3019740	S.L. Makris et al. Terminology of developmental abnormalities in common laboratory mammals (version 2). Reproductive toxicology 28 (2009) 371-434.