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Special Review Decision SRD2022-01

Special Review Decisions: Naled

Final Decision Document

(publié aussi en français)

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Special review decisions

Naled (1,2-dibromo-2,2-dichloroethyl dimethyl phosphate) is an organophosphate pesticide used for the control of insects in a wide variety of use areas, including agricultural (food and feed) crops, outdoor ornamentals, greenhouse food crops and ornamentals, in/around structural sites, woodlands, and livestock pastures. Currently registered pest control products containing naled are listed in Appendix I.

Pursuant to subsection 17(1) of the *Pest Control Products Act*, Health Canada's Pest Management Regulatory Agency (PMRA) initiated a special review of naled based on the toxicology information submitted under section 12 of the *Pest Control Products Act*, following the re-evaluation of naled. The aspect of concern for this special review under subsection 17(1) of the *Pest Control Products Act* is relevant to human health (potential occupational risks).

Health Canada also initiated a special review of naled pursuant to subsection 17(2) of the *Pest Control Products Act*, based on the prohibition of all uses of naled in the European Union for human health and environmental concerns. The aspects of concern identified for the special review under subsection 17(2) of the *Pest Control Products Act* are potential occupational and dietary risks, and, potential risk to aquatic and terrestrial organisms.

Health Canada evaluated the aspects of concern that prompted the above two special reviews in accordance with subsection 18(4) of the *Pest Control Products Act*. The proposed special review decisions were published for consultation[1] in the Proposed Special Review Decisions PSRD2019-02, *Special Review of Naled and Its Associated End-use Product under subsection 17(1) of Pest Control Products Act* and PSRD2019-03, *Special Review of Naled and Its Associated End use Product under subsection 17(2) of Pest Control Products Act.*

The final decision for the two special reviews of naled pursuant to subsection 17(1) and 17(2) of the *Pest Control Products Act* have been combined into one document because the aspect of concern regarding potential occupational risks and the associated risks identified are the same in both special reviews.

All pest control products containing naled that are registered in Canada are subject to the special review decisions. This document presents the final regulatory decision for these two special reviews of naled.

Science evaluation of the aspects of concern summary for both special reviews

Comments and additional information were received during the consultation period of both special reviews, see Appendix II for a list of commenters. Comments are summarized in Appendix III with the responses from Health Canada.

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

The final special review decision considered the comments and information received during the consultation of PSRD2019-02 and PSRD2019-03. The outcome of the revised assessment of the aspects of concern based on additional information received is outlined below:

Potential occupational risks (special reviews under subsection 17(1) and 17(2) of *Pest Control Products Act*):

- The information received did not result in a change to the toxicology reference values for naled established for the human health risk assessment presented in PSRD2019-02 and PSRD2019-03. However, the dermal reference values for dichlorvos, a transformation product of naled, were updated for the scenarios involving combined exposure to both naled and dichlorvos based on the results of a newly received dermal toxicity study conducted with dichlorvos (Appendix IV).

- Additional information resulted in revisions to the occupational risk assessments for all uses, with changes in the final risk outcomes for certain uses (see Science evaluation update and Appendix IV for more details). This resulted in changes to the proposed special review decision (related to occupational risk) as described in PSRD2019-02 and PSRD2019-03:

    - Occupational risks for application on broccoli, Brussels sprouts, cabbage, cauliflower, lettuce, onion (bulb or seed) and strawberry are shown to be acceptable and these uses will be retained. Additional mitigation measures will be implemented, including personal protective equipment, engineering controls and/or limits to amount of product handled per day. Amendments to the product label will reflect these new measures.
    - Occupational risks for groundboom application to tomatoes (field) are shown to be acceptable and this use will be retained. Additional mitigation measures will be implemented, including personal protective equipment and engineering controls. Amendments to the product label will reflect these new measures. Occupational risks are not shown to be acceptable for aerial application to tomatoes. Therefore, aerial application to tomatoes is prohibited and the label will indicate ground application only to tomatoes (field).
    - Occupational risks for application to outdoor ornamentals are shown to be acceptable. Additional mitigation measures will be implemented, including personal protective equipment, engineering controls and limits to amount of product handled per day. Amendments to the product label will reflect these new measures. Application by handheld mistblower will be prohibited and a statement to this effect will be added to the label.
    - Occupational risks for aerial application in livestock pastures, feedlots, pastures (dairy cattle present) for adult mosquitoes, gnats and house fly treatment, are shown to be acceptable. Additional mitigation measures will be implemented, including personal protective equipment, engineering controls and limits to amount of product handled per day. Amendments to the product label will reflect these new measures. Application by Ultra Low Volume

(ULV)/mistblower tractor or handheld mistblower will be prohibited and statements to this effect will be added to the label.
    - Occupational risks for aerial application in corrals, adjacent pastures, holding pens (dairy or beef cattle, sheep, horses, hogs present) for mosquitoes and adult house fly treatment are shown to be acceptable. Additional mitigation measures will be implemented, including personal protective equipment, engineering controls and limits to amount of product handled per day. Amendments to the product label will reflect these new measures.
    - Occupational risks are not shown to be acceptable for aerial and groundboom application to rangeland, field areas and pastures for grasshopper treatment; for application in woodlands for mosquito, gnat and housefly treatment; for alfalfa, clover, vetch, peas (processing), beans (dry or field), lima beans, potato, and sugar beets. Therefore, these uses will be cancelled.
    - Occupational risks for postapplication workers are not shown to be acceptable for all greenhouse food and non-food crops (cucumbers, tomatoes, eggplants, peppers, roses and cut flowers) including application by vapour cold pipe treatment and automated fogging equipment; and in and around dairy barns, livestock barns, pig pens, poultry houses, cider mills, and wineries for control of mosquitos, gnats, houseflies, lesser houseflies and fruit flies. Therefore, these uses will be cancelled.

Potential dietary risk (special review under subsection 17(2) of *Pest Control Products Act*):

- The information received did not result in a change to the dietary assessment presented in PSRD2019-03.

Potential risk to aquatic and terrestrial organisms (special review under subsection 17(2) of *Pest Control Products Act*):

- Following consideration of comments and information submitted during the consultation period for PSRD2019-03, the aquatic risk assessment for runoff was revised for naled and dichlorvos. Based on an evaluation of the available information and revised use pattern, the risks associated with the use of naled was found to be acceptable with additional risk mitigations measures including buffer zones and precautionary statements which will be added to the label.

Special review decisions for naled

Health Canada has evaluated the aspects of concern, under subsection 17(1) and subsection 17(2) of the *Pest Control Products Act*, that prompted the special reviews of pest control products containing naled in accordance with subsection 18(4) of the *Pest Control Products Act*. Health Canada's Pest Management Regulatory Agency, under the authority of the *Pest Control Products Act*, has determined that continued registration of certain uses are acceptable with additional mitigation measures (Appendix VI). On this basis, Health Canada is amending the current registrations of naled products for sale and use in Canada to implement these risk mitigation measures, pursuant to subsection 21(2) of the *Pest Control Product Act*.

The assessments of the aspects of concern from both special reviews indicated that the risks to human health and the environment for the following uses of naled are considered to be acceptable. The following uses are to be retained with the implementation of additional mitigation measures, to be shown on the product label:

- broccoli, Brussels sprouts, cabbage, cauliflower, lettuce, onion, strawberry
- tomato (ground application)
- outdoor ornamentals
- livestock pastures, feed lots, corrals, holding pens (aerial application for mosquitoes, houseflies or gnats)

The assessments indicated that the risk to human health (occupational) for the following uses of naled is not considered to be acceptable, and these uses are to be cancelled:

- tomatoes (aerial application)
- beans (dry or field), lima beans, peas (processing), alfalfa, clover, vetch, potato, sugar beets
- rangeland, field areas, and pastures (aerial application for grasshopper treatment)
- all greenhouse uses (roses and ornamentals grown for cut flowers, tomatoes, cucumbers, eggplants, peppers)
- in and around dairy barns, livestock barns, pig pens, poultry houses, cider mills, wineries
- woodland

Special review under subsection 17(1) of the *Pest Control Products Act*

Evaluation of available scientific information related to occupational risk found that the potential risk to human health is considered to be acceptable with additional risk mitigation measures. Therefore, continued registration of products containing naled is acceptable with the following mitigation measures (Appendix VI):

Human Health

- Cancellation of the following uses due to potential risks to human health:
    - beans (dry or field), lima beans, peas (processing), alfalfa, clover, vetch, potato, sugar beets
    - rangeland, field areas, and pastures (aerial application for grasshopper treatment)
    - all greenhouse uses (roses and ornamentals grown for cut flowers, tomatoes, cucumbers, eggplants, peppers)
    - all structural uses including indoor uses (in and around dairy barns, livestock barns, pig pens, poultry houses, cider mills, and wineries), and
    - woodland

- Additional mitigation measures for the remaining uses:
    - Prohibition of use of the following types of application equipment for all crops/sites:
        - ultra-low volume sprayer
        - handheld mistblower/fogger.
    - Prohibition of aerial application for tomato.
    - Additional engineering controls such as:
        - closed mix/load system for all equipment except handheld
        - closed cab when using larger amounts of product per day
    - Additional PPE requirements for all workers who mix, load or apply the end-use product containing naled
    - Limitation on the amount that workers can handle per day for certain uses/applications

- These same risk mitigation measures related to human health (occupational) are required for the special review under subsection 17(2) of the *Pest Control Products Act*.

Special review under subsection 17(2) of the *Pest Control Products Act*

Evaluation of available scientific information related to the aspect of concern for dietary risk indicated that under the current conditions of use, the dietary risk (food and drinking water) is considered to be acceptable. No additional mitigation measures are required.

Evaluation of available scientific information related to the aspects of concern for occupational risk indicated that the risks to human health are considered to be acceptable with the implementation of the same risk mitigation measures (related to human health) set out in the previous section in relation to the special review under subsection 17(1) of the *Pest Control Products Act*.

Evaluation of available scientific information related to the environmental aspects of concern indicated that the risks to aquatic and terrestrial species are considered to be acceptable with the implementation of the following additional risk mitigation measures:

Environment

- Buffer zones to protect aquatic habitats.
- Label amendments include standard environmental precautions regarding toxicity, runoff, not to be used for aquatic pests, minimum spray volume of 10 L and removal of No. 2 fuel oil as a diluent for aerial application.

Based on the above, continued registration of products containing naled is acceptable with additional mitigation measures (Appendix VI).

Next steps

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

As noted in PSRD2019-02, Health Canada will be initiating a cumulative risk assessment for the organophosphate class of chemicals upon completion of the re-evaluation of the individual chemicals in this group. These decisions in the current document for the naled special reviews represent the last of the re-evaluations/special reviews of the organophosphates in this re-evaluation cycle, and as such the organophosphate cumulative risk assessment will be initiated shortly, with a formal announcement to follow.

Other information

Any person may file a notice of objection[2] regarding these decisions on naled within 60 days from the date of publication of this Special Review Decision document. 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.

The relevant confidential test data on which the decisions are based (as referenced in PSRD2019-02, PSRD2019-03 and this document) are available for public inspection, upon application, in the PMRA's Reading Room. For more information, please contact the PMRA's Pest Management Information Service.

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

Science evaluation update related to the aspects of concern for the two special reviews

1.0 Potential occupational risks (special reviews under subsection 17(1) and 17(2) of *Pest Control Products Act*):

1.1 Toxicology summary

The toxicology assessment for naled was previously conducted and summarized in PSRD2019-02 and PSRD2019-03. Comments were received from the registrant concerning various aspects of the assessment, including the point of departure selected for the dermal risk assessment, the magnitude of the factors applied for the dermal risk assessment, the methods used in the conduct of the benchmark dose modelling, and the potential application of chemical-specific adjustment factors for the human health risk assessment. In addition, a recently conducted 28-day dermal toxicity study performed with female rats exposed to dichlorvos, a transformation product of naled, was submitted to Health Canada. Overall, the review of the data and comments submitted did not result in a change to the reference values established for the human health risk assessment outlined in the PSRDs for naled. However, based on the results of the newly conducted 28-day dermal toxicity study with dichlorvos, the dermal risk assessment for dichlorvos was updated for the scenarios involving combined exposure to both naled and dichlorvos. Detailed responses to comments and the updated toxicology reference values are presented in Appendix IV. This updated risk assessment is considered protective of the health of all Canadians.

1.2 Occupational exposure and risk assessment

In PSRD2019-02 and PSRD2019-03, Health Canada had proposed cancellation of all crops due to potential risks to workers who mix, load or apply the product and workers entering indoor treated sites to conduct postapplication activities.

During the PSRD consultation period, additional information and data were received from the registrant and a greenhouse vegetable grower group. This included specific information for postapplication use in greenhouses such as application equipment, critical timing of naled application, and a description of greenhouse worker clean-up activities. These data and information, as well as the updated toxicology reference values for dichlorvos and updated unit exposure values for mixer, loaders and applicators from the Agricultural Handlers Exposure Task Force (AHETF) studies, were considered and incorporated into the revised assessment to the extent possible. Health Canada's responses to specific comments are in Appendix IV. Details and tables regarding the revised occupational risk assessment are presented in Appendix V.

As a result of the comments and additional data and information submitted, some of the outdoor agricultural uses previously proposed for cancellation are now acceptable for continued registration provided that the mitigation measures outlined in Appendix VI are followed.

For handheld mistblower/fogger equipment, no comments or data were submitted during the PSRD comment period; however, this application scenario was assessed based on data from two recent worker exposure studies. Risks were not shown to be acceptable and, therefore, use of this equipment for application of naled will be prohibited.

2.0 Potential dietary risks (special review under subsection 17(2) of *Pest Control Products Act*):

The dietary risk assessment for the special review was presented in PSRD2019-03. The dietary (food and drinking water) risks associated with the use of naled, as well as combined dietary exposure to naled and dichlorvos (transformation product of naled), were shown to be acceptable. No comments were received on the dietary risk assessment. The current Canadian MRLs for naled and dichlorvos will be maintained.

3.0 Potential risks to aquatic and terrestrial organisms (special review under subsection 17(2) of *Pest Control Products Act*):

Comments submitted during the consultation period of the Proposed Special Review Decision (PSRD2019-03) have been reviewed and considered in the current special review decision for naled. The following revisions were made to the aquatic risk assessment for runoff:

- HC_5 for aquatic invertebrates for naled was replaced by the most sensitive endpoints for freshwater and marine invertebrates.
- Previously published fate parameters set as "stable" for modelling naled were re-examined.
- Modelled concentrations for runoff were re-calculated.
    - Modelling included lower and higher application rates for representative crops.
- Surface water monitoring data was included.

No comments were received regarding risks to terrestrial organisms. Therefore, the risk assessment and required risk mitigation for terrestrial organisms is consistent with the proposed special review decision (PSRD2019-03).

3.1 Fate and behaviour in the environment

A study on the soil surface photolysis of naled was submitted. The study results reported first-order half-lives of naled degradation of 0.54 hours in sunlight and 0.58 hours in dark, indicating that minimal photolysis took place on the soil surface and the dominant process was related to factors in the soil (potentially also including microbial action). The registrant had suggested that the half-life from the photolysis study with soil would be more appropriate for representing the degradation of naled in soil, and that this should be used as the water modelling input parameter of soil half-life for naled. The submitted photolysis study was not of better quality than the soil degradation study used for modelling. The soil degradation study used for the assessment was determined to be suitable for use for the DT_{50} endpoint and as the water modelling input for a soil half-life for naled. The soil surface photolysis study does, however, contribute to the body of evidence supporting the rapid transformation of naled in the environment. The results of this study also indicates that dichlorvos is produced as a transformation product under both light and dark conditions on soil at similar amounts (maximum of 15% AR at 0.5 hours). However, both naled and dichlorvos accounted for < 3% AR by 3 hours after treatment.

Naled is expected to transform rapidly in the environment with most reported dissipation half-lives less than 1 day. Although a conservative 1 day soil half-life was used for water modelling, laboratory studies indicate that a half-life closer to 4 hours is likely to be more representative. The results of the soil photolysis study also supported that naled transforms within a few hours once it contacts soil. Rapid hydrolysis and biodegradation in soil decrease the availability of naled residues for runoff.

Dichlorvos is a transformation product of naled primarily produced through indirect photolysis (water and soil) and anaerobic biotransformation processes in water/sediment. Dichlorvos was not detected as a transformation product when naled was applied directly to soil in a biotransformation study. Based on the available information, it is expected that dichlorvos will not be produced in significant amounts through phototransformation in soil. In general, it is not expected that dichlorvos will be produced in detectable quantities in soil from the application of naled, and therefore would not be available for runoff.

For more information see PSRD2019-03.

3.2 Environmental toxicology

The additional ecotoxicology information provided during the consultation period did not present a more sensitive endpoint for naled or dichlorvos. For the proposed decision, the HC_5 for aquatic invertebrates combined data for freshwater and marine organisms in the same species sensitivity distribution (SSD). However, following the review of available information for the revised risk assessment, freshwater and marine data were separated for SSDs following the PMRA's current approach. When data were separated, there were not enough data points to determine an SSD for marine invertebrates and for freshwater species, as study details were lacking, including information on test substances. Therefore, the PMRA did not calculate an HC_5 and instead used the most sensitive endpoints for freshwater and marine invertebrates as a conservative approach.

In addition, the following corrections were made:

- the acute fish endpoint for dichlorvos reported in PSRD2019-03 was incorrect, and was corrected for the revised risk assessment,
- uncertainty factors were not applied consistently in PSRD2019-03 and were corrected as required for the revised risk assessment.

See Appendix V, Table 2 for a summary of the revised endpoints. For more information on the toxicity endpoints for naled and dichlorvos, see PSRD2019-03.

3.3 Environmental risk characterization

No new fate or ecotoxicity data was submitted that could be used to further refine the environmental risk assessment.

Runoff

Modelling is initially conducted to provide a conservative estimate of exposure for the aquatic risk assessment based on runoff. If risks are acceptable using conservative assumptions there is reasonable certainty that harmful effects will not result from the use of a pesticide. Following this, if risks are identified, modelling can be recalculated using more refined exposure parameters, provided they continue to be supported by a scientific assessment of the data. The modelled exposure estimates for naled reported in the proposed decision used a conservative approach. Fate parameters for aqueous photolysis, aerobic aquatic and anaerobic aquatic (sediment) half-lives were set as stable. The fate parameters for naled were re-examined for the final decision and refined based on half-life values reported in available laboratory studies (see Appendix V, Table 1).

Estimated environmental concentrations (EECs) in water were modelled using the Pesticide in Water Calculator (PWC) using refined exposure parameters (Appendix V, Table 1). The maximum cumulative application rate as well as a range of lower application rates and various regional scenarios were used to provide a representative analysis of the use pattern for the commercial end-use product Dibrom Insecticide (see Appendix V, Tables 3 and 4 for a summary of EECs and risk quotients for runoff). EECs were calculated for 15-cm (amphibian assessment) and 80-cm depth (other aquatic organisms) waterbodies. Risk quotients (RQs) for modelled EECs for runoff are presented and discussed for the revised risk assessment. This is one line of evidence for evaluating the risks to aquatic organisms from runoff, but has been combined with other information in a weight of evidence to support a final risk conclusion for naled. Risk conclusions from modelling are summarized as follows:

- Based on RQs using modelled EECs, risks to fish, amphibians and aquatic plants were acceptable for both naled and dichlorvos (acute and chronic); these data were not included in this document.
    - For amphibians, acute RQs for naled marginally exceeded the LOC for modelling using a runoff scenario for the Atlantic region (RQ = 2.5), but were not a concern for other scenarios (RQ < 1). Given the conservatisms of modelling, the potential risk identified for amphibians is not considered to be of concern.
- For marine invertebrates, the acute and chronic RQs for naled marginally exceeded the LOC for the highest cumulative application rate (RQs = 1.5 and 4, respectively) and Atlantic scenario, but was ≤ 1 for other regions. The LOC was not exceeded for dichlorvos toxicity to marine invertebrates, acute or chronic.
- For freshwater invertebrates, the LOC was exceeded for numerous crop/site scenarios based on modelled EECs:
    - Naled: RQs up to 33 and 13 (maximum rates) for acute and chronic exposure
    - Dichlorvos:
        - RQs up to 34 (minimum rates) and 43 (maximum rates), acute exposure
        - RQs up to 43 (minimum rates) and 26 (maximum rates), chronic exposure.

Other information was also considered to contextualize the potential risks, such as modelling conservatisms, details about the use pattern, and monitoring data. In general, the revised use pattern for naled is relatively small (broccoli, Brussels sprouts, cauliflower, strawberries, cabbage, lettuce, onion, tomato, outdoor ornamentals, livestock pastures and feedlots). RQs were highest for modelled EECs for vegetables in the Atlantic region (for crops representative of labelled uses). For other regional scenarios RQs were lower and were ≤ 9 for application to feedlots and livestock pastures. Hectarages of various vegetable crops grown in Canada, reported for each province by Statistics Canada, indicated that the area of crops registered for naled in the Atlantic region is low compared to the rest of Canada. For example, the estimated area of cabbage grown in Nova Scotia is 123 ha versus 2603 ha in Ontario, and is 2% of the total area grown for cabbage in Canada. The area planted to cabbage in other Atlantic provinces is lower (45 to 80 ha per province). Modelling is based on the assumption that 100% of the watershed being modelled is planted to one crop and all of it is being treated with the active ingredient. In reality, vegetable growing areas tend to comprise a mix of different crops and not all will be treated with the same active ingredients or at the same time. Thus, when considering the use pattern for these vegetable crops and conservatisms in the modelling, the RQs likely overestimate the potential for exposure with low hectarage crops.

Due to the conservative nature of the models used for runoff, more weight was given to the body of information presented in the fate data itself. The available fate studies indicate that due to rapid transformation processes in the soil environment, naled is unlikely to be available in significant amounts for movement through runoff beyond the day of application. In addition, production of measureable levels of dichlorvos from naled in soil is not expected and therefore potential entry of dichlorvos into waterbodies through runoff is also expected to be minimal. Volatilization (from soil and water) and spray drift are likely to be the most important modes of transport for naled from the use of Dibrom Insecticide.

Water monitoring data indicate that naled and dichlorvos are not detected frequently in samples from various locations in Canada (2005 to 2018). Locations of sampling are reflective of areas where naled is used and the majority of detections are at levels that would not pose harm to aquatic organisms. A higher detection frequency noted for naled and dichlorvos in British Columbia (approximately 32 samples between 2005 and 2007) can be attributed to a very low limit of detection. Naled was not detected in any other samples (n = 1225). Although the water monitoring sampling data is not extensive for naled or dichlorvos, the available information supports that entry of naled and dichlorvos into adjacent waterbodies from the use of Dibrom Insecticide is expected to be minimal. It should be noted that dichlorvos is itself a registered active ingredient and was registered for some outdoor uses during the period of time that water monitoring sampling took place. A summary of available water monitoring data is presented in Appendix V, Table 6.

Based on the weight of evidence, which indicates that both naled and its transformation product dichlorvos are short-lived in the environment, dichlorvos produced from naled in soil is expected to be very low, small use pattern and hectarages of crops registered for naled, and low levels found in water monitoring data for naled and dichlorvos, the risks to aquatic organisms from runoff due to the use of Dibrom Insecticide are acceptable at currently registered application rates for approved crops.

Spray Drift

Buffer zones were re-calculated for the approved use pattern using revised acute endpoints for aquatic invertebrates for naled. Buffer zones for freshwater habitats are higher than published in PSRD2019-03, but are lower for marine habitats (see label amendments, Appendix VI).

List of abbreviations

%	percent
<	less than
µg	microgram
♀	female
♂	male
a.i.	active ingredient
AChE	acetylcholinesterase
ADI	acceptable daily intake
AHETF	Agricultural Handler Exposure Task Force
ANOVA	analysis of variance
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
BChE	brain cholinesterase
BMD	benchmark dose
BMDL	benchmark dose at the lower 95% confidence limit
BMR	benchmark response
bw	body weight
CAF	composite assessment factor
CHC	Canadian Horticultural Council
ChE	cholinesterase
cm	centimetre(s)
cm^2	centimetres squared
CSAF	chemical specific adjustment factor
CV	coefficient of variance
d	day(s)
DA	dermal absorption
DFR	dislodgeable foliar residue
EC_{50}	effective concentration
EChE	erythrocyte cholinesterase
EEC	estimated environmental concentration
EFSA	European Food Safety Authority
g	gram(s)
h	hour(s)
ha	hectare
HC_5	hazardous concentration to 5% of the species
hr	hour
J	joule
kg	kilogram(s)
K_I	dissociation constant
k_i	bimolecular rate constant
k_p	phosphorylation constants
L	litre(s)
LC_{50}	lethal concentration 50%
LOAEL	lowest observed adverse effect level
LOC	level of concern

LOD	limit of detection
m	metre(s)
M/L	mixer/loader
M/L/A	mixer/loader/applicator
mg	milligram(s)
mm	milimetre(s)
MOE	margin of exposure
mol	mole
MRL	maximum residue limit
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
ON	Ontario
PHED	Pesticide Handler Exposure Database
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PoD	point of departure
PPE	personal protective equipment
PRVD	Proposed Re-evaluation Decision
PSRD	Proposed Special Review Decision
REI	restricted-entry interval
RQ	risk quotient
RVD	Re-evaluation Decision
SRD	Special Review Decision
SSD	species sensitivity distribution
TC	transfer coefficient
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
WHO	World Health Organization

Appendix I Registered naled products in Canada

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

Registration number	Marketing class	Registrant	Product name	Formulation type	Guarantee
23202	Technical	AMVAC Chemical Corporation	AMVAC Naled Technical	Solution	94.5%
7442	Commercial	Loveland Products Canada Inc.	Dibrom Insecticide	Emulsifiable concentrate	900 g/L

[1] As of 02 June 2021, excluding discontinued products or products with a submission for discontinuation.

Appendix II List of commenters to PSRD2019-02 and PSRD2019-03

List of commenters' affiliations for comments submitted in response to PSRD2019-02 and PSRD2019-03.

Category	Commenter
Agricultural	Canadian Horticulture Council
Registrant	AMVAC Chemical Corporation

Appendix III Comments and responses

Health Canada received comments from the registrant and stakeholders in response to the consultation documents Proposed Special Review Decisions, PSRD2019-02, *Special Review of Naled and Its Associated End-use Product under subsection 17(1) of Pest Control Products Act* and PSRD2019-03, *Special Review of Naled and Its Associated End use Product under subsection 17(2) of Pest Control Products Act*. The consolidated comments related to the aspects of concern of these special reviews and Health Canada's responses to those comments are provided below.

1.0 Comments related to potential occupational risks (special reviews under subsection 17(1) and 17(2) of *Pest Control Products Act*):

1.1 Comments related to toxicology

Comment - Point of departure for the naled dermal risk assessment

The registrant recommended updating the dermal risk assessment for naled by replacing the point of departure (PoD) selected from the 28-day dermal toxicity study conducted in 1986 (PMRA# 1217658) with the NOAEL of 10 mg/kg bw/day from a more recent 28-day dermal toxicity study conducted in 2000 (PMRA# 3014630, 3014631 and 3014632), citing several limitations with the older dermal toxicity study.

Health Canada response:

As presented in PSRD2019-02 and PSRD2019-03, dermal risk assessments were conducted for short-, intermediate- and long-term naled exposure scenarios. For all of the dermal exposure scenarios, the PoD from the rat 28-day dermal toxicity study conducted in 1986 was selected for risk assessment. Benchmark dose modelling (BMD) was performed by Health Canada on the brain cholinesterase (BChE) data from this study, and a $BMDL_{10}$ of 1.96 mg/kg bw/day was derived. A target MOE of 300 was applied for the short- and intermediate-term dermal exposure scenarios. In addition to the standard uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variability, an extra 3-fold uncertainty factor was applied for database deficiency concerns. These concerns related to uncertainty as to whether the sensitivity of the young that was identified by the oral route would also be manifested via the dermal route. For the long-term dermal exposure scenario, a target MOE of 1000 was applied with an additional 10-fold database deficiency factor to address both the potential sensitivity of the young and concerns related to the increased toxicity that was noted with increased duration of dosing in oral studies.

The registrant cited concerns regarding the severe dermal irritation noted at the mid- and high-dose levels in the older 28-day dermal toxicity study, suggesting that this likely led to increased absorption of naled through the damaged skin, resulting in greater cholinesterase inhibition. Other concerns raised by the registrant included the lower purity of the test substance and the relatively younger age of the animals used in the older 28-day dermal toxicity study. However, a comparison of the methods and results of the two 28-day dermal toxicity studies indicated that the test animals were of similar age and a comparable degree of dermal irritation was produced. Furthermore, the purity of the test material used in both studies falls within the range of purities tested in the supporting toxicology database. Overall, Health Canada does not consider these issues to invalidate the results identified in the older dermal toxicity study.

The registrant also suggested that a NOAEL/LOAEL approach should be used to determine the PoDs in the 28-day dermal toxicity studies rather than the BMD approach, indicating that the dose selection in the older dermal toxicity study and the results from the newer study were not ideal for BMD modeling. To support this statement, the registrant cited the USEPA guidance document on BMD modeling, which stated "of the designs evaluated, the best results (that is those with the narrowest confidence intervals) were obtained when two dose levels had response rates above the background level, one of which was near the BMR". Health Canada notes that this point has been misinterpreted, as it simply points to optimal parameters in designing an ideal study when the intention is to have the results analyzed by BMD modeling. Health Canada's PMRA currently follows the EFSA guidance on BMD modeling (EFSA, 2017),[3] which also recommends BMD modeling over the NOAEL/LOAEL approach. The EFSA BMD guidance and Proast software were chosen over the USEPA BMD guidance and software because it allows for the analysis of individual animal data on the log scale, as well as avoidance of the use of hard parameter constraints, and minimises the need for specification testing. Additionally, for dichotomous outcomes, it allows the use of model averaging.

In both of the rat 28-day dermal toxicity studies, inhibition of BChE activity was noted. In the older dermal toxicity study, statistically significant BChE inhibition was observed at the mid- and high-dose levels in both sexes. Although there was no inhibition of BChE close to the benchmark dose response (BMR) of 10% observed in this study, the BMD analysis conducted by Health Canada was considered scientifically valid and followed the EFSA BMD guidance. In the more recent dermal toxicity study, statistically significant inhibition of BChE activity was only noted at the high-dose level in both sexes. However, the degree of inhibition noted in female rats at the low-dose level was greater than 10%, a value that Health Canada normally considers toxicologically significant. Since a clear dose-response relationship was not achieved, the use of a NOAEL/LOAEL approach, as recommended by the registrant, is not ideal.

Subsequent to the completion of the human health risk assessment of naled outlined in PSRD2019-02 and PSRD2019-03, the individual animal data for the more recent 28-day dermal toxicity study was made available to Health Canada, allowing the conduct of BMD analysis for this dermal toxicity study. The results of this BMD analysis provided a $BMDL_{10}$ of 3.93 mg/kg bw/day for the inhibition of BChE activity, which was twofold greater than the value of 1.96 mg/kg bw/day previously calculated by Health Canada for the older 28-day dermal toxicity study. However, in the newer 28-dermal toxicity study, the number of animals available for BChE assessment was limited (five rats/sex/dose level, with only four rats in the control group) as compared to that in the

[3] EFSA, 2017. Update: use of the benchmark dose approach in risk assessment. European Food Safety Authority, EFSA Journal, 2017, 15(1):4658.

older dermal toxicity study (12 rats/sex/dose level). Data from the older dermal study also demonstrated lower variability compared to that from the more recent one.

Overall, based on the detailed analysis of both of these dermal toxicity studies, Health Canada has concluded that it is appropriate to continue to use the $BMDL_{10}$ of 1.96 mg/kg bw/day derived from the 1986 dermal toxicity study for all of the dermal exposure scenarios for naled. As such, the point of departure of 1.96 mg/kg bw/day that was presented in PSRD2019-02 and PSRD2019-03 for the dermal risk assessment of naled remains unchanged.

Comment - Magnitude of the uncertainty factors applied for the naled dermal risk assessment

The registrant recommended the removal of the additional threefold uncertainty factor applied to the naled long-term dermal risk assessment to account for the lack of a dermal exposure study longer than 28 days.

Health Canada response:

Throughout the naled toxicology database, the inhibition of BChE activity was considered to be the most sensitive indicator of toxicity. As such, its use in risk assessment was considered protective of other neurological and systemic effects. With this knowledge, Health Canada conducted a BMD analysis of BChE activity from exposed rats for oral toxicity studies of varying durations, ranging from acute to two years. The results of this BMD analysis demonstrated a clear durational effect with increased inhibition of BChE activity noted in longer-term studies (Table 1). Given this clear durational effect by the oral route of exposure, an additional threefold factor was applied for the risk assessment of naled whenever a short-term toxicity study was selected for a longer-term exposure scenario. While the registrant stated that the USEPA data demonstrated a steady-state inhibition of cholinesterase activity after 28 days of exposure to organophosphates, the Health Canada's assessment of cholinesterase inhibition in oral toxicity studies demonstrates a different trend for naled. Therefore, the extra threefold factor that was applied for a durational effect in PSRD2019-02/03 remains unchanged for the long-term dermal risk assessment of naled.

Table 1 Benchmark dose values calculated for BChE inhibition in naled acute, 7-day, 28-day and 2-year repeat-dose oral studies in adult rats

BMD_{10} Values for BChE	Acute (gavage)[4]	7-day (gavage)[5]	28-day (gavage) (PMRA# 1217657)	2-year Carcinogenicity (gavage) (PMRA# 1217688)
BMD_{10} (♂/♀ combined)	16 mg/kg bw	5.8 mg/kg bw/day	1.967 mg/kg bw/day	0.53 mg/kg bw/day

4 2002. Naled: Acute Cholinesterase Inhibition Study in Rats. DACO 4.5.12 (PSRD2019-02; PMRA# 1847172).

5 2003. Naled: Repeat Dose Cholinesterase Inhibition Study in Pre-weaning and Young Adult Rats DACO 4.5.12 (PSRD2019-02; PMRA# 1847170).

Comment - Point of departure for the dichlorvos oral risk assessment

The registrant recommended replacing the dichlorvos oral PoD of 0.011 mg/kg bw/day derived from a 7-day oral cholinesterase study with that from a 28-day oral (gavage) immunotoxicity study conducted in rats in 2012 (PMRA# 2844666).

Health Canada response:

The same comment was received following the publication of the Proposed Re-evaluation Decision document for dichlorvos (PRVD2017-16), and was addressed in the final dichlorvos re-evaluation decision document (RVD2020-08). It was concluded that the registrant had not provided an acceptable rationale to indicate that the use of the 7-day oral cholinesterase inhibition study for risk assessment was invalid or inappropriate. Therefore, the $BMDL_{10}$ that was previously generated by Health Canada (0.011 mg/kg bw/day) from the 7-day cholinesterase study will continue to be used for the human health risk assessment of dichlorvos.

Comment - Point of departure for the dichlorvos dermal risk assessment

The registrant recommended that the PoD used for the dichlorvos dermal risk assessment, which was derived from a 7-day oral cholinesterase inhibition study, be replaced with that from a newly submitted 28-day dermal toxicity (PMRA# 3003818) study in female rats. The registrant derived a $BMDL_{10}$ for BChE of 0.67 mg/kg bw/day from the dermal toxicity study, and suggested that it be used as the PoD for the dichlorvos dermal risk assessment.

Health Canada response:

This comment was received in response to the proposed special review decision for naled (PSRD2019-02 and PSRD2019-03), but was addressed in the recently published final Re-evaluation Decision document for dichlorvos (RVD2020-08). As outlined in RVD2020-08, it was considered appropriate to update the dermal risk assessment for dichlorvos using the PoD from this new 28-day dermal toxicity study. In this study, statistically significant treatment-related inhibition of BChE activity was evident for rats at the highest dose tested. Health Canada conducted a BMD analysis using the EFSA BMD guidance (EFSA, 2017[3]) and Proast software, resulting in a $BMDL_{10}$ of 1.2 mg/kg bw/day for females. The full study details and results for the 28-day dermal toxicity study conducted with dichlorvos appear in RVD2020-08. The short-, intermediate- and long-term dermal toxicology reference values and the reference value for the dermal component of the aggregate risk assessment of dichlorvos have been updated using the results from the new dermal toxicity study, as further explained in RVD2020-08 (Appendix III, Table 3).

Comment - Chemical-specific adjustment factors (CSAF) for naled and dichlorvos

The registrant provided information to support reductions of the intra- and interspecies toxicodynamic uncertainty factors that were used in Health Canada's human health risk assessments for naled and dichlorvos (PMRA# 3003814) based on the results of:

A. An in vitro research program that measured the bimolecular rate constant for naled and dichlorvos for acetylcholinesterase (AChE) derived from rats and humans (PMRA# 3036897 and 3036898);

B. A computational modeling program to provide supplementary evidence for the equivalence of rat and human AChE and inhibition following exposure to naled and dichlorvos (PMRA# 2875289);

C. A summary document calculating CSAFs for dichlorvos and naled based on the outcomes of the inhibition kinetics and computational modelling studies, also incorporating information from the published literature (PMRA# 3036898).

Health Canada response:

Health Canada agrees that CSAFs could be used to replace the standard 100-fold uncertainty factor for interspecies and intraspecies factors if it was demonstrated that no significant differences were observed between human and rat enzymes, nor among the human population with regards to AChE inhibition. In addition, the World Health Organization (WHO, 2001)[6] criteria for applying CSAFs would have to be met. However, key information was missing and limitations were noted with the in vitro inhibition kinetic assay and the computational modelling, as well as with the rationales to support reducing the toxicodynamic components of the intra- and interspecies uncertainty factors. These limitations are summarized below.

A. In vitro inhibition kinetic assay

A report characterizing the inhibition kinetics of dichlorvos and naled on AChE from erythrocytes of human and rat origin was submitted. Although brain AChE is the target of naled and dichlorvos, the registrant stated that the AChE of erythrocytes was the same gene product as neural AChE, and thus, comparison of the kinetic parameters from human and rat erythrocytes could be used in addressing the interspecies uncertainty factor applied in the health risk assessment. To accomplish this, erythrocyte "ghost" cell membranes were isolated from human and rat blood samples as the source of AChE. The inhibition kinetic constants for each of the blood samples for the naled and dichlorvos inhibition of acetylthiocholine hydrolysis by rat and human AChE were determined.

In reviewing the in vitro kinetic assays, Health Canada determined that key information was omitted and that there were significant limitations with the conduct of the assay. Insufficient details were presented pertaining to the test material used, the purity of the cell membrane samples, along with how the blood samples were collected and handled. Furthermore, the raw data from the assays were not provided, and insufficient details were provided regarding the handling of the data and statistical analyses. Limitations noted with the in vitro assay included the performance of the positive control substance as well as a lack of justification regarding several aspects of the in vitro test methods. These included the pre-incubation of the enzyme with the inhibitor, and the amount of

6 2001. World Health Organization/International Programme on Chemical Safety. *Guidance Document for the Use of Data in Development of Chemical-Specific Adjustment Factors (CSAFs) for Interspecies Differences and Human Variability in Dose/Concentration–Response Assessment*.

erythrocyte preparation added to each reaction being normalized according to the absorbance value instead of protein concentration. Another limitation was the lack of information demonstrating the kinetic equivalence of AChE-catalyzed hydrolysis of acetylthiocholine, the non-physiological substrate used for inhibition assays, relative to hydrolysis of acetylcholine, the physiological substrate of AChE. In addition to these omissions and limitations, a high degree of variation was observed for the data obtained for all of the inhibition kinetic parameters. Given the high degree of variation in the data sets, and uncertainty regarding the data handling, these analyses regarding differences between human and rat inhibition kinetic parameters are not conclusive. Therefore, the information provided is insufficient to determine the comparative rates of AChE inhibition between humans and rats for either naled or dichlorvos.

B. Computational modelling

Computational molecular modelling was submitted that tested whether a relatively diverse set of acetylcholinesterase-inhibitory forms of organophosphate compounds would interact similarly with rat and human brain AChE. In silico modelling was used to predict the degree of 3D structural similarity between human and rat AChE across various mechanistic stages of inhibition and to predict the interactions of these enzymes with dichlorvos and naled. Docking studies were carried out to simulate the 3D structures of human and rat AChE enzymes in complex across the different stages of inhibition. According to the registrant, the protein sequences of brain acetylcholinesterase in rat and mouse exhibit 98.2% amino acid identity; therefore, the study used the experimentally determined 3D structure of mouse acetylcholinesterase as a basis for in silico mutagenesis to build the predicted 3D structure of rat AChE. The conserved active site residues were reported to support the hypothesis of active-site similarity.

In examining the information submitted for the computational modelling for naled, Health Canada noted several uncertainties and limitations. One of the major limitations was the absence of an experimentally-determined X-ray crystallographic structure for rat AChE. In addition, information on the identity, quality and quantity of protein sequences used to generate the alignments demonstrating percent identity between AChE rat and mouse enzymes was not provided, which made it difficult to assess the accuracy of the alignment used to justify the mouse 3D structure as a basis for building the rat 3D structure. The similarity was high between the experimentally determined human and predicted rat AChE structures, as well as the human and rat enzymes for predicted interactions with naled across various stages of inhibition. However, differences were predicted to exist between rat and human AChE enzymes for naled bound in the transition state and between the *R*- and *S*- enantiomers of naled bound in the reversible complex. Also, any differences in post-translational modification sites, domain structure, or prevalence of AChE mutations were not compared between human and rat enzymes, and information was not provided on the stereochemistry of the inhibitor used in the in vitro inhibition kinetic assay, how this relates to the stereochemistry of the product that is manufactured by the registrant, and how this could potentially impact the toxicity of naled. Although information was provided describing the intra-human differences in post-translational modification sites, domain structure, prevalence of AChE mutations, and the impact on enzyme activity to address intra-human differences, similar information was not provided comparing these factors between rat and human enzymes. This would be necessary to demonstrate structural similarity of the human and rat AChE to lend support to the validity of using computational docking studies as a demonstration of similarity between rat and human enzymes.

Overall, the predictions generated from the computational modelling study support the likelihood of a high degree of similarity between human and rat AChE. However, this information should be considered supplemental, since predictions cannot replace an experimentally determined X-ray crystallographic structure of rat AChE. Therefore, it was concluded by Health Canada that the provided information is insufficient to adequately demonstrate the structural similarity of human and rat AChE enzymes in complex with naled. A similar conclusion was reached regarding the computational modelling information provided for dichlorvos (see RVD2020-08).

C. Rationale for CSAFs for dichlorvos and naled

In the WHO paradigm, the 10-fold interspecies uncertainty factor is composed of a fourfold factor for toxicokinetics and a 2.5-fold factor for toxicodynamics, while the 10-fold intraspecies uncertainty factor is composed of a 3.2-fold factor for toxicokinetics and a 3.2-fold factor for toxicodynamics. The registrant used the inhibition kinetics and computational modelling data, along with information summarized from the published literature, to address the criteria of the WHO for justifying the reduction of the toxicodynamic components of the inter- and intra-species uncertainty factors. The registrant contended that the bimolecular rate constant (k_i) for EChE inhibition generated from the in vitro experiments is directly proportional to the rate of in vivo BChE inhibition, and that the ratio of the human to rat k_i values could be used to replace the default interspecies 2.5-fold toxicodynamic factor. Accordingly, the registrant suggested replacing the default 2.5-fold toxicodynamic interspecies value with onefold for dichlorvos and 0.5-fold for naled. The registrant also argued that the default 3.2-fold toxicodynamic portion of the intraspecies factor could be reduced to onefold for both dichlorvos and naled since they stated that there were no statistically significant differences across ethnicity, sex or age for the human in vitro k_i data. The registrant also supported this approach by examining coefficients of variation across repeated subsample data collected for naled from four human samples in an attempt to distinguish experimental from biological variability. Overall, the registrant recommended that the total intra- and interspecies uncertainty factors should be reduced from the default 100-fold to 6.4-fold for naled and 12.8-fold for dichlorvos.

Interspecies uncertainty factor

Key limitations identified with the information provided by the registrant to support a reduction of the interspecies uncertainty factor included the lack of a justification for using different numbers of samples for humans and rats, and for using individual versus pooled samples for humans and rats, respectively. There was also no demonstration of how the samples used in the study adequately represented their respective populations, including the most sensitive subset of the population. As well, an assumption was made by the registrant that if the mean human and rat k_i values were statistically significantly different, then the interspecies toxicodynamic CSAF could be calculated as the ratio of these values. However, the more appropriate approach would involve using the upper one-sided 95% confidence limit to establish the CSAF, taking the largest ratio of human to rat k_i values that is compatible with the data given the assumptions used in the analysis to ensure sufficient margins of safety. A robust demonstration of the homogeneity of the human population, such that no sex-, age- or ethnicity-related differences were noted in sensitivity, would be necessary for the confidence interval to be taken as applicable to the entire human population for comparison to rats, and this was not accomplished. Based on these limitations, as well as those summarized above for the in vitro assays, the data are insufficient to conclude similarity of human and rat AChE enzymes, or to adequately characterize their difference. Therefore, the toxicodynamic component of the interspecies uncertainty factor should not be altered from the default value of 2.5-fold.

Intraspecies uncertainty factor

Several limitations were identified with the information provided by the registrant to support a reduction of the intraspecies uncertainty factor. Major limitations related to the fact that samples were collected from only three different ethnicities. This is not an adequate representation of the Canadian population, and that there was an insufficient number of individuals representing the various ethnic groups, and the subsets within these groups. This precluded the conduct of a credible statistical analysis for the identification of potential differences in AChE inhibition within the Canadian human population. Given that sensitivity of the young has been identified with respect to AChE inhibition in the naled database, the fact that no human samples from young children (less than 10 years old) or samples from juvenile rats were available for the in vitro inhibition kinetic experiments is another significant limitation. Also, insufficient information was provided to justify that increased EChE activity in pregnant women reported in the literature was not relevant to the toxicodynamics of AChE inhibition. The registrant stated that ANOVA comparisons of kinetic constants for naled and dichlorvos did not reveal any statistically significant differences across ethnicity, sex and age, but did not provide the results of this analysis. However, the more appropriate statistical approach would involve using the upper one-sided 95% confidence limit for population variance to establish the CSAF. In addition, the variability analysis provided by the registrant was not considered sufficiently robust to distinguish experimental from biological variability in the human data. Subsample data for naled were provided for four samples only, no subsample data were provided for dichlorvos, and the subsamples were technical, rather than biological, replicates. Further, a more appropriate approach would involve components of variance analysis for k_i values on the log scale, rather than the examination of coefficients of variation conducted by the registrant. Using the components of variance method to analyze the limited subsample data that was available, the results indicated that biological variation was greater than the experimental variation, which was contrary to the registrant’s conclusion, and would not support a reduction in the default intraspecies uncertainty factor. It is also unknown if the variation that exists for human BChE is equivalent to that reported in this study for human EChE since the in vitro studies used erythrocyte derived AChE while the target of organophosphate inhibitors is AChE in the brain. Based on these limitations, as well as those summarized above for the in vitro assays, the data are insufficient to conclude similarity of AChE enzymes across the human population. Therefore, the toxicodynamic component of the intraspecies uncertainty factor should not be altered from the default value of 3.2-fold.

In summary, there were significant limitations noted with the information submitted to support derivation of CSAFs for naled and dichlorvos. Although the predictions from the computational modelling were considered to support the likelihood of a high degree of similarity between human and rat AChE in a supplemental manner, the limitations with the in vitro AChE inhibition kinetic assays precluded the determination of comparative rates of AChE inhibition between humans and rats for either naled or dichlorvos. Additional limitations included those regarding insufficient sample size, inadequate representation of ethnic groups and sensitive age groups in the human samples, unavailability of raw data, and lack of transparency in data handling. Overall, several criteria in the WHO guidance for estimating CSAFs using in vitro studies were not met, and Health Canada has concluded that there is insufficient support for the proposed CSAFs for naled and dichlorvos. Therefore, the standard uncertainty factor of 100-fold will continue to be used for the human health risk assessments of both naled and dichlorvos.

Overall, review of the comments and data submitted by the registrant resulted in a change to the point of departure for the combined dermal risk assessment for naled and dichlorvos based on the recently conducted 28-day dermal toxicity conducted with dichlorvos. The remaining reference values that were established for naled, and presented in PSRD2019-02 and PSRD2019-03, will continue to be used. The revised toxicology reference values for dichlorvos are presented in Appendix III, Table 3 in Re-evaluation Decision RVD2020-08, *Dichlorvos and Its associated end-use products.*

1.2 Comments related to occupational exposure

Comment – General information provided

The registrant provided information about the use of their product including the most important uses on crops (indoor and outdoor) and non-crop areas, application equipment, timing of use (postharvest vs. pre-harvest), etc.

Health Canada response:

This information was considered in the risk assessment and the assessment was revised where appropriate (for example, the greenhouse postapplication assessment was changed from long-term to short-term in duration, resulting in a target MOE of 300 for naled rather than 1000). Please refer to Appendix IV for the updated risk assessment.

Comment – Greenhouse Postharvest use / Greenhouse vegetable crop clean-out

The registrant and Canadian Horticulture Council (CHC) provided specific information on the postharvest greenhouse vegetable use. This included a description on what tasks the worker would be doing in the greenhouse after the crop is harvested and treated, and how much exposure would be expected, qualitatively.

Health Canada response:

Based on the comments received, follow-up discussions with the CHC, and information on crop profiles, a transfer coefficient (TC) specific to workers who perform postharvest clean-up activities on specific greenhouse vegetable crops was selected for use in dermal postapplication risk assessments. Previously for greenhouse vegetables (tomato, cucumber, peppers, and eggplants), a TC of 1400 cm^2/hr was used to estimate exposure for workers doing any postapplication task, as there was no specific TC for postharvest clean-up. The Agricultural Re-Entry Task Force (ARTF) studies in the greenhouse vegetable cluster were reviewed and a lower TC of 640 cm^2/hr was selected to be more representative of the tasks conducted while removing dead plant material and cleaning out a greenhouse. This new TC was used in the revised dermal postapplication risk assessment for naled, and will be used in future greenhouse postharvest clean out scenarios. Please refer to Appendix IV for the updated risk assessment.

Comment – Greenhouse risk assessment not based on data

The registrant stated that the determination of unacceptable risk in greenhouses was not based on actual naled or dichlorvos data. The dermal assessment was based on surrogate data and there were no actual inhalation exposure assessments.

Health Canada response:

The current greenhouse exposure and risk assessment for naled was based on the data available.

In the absence of naled- or dichlorvos-specific data to estimate dermal exposure for postapplication workers, Health Canada relied upon transfer coefficients derived from studies conducted by the ARTF, of which AMVAC is a member. For further information on the generic use of TCs, that is, the use of TCs between different active ingredients, please refer to Health Canada's Regulatory Proposal PRO2014-02, *Updated Agricultural Transfer Coefficients for Assessing Occupational Exposure to Pesticides.*

Similarly, in the absence of naled-specific DFR data for greenhouses or DFR data for dichlorvos resulting from naled application in greenhouses, Health Canada relied on standard assumptions to estimate DFR, as noted in Health Canada's Science Policy Note SPN2014-02, *Estimating Dislodgeable Foliar Residues and Turf Transferable Residues in Occupational and Residential Postapplication Exposure Assessments.* Please also refer to the response to the next comment below.

No data were available to estimate inhalation exposure of naled, and dichlorvos resulting from naled application in greenhouses. Inhalation risks of concern for all indoor scenarios are expected based on the volatility and toxicity of naled and dichlorvos. A worker exposure study (for example, passive dosimetry or biomonitoring), or air concentration study, could be considered for better characterization of greenhouse postapplication inhalation risks.

Health Canada acknowledges that provision of a new greenhouse DFR study and ambient air concentration and dissipation study or a passive dosimetry/biological monitoring study following application of naled may help refine the greenhouse risk assessment. Registrants have the option to submit new studies and additional information to Health Canada to amend registrations. All new applications will be processed according to PMRA Guidance Document, *Management of Submissions Policy*.

Comment – Greenhouse dislodgeable foliar residue default

The registrant did not agree with the use of the greenhouse default initial deposition of dislodgeable foliar residue (DFR) on greenhouse crops in the dermal risk assessment, nor did they agree with the assumption that the Canadian outdoor broccoli DFR data that were being used for the outdoor risk assessment, were inappropriate for an indoor risk assessment. The registrant proposed using 2.9% for the initial concentration after application of naled instead of the default of 25%. The 2.9% was based on a turf transferrable residue study that was conducted in Florida during and after mosquito abatement using a fogger over turf. This initial deposition of 2.9% was also supported by the results of the outdoor broccoli DFR study that was used in the outdoor dermal risk assessment.

Health Canada response:

In the absence of chemical-specific data, as is the case for naled in greenhouses, Health Canada relied on standard assumptions to estimate DFR, as noted in Health Canada's Science Policy Note SPN2014-02, *Estimating Dislodgeable Foliar Residues and Turf Transferable Residues in Occupational and Residential Postapplication Exposure Assessments.*

The turf transferrable residue (TTR) study cannot be used to represent dislodgeable foliar residues on greenhouse-grown vegetables for several reasons.

a. TTR studies use a different collection technique. They use a modified California Roller method where a large weighted PVC rolling pin is wrapped in cotton sampling medium and rolled over a framed area of grass to collect turf residues. Whereas in a DFR study, leaf punches are collected and agitated in an aqueous surfactant solution to extract residues. For a postapplication exposure assessment, dermal exposure is estimated using TCs derived from DFR residues measured using leaf punches. Since the TC is based on leaf punch samples, the TC can only be used with DFR values measured using the leaf punch technique. The relationship of residues measured using the modified California roller to the TCs used for the greenhouse assessment is not known.
b. The TTR study and the broccoli DFR study were conducted outdoors and the results cannot be used for an indoor risk assessment. Climatic conditions play an important role in initial concentration and dissipation of DFR over time.
c. The foliage type and general crop morphology between turf and greenhouse grown cucumbers, tomatoes, eggplants and peppers is much different and is not acceptable as a surrogate crop.

Health Canada will continue to use the standard greenhouse initial DFR value of 25% of the application rate. However, based on a recent analysis of a number of greenhouse DFR studies using several pesticides, the DFR dissipation rate has been updated from 0% to 2% dissipation per day. The dermal postapplication risk assessment for naled was revised with this input. Due to the volatility of naled and dichlorvos, Health Canada agrees that the initial DFR concentration is likely lower than the default value of 25%; however, chemical-specific greenhouse data is required to refine the risk assessment. Please refer to Appendix IV for the updated risk assessment.

Comment – Inhalation of dichlorvos through greenhouse fogging treatment

The registrant suggests using dichlorvos air concentration data as a surrogate for naled air concentration data since both chemicals are volatile and have a similar chemical structure. A literature study was mentioned, as was the possibility of adding a respirator and appropriate ventilation procedures and re-entry times.

Health Canada response:

Due to the high volatility of naled and dichlorvos and the very specific use pattern in greenhouses, only chemical-specific data would be considered acceptable for estimating worker exposure and risk. While dichlorvos may have a similar chemical structure to naled, the degree and rate of formation of dichlorvos following naled application are not known. In addition, workers could be exposed to both naled and dichlorvos at the same time, and separate and combined risk assessments for naled and dichlorvos would need to be conducted, since their toxicological profiles are different. Therefore, dichlorvos data from application of dichlorvos alone is not considered to be acceptable for estimating exposure and risk of both naled and dichlorvos following application of naled.

Comment – Inhalation of organophosphates (OPs) used in greenhouses

The registrant suggested three literature studies that could provide insight into the dissipation of OP compounds under different use scenarios. The studies were conducted in several types of greenhouses in Brazil, Spain and Greece, using different types of application equipment and a variety of OP chemicals.

Health Canada response:

As noted above, chemical-specific data are required for inhalation risk assessment.

Comment – Refined dermal dose (RDD) for naled based on in vitro dermal absorption of rat and human skin

The registrant recommended updating the dermal risk assessment for naled by adjusting the naled dermal point of departure based on the lower permeability of human skin when compared to rat skin. This was supported with two cited dermal absorption studies, one rat in vivo and one human and rat in vitro, both of which form the basis for a triple pack approach. The lowest adjustment factor would be 2.55, calculated from the 24 hr time point at the 1:1000 dilution measurement, where it provided the highest dermal absorption in both studies and yielded the lowest adjustment factor. The RDD would therefore be calculated to be 2.55 times higher than the point of departure selected to represent dermal exposure. Similar USEPA examples were provided.

Health Canada response:

Since the dermal risk assessment for naled was based on a dermal toxicology study ($BMDL_{10}$ of 1.96 mg/kg bw/day derived from the 28-day dermal toxicity study in rats), a dermal absorption value is not required. The registrant's proposal is to adjust the dermal toxicology reference value (that is the $BMDL_{10}$) to account for differences in dermal absorption between rats and humans. As noted in Health Canada's Science Policy Note 2008-01, *The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides*, Health Canada applies an uncertainty factor of 10-fold for interspecies extrapolation to address the uncertainty inherent in the extrapolation of information from experimental animal species to humans, and is based on the assumption that humans are more sensitive than experimental animals. Dermal absorption is only one aspect in the overall consideration of differences between rats and humans. As further described in SPN2008-01, the 10-fold interspecies uncertainty factor may be considered to be composed of a fourfold factor for toxicokinetics and a 2.5-fold factor for toxicodynamics (WHO, 2001).[6] As outlined by WHO, as well as in the Health Canada response to the proposed application of CSAFs in the toxicology comments above, extensive data are required to adjust the standard interspecies factor. The toxicokinetic component of the interspecies factor includes consideration of absorption, distribution, metabolism and excretion of the test chemical. The adjustment proposed by the registrant is not supported by data other than the cited in vitro and in vivo dermal absorption studies, and their relevance to the toxicology study and to the dermal exposure scenarios is not known. In addition, dermal absorption only encompasses one aspect of the toxicokinetics. Furthermore, by adjusting the point of departure directly and not as a means to adjust the interspecies toxicokinetic default factor, greater weight is assigned to the interspecies differences than is deemed appropriate. For these reasons, Health Canada did not accept the registrant's rationale to adjust the naled dermal reference value.

Comment – Dermal absorption study

A study, "Dermal Absorption of dichlorvos in rats" (Jeffcoat 1990), was submitted.

Health Canada response:

In PSRD2019-02 and PSRD2019-03, a dermal absorption factor of 30%, based on an USEPA review of the Jeffcoat (1990) study, was used in the dichlorvos dermal risk assessment. However, as described in the Health Canada response to toxicology comments above, a dermal absorption value is no longer required as the short-, intermediate- and long-term dermal toxicology reference values used in the risk assessment of dichlorvos have been updated using the results from the new dermal toxicity study. Please refer to Appendix IV for the updated risk assessment.

Comment – General information provided

CHC provided use information on greenhouse vegetable crops including frequency of harvesting, crop cycles, use of biologicals preventing naled use during the production cycles, greenhouse volume, and application equipment.

Health Canada response:

This information was considered in the risk assessment and the assessment was revised where appropriate (for example, the greenhouse postapplication assessment was changed from long-term to short-term in duration, resulting in a target MOE of 300 for naled, rather than 1000). Please refer to Appendix IV for the updated risk assessment.

Comment – Vapour treatment

Information was provided on vapour treatment of naled in greenhouses. CHC does not agree that the PHED backpack exposure study is an appropriate surrogate for the greenhouse vapour application. They also noted that the risk assessment did not appear to account for the use of chemical-resistant coveralls and a respirator as PPE, which are listed on the label.

Health Canada response:

No studies were available to estimate worker exposure for vapour treatment, which is workers applying a pesticide using a squeeze bottle.

In the absence of a specific exposure study for the vapour treatment, several exposure studies were considered. None of them were considered ideal. Regardless of which study or application equipment scenario was used, worker risks were not shown to be acceptable. The risk assessment did, however, include chemical-resistant coveralls and a respirator.

The mix/load component of the assessment, including vapour treatment, was updated with the more recent AHETF study, resulting in a slightly lower exposure estimate. However, risks still were not shown to be acceptable.

Comment – Restricted-entry interval (REI)

CHC indicated that a longer REI may be acceptable for the postharvest clean-up activities in greenhouse vegetables as they do not have the same agronomic demands as an actively growing crop. However, postharvest clean-up requires a lot of farm labour, and the flexibility of workable REIs would require further dialogue with the sector.

Health Canada response:

The dermal risk assessment was updated for naled and dichlorvos, as described above. However, risks were still not shown to be acceptable for dermal and inhalation exposure for both application and postapplication exposure. REIs were not considered for this assessment, as the risk concerns are multifaceted and REIs would only address a small aspect of the overall risk picture. For example, REIs would not address the applicator risk.

Comment – Gloves

Increased use of PPE (such as gloves) by greenhouse workers in postapplication activities could reduce dermal exposure to acceptable levels.

Health Canada response:

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

Before Health Canada can estimate risk to workers wearing gloves, worker exposure studies comparable to those currently used by Health Canada are required. Studies that are currently used are discussed in the Regulatory Proposal PRO2014-14 *Updated Agricultural Transfer Coefficients for Assessing Occupational Postapplication Exposure to Pesticides*. Most, if not all, studies conducted by the ARTF, submitted by registrants, or available in the scientific literature that are used to determine Health Canada's TCs do not include gloves as a basis to estimate exposure. Gloves may have been worn in some of the studies; however, they were used as dosimeters to measure hand exposure without gloves, rather than exposure with protection from the gloves. While one limited study showed significant reduction in hand exposure when wearing gloves during tomato harvesting (Rech et al., 1989),[7] a number of other available studies suggest that exposure may actually increase when gloves are worn

7 Rech, C.; Bissell, S.; Margotich, S. 1989. Worker Exposure to Chlorothalonil Residues during the harvest of fresh market pole tomatoes. Report HS-1456. California Department of Food and Agriculture. June 19, 1989.

(Brouwer, 2000;[8] Boman et al., 2005;[9] Garrigou et al., 2011;[10] Graves et al., 1995;[11] Keifer, 2000;[12] Rawson et al., 2005[13]). Health Canada is currently participating in a working group that includes grower and industry representatives. The purpose of the working group is to a) investigate the use of gloves as a risk mitigation option for postapplication workers in pesticide treated areas and b) to investigate more efficient ways to gather postapplication worker information to ensure that risk assessments are kept up-to-date in reflecting activities that occur in the field. The scope of this information gathering includes both agricultural crops and ornamentals. The role of Health Canada on this working group is to provide regulatory advice and direction for any proposals suggested by the working group to meet the project goals. Currently, the working group is considering conducting studies to estimate the degree of protection offered by chemical-resistant gloves while performing activities in various crops for the purpose of determining a default protection factor of gloves for postapplication workers. Based on the outcome of these studies, Health Canada may consider gloves as a mitigation measure for postapplication workers in the future. Presently, such data are not available.

Comment – Greenhouse ventilation

CHC provided a published greenhouse ventilation study as well as details of greenhouse ventilation practices.

Health Canada response:

The submitted study cannot be used to refine the risk assessment as it did not measure air concentrations of naled and dichlorvos. Health Canada recommends that any studies measuring air concentrations of volatile pesticides in greenhouses be conducted under various levels and types of ventilation, in order to have an understanding of the effect of ventilation on air concentrations.

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8 Brouwer, D.H., de Vreede, S.A.F., Meuling.,W.J.A., van Hemmen, J.J. 2000. Determination of the efficiency for pesticide exposure reduction with protective clothing: a field study using biological monitoring. Chapter 5 In: Assessment of Occupational Exposure to Pesticides in Dutch Bulb Culture and Glasshouse Horticulture. Doctoral Thesis of D.H. Brouwer. pp.158-179.

9 Boman, A., Estlander,T.,Wahlberg J.E., Maibach, H.I. 2005. Protective Gloves for Occupational Use Second edition. CRC Press LLC.

10 Garrigou, A., Baldi I.,Le Frious P., Anselm R., Vallier M. 2011. Ergonomic contribution to chemical risks prevention: an ergotoxicologcial investigation of the effectiveness of coverall against plant pest risk in viticulture. 42: 321-330.

11 Graves, CJ., Edwards, C., Marks R. 1995. The effects of protective occlusive gloves on stratum corneum barrier properties. Contact Derm 33: 183-187.

12 Keifer, M.C., 2000. Effectiveness of Interventions in Reducing Pesticide Overexposure and Poisonings. American Journal of Preventive Medicine. 18 (4S); 80-89.

13 Rawson, B.V., Cocker, J., Evans, P.G. Wheeler, J.P. and Akrill, P.M. 2005. Internal contamination of Gloves: routes and Consequences. Ann. Occup. Hyg. 49 (6): 535-541.

2.0 Comments related to potential risks to aquatic organisms (special review under subsection 17(2) of *Pest Control Products Act*):

Comment – Soil aerobic biotransformation half-life should be reconsidered

The commenter is proposing that a first-order photolysis half-life replace the soil biotransformation value used for the water modelling for naled.

Health Canada response:

The photolysis study by McGovern was not of better quality than the study used to characterize soil degradation. For the soil degradation study, results of CO_2 and unextracted residues suggest minimal loss due to volatility so this study is still suitable for the DT_{50} endpoint. For modelling, a one-day half-life was chosen as a conservative estimate.

Comment – Using an inert substrate gives a more relevant representation of photolysis on a soil surface

Degradation of naled through microbial metabolism is very rapid. The commenter suggested that a more appropriate representation of phototransformation on a soil-based substrate would occur on an inactivated surface.

Health Canada response:

A study measuring photolysis on dried cotton leaves suggested that naled was transformed to dichlorvos in less than 2 hours compared to only low conversion in the dark control. Rapid debromination of naled occurs when it is exposed to light, and dichlorvos is produced as a transformation product. This study can be used to support that naled is expected to be very short-lived in the terrestrial environment. Dichlorvos was measured as a transformation product of naled through photolysis on an inert substrate; however in soil, the production of dichlorvos is expected to be minor or not detected, and dichlorvos is expected to dissipate rapidly.

Comment – Aqueous phototransformation of naled in the presence of photosensitizers is an important process to consider

The registrant indicated that there is a line of evidence to suggest that phototransformation in aquatic systems is accelerated in the presence of photosensitizers. Given that photosensitizers are part of the natural environment it was suggested that this point be considered as an important line of evidence for describing the persistence of naled in the aquatic environment.

Health Canada response:

Health Canada agrees with this comment and the contribution of indirect phototransformation to the dissipation of naled in the environment was considered in the weight of evidence showing that naled is expected to be short-lived in the environment. The first-order half-life from the aquatic photolysis study which was based on sensitized/irradiated samples (0.98 days) was used for calculating revised EECs for the risk assessment for runoff. The revised aquatic risk assessment included a discussion of multiple lines of evidence regarding the fate of naled in the environment (see Section 3.1).

Comment – Shorter dissipation half-lives for aerobic and anaerobic aquatic studies should be considered

The registrant suggested there is evidence to indicate that the half-life under aerobic and anaerobic aquatic conditions for naled is significantly faster than “stable”, which was indicated in PSRD2019-03, and that the sediment-based half-life for naled should be set at 6 hours.

Health Canada response:

An initial value of “stable” was used for naled for water modelling because the studies were considered to be unacceptable due to numerous deficiencies. Therefore, “stable” was used in the absence of acceptable data to model for naled. As has been demonstrated by various lines of evidence, however, naled is not expected to be long-lived in the environment. Modelled EECs for runoff of naled and dichlorvos were re-assessed using shorter dissipation half-lives for aerobic and anaerobic aquatic biotransformation of naled. The following parameters were used: water half-life, 0.26 days (based on aerobic water biotransformation) and sediment half-life, 0.14 days (based on anaerobic water biotransformation), or 6.2 hours and 3.4 hours, respectively (see Section 3.1).

Comment – Hydrolysis of naled is the predominant process such that dichlorvos formation would not pose a hazard to aquatic species.

Health Canada response:

Health Canada concurs that hydrolysis is a major route of transformation of naled. Based on available information, dichlorvos was not formed as a transformation product in either the laboratory study of hydrolysis or aerobic soil biotransformation with naled. Dichlorvos is, however, produced in water through photolysis in the presence of photosensitizers up to 20% AR after one day. This could contribute to the presence of residues of dichlorvos in water if naled enters water through runoff or spray drift. For further discussion, see Section 3.1.

Comment – The sediment-based half-life for dichlorvos should be set at 12 hours based on the aerobic water/sediment study with naled.

Health Canada response:

For modelling EECs for runoff for dichlorvos, the dissipation half-life from the aerobic water biotransformation study (0.42 days or 10 hours) was used for the water half-life for dichlorvos. This value is slightly lower than the value suggested by the registrant (12 hours) from the aerobic aquatic study.

The value used for the sediment half-life, 23.5 days, was derived from curve-fitting the data from the anaerobic water biotransformation study with naled. These parameters were not modified for the modelling of environmental concentrations in runoff.

Comment - Use of flow-through systems and initial maximum concentrations to determine aquatic toxicity endpoints for naled (and dichlorvos) for regulatory purposes are overly conservative.

The registrant indicated that the rapid decline of naled and dichlorvos in water should be considered when determining relevant exposure concentrations within the 48-hour period of a toxicity test.

Health Canada response:

This is a standard approach for a chemical that is unstable in water. Use of a flow-through system is a way to standardize an approach for determining a toxicity value. For static toxicity tests, a mean concentration over the duration of the study can be considered if measured concentrations are available. The environmental fate data and the exposure modelling address the issue of persistence. For non-persistent chemicals the fate assessment and modelling will show low exposure and therefore low risk as compared to a more persistent but equally toxic chemical. The water modelling conducted for the ecoscenario for PSRD2019-03 used the most conservative exposure parameters. However, the modelled environmental concentrations were revised for this assessment (see Section 3.1) and exposure parameters were reassessed. For the risk assessment, the duration of the toxicity studies are matched with the appropriate exposure duration for the estimated concentrations in runoff to determine a risk quotient.

Comment – An aquatic half-life of 6 hours for naled should be used.

Health Canada response:

Modelled EEC's in runoff were re-calculated for naled for a revised aquatic risk assessment after input parameters were reassessed. This included an aerobic water DT_{50} of 6 hours and an anaerobic sediment DT_{50} of 3 hours (see Section 3.1). In addition, the average modeled concentrations were matched with the time period for the toxicological endpoint to determine the risk quotient. If the time period of the toxicity study could not be matched, the next lowest available EEC time period was used (for example, a 24-h LC_{50} would be matched with a peak EEC).

Comment – Additional fish toxicity endpoints for a formulated naled test substance were provided and should be used for the risk assessment for fish and amphibians.

Health Canada response:

The three toxicity studies provided by the registrant were conducted with rainbow trout (*Salmo gairdneri*) using a flow-through test system and three formulations of naled. The results of the studies were within the range of other tests conducted with rainbow trout that were available for PSRD2019-03.

A more sensitive endpoint for freshwater fish was available (lake trout) and was used for the risk assessment. Therefore, the additional rainbow trout studies would not change the results of the risk assessment for naled.

Comment – Available evidence suggests that naled does not pose an unacceptable risk to amphibians.

The registrant provided a citation for a USEPA document, indicating that it contained an acute toxicity endpoint for tadpoles (simulated field study) and proposed it be used in the risk assessment for naled.

Health Canada response:

Health Canada did not identify risks to amphibians from naled; therefore, this information did not affect the outcome of the risk assessment.

Comment – Water monitoring data (Quebec; Giroux, 2019) should be considered in the risk assessment, including an analysis of uses in catchments where samples were collected; in the absence of detections, one-half the limit of detection (in other words, 0.025 µg/L) should be used as the exposure concentration.

Health Canada response:

The water monitoring data from Giroux, 2019 was received by Health Canada and included in an updated analysis of all available Canadian water monitoring data. The use of one-half the limit of detection, in the absence of detections, is the standard practice used by Health Canada for pesticide water monitoring data.

Comment - Down-gradient or full perimeter use of vegetative buffer strips should be considered as a mitigative measure for risk to aquatic organisms from runoff.

Health Canada response:

The potential use and effectiveness of vegetative filter strips were considered as a mitigative measure but were not mandated in label instructions for Dibrom Insecticide. The revised risk assessment conducted by Health Canada concluded that risks to aquatic organisms due to runoff of naled are acceptable and further mitigation for runoff was not required.

3.0 Comments related to other considerations

Comment – Guidance for new exposure studies

The registrant and CHC provided comments regarding potential discussions with Health Canada for guidance in the development and design of new greenhouse studies to assess inhalation and dermal exposure to workers for consideration in the final special review decision.

Health Canada response:

The current exposure and risk assessment for naled was based on the data available at the time. No additional scientific data was required during the consultation period for the Proposed Special Review Decisions PSRD2019-02 and PSRD2019-03. However, registrants and stakeholders were encouraged to provide available information that may address uncertainties in the available information database of naled before the end of the consultation period for consideration in the final special review decision. Registrants have the option to submit new studies and additional information to Health Canada to amend registrations. All new applications will be processed according to PMRA Guidance Document, *Management of Submissions Policy.*

Comment – Uses of naled

The registrant identified the key uses of naled (Dibrom Insecticide). These priority uses were communicated to the Agency in response to PSRD2019-02 and PSRD2019-03:

- The **most important use** of naled was in greenhouses for the production of cucumbers, eggplants, peppers, tomatoes and cut flowers.
- **Other priority crop uses** of naled were: broccoli, cabbage, lettuce and onions.
- **Key non-crop uses** of naled were identified as livestock pastures and feedlots, and woodland areas.

Health Canada response:

Based on the revised risk assessment, some key uses of naled are being cancelled, and some are retained. While use on alfalfa, clover, vetch, peas, beans, lima beans, sugar beet and potato will be cancelled, these uses were not identified as key uses.

- **Most important use - greenhouse uses:** Greenhouse uses will be cancelled as health risks are not shown to be acceptable (occupational risk).
- **Other priority crop uses:** These uses are being retained.
- **Key non-crop uses:** The use of naled in livestock pastures and feedlots is being retained. The use of naled in woodland areas will be cancelled as health risks were not shown to be acceptable (occupational risk). The importance of the impact of these pests on woodland areas has not been demonstrated.

Comment – Greenhouse vegetables

Comments from CHC were received in response to the proposed cancellation of naled on greenhouse vegetables. The value of the use of naled for end-of-cycle crop clean up was detailed.

Health Canada response:

Health Canada recognizes the value of naled to the production of greenhouse cucumbers, eggplants, peppers and tomatoes. However, the health risk to workers was not shown to be acceptable, and therefore, this use is cancelled.

Appendix IV Occupational/residential mixer/loader/applicator (MLA) and postapplication exposure and risk estimates for naled

Details and tables for the revised risk assessment are included in this appendix. Please refer to PSRD2019-02 and PSRD2019-03 for additional information.

Greenhouse end-of-cycle clean out

The occupational MLA and postapplication risk assessment was revised to account for only one application per year.

Agricultural handlers exposure task force data for MLA

Mixer/loader and applicator assessments were updated using recent AHETF data. For this assessment, open mix/load liquid, open cab groundboom, closed cab airblast, and aerial application were updated using the new data (AHETF 2009, 2012, 2014, 2015).

Handheld mistblower/fogger MLA

At the time the PSRDs were completed, data were not available to assess handheld airblast/mistblower equipment. It was expected that worker exposure would be significant while using this type of equipment and for this reason handheld mistblowers were proposed to be prohibited. Since that time, data were submitted to the Health Canada and these worker exposure studies (Testman 2015 [PMRA# 2905452] and Thouvenin 2016) were used to conduct a risk assessment.

Postapplication exposure to workers who are cleaning out a greenhouse

For workers performing postapplication activities in a greenhouse after harvest is completed, the exposure assessment was revised based on the comments submitted during the comment period.

There were two significant changes.

- Since the postharvest clean-up occurs once per year, the exposure duration was changed from long-term to short-term resulting in a change of the target MOE for naled of 300 rather than 1000.
- Based on use information provided, a new transfer coefficient (TC) specific to workers who perform postharvest clean-up activities on specific greenhouse vegetable crops was selected for use in dermal postapplication risk assessments. Thus, the TC was revised from 1400 cm^2/hr for workers doing any postapplication task to 640 cm^2/hr for workers conducting tasks for pos-harvest clean-up. See response to comments above for details.

Table 1 Mixer/loader/applicator exposure and risk assessment of naled by groundboom application

Crop	Application rate (kg a.i./ha)	ATPD (ha/day)[a]	Amount handled per day (kg a.i./day)	Dermal MOE[b,d]	Inhalation MOE[c,e]	Combined MOE[f]
PPE: Mid-level PPE + open M/L + open cab + respirator [g]						
Broccoli, Brussels sprouts, cabbage, cauliflower	1.9	26	49	70	460	68
Lettuce	1.44	26	37	92	600	90
Onion	0.48	26	12.48	280	1800	270
Strawberries	0.95	26	25	140	910	140
Tomatoes	1.728	26	45	77	500	75
Ornamentals	0.324	26	8	410	2700	400
PPE: Max-level PPE + closed M/L + open cab + respirator [g]						
Alfalfa, clover, vetch – custom	1.9	200	380	21	76	20
Alfalfa, clover, vetch – custom	0.950	360	342	23	85	22
Rangeland, field areas, pastures (dairy cattle present) – custom	0.864	360	311	26	93	24
Rangeland, field areas, pastures (dairy cattle present) – custom	0.477	360	171	47	170	43
Peas, beans, lima beans – custom	1.9	200	380	21	76	20
Peas, beans, lima beans – custom	0.950	360	342	23	85	22
Broccoli, Brussels sprouts, cabbage, cauliflower – custom	1.9	26	49	160	590	150
Broccoli, Brussels sprouts, cabbage, cauliflower – custom	0.95	26	25	330	1200	300
Lettuce – custom	1.44	26	37	220	780	200
Lettuce – custom	0.95	26	25	330	1200	300
Onion – custom	0.48	26	12	640	2300	600
Potatoes – custom	0.95	360	342	23	85	22
Potatoes – farmer	0.95	85	81	100	360	92
Strawberries – custom	0.95	26	25	330	1200	300
Tomatoes – custom	1.728	26	45	180	650	170
Tomatoes – custom	0.95	26	25	330	1200	300
Tomatoes – farmer	1.728	9	16	520	1900	480
Tomatoes – farmer	0.95	9	9	940	3400	870
Sugar beet – custom	1.9	360	684	12	42	11
Ornamentals	0.324	26	8	950	3400	880
Ornamentals	0.108	26	3	2900	10 000	2700
PPE: closed M/L (Max-level PPE) + closed cab (mid-level PPE) [g]						

Crop	Application rate (kg a.i./ha)	ATPD (ha/day)[a]	Amount handled per day (kg a.i./day)	Dermal MOE[b,d]	Inhalation MOE[c,e]	Combined MOE[f]
PPE: Mid-level PPE + open M/L + open cab + respirator [g]						
Broccoli, Brussels sprouts, cabbage, cauliflower	1.9	26	49	70	460	68
Lettuce	1.44	26	37	92	600	90
Onion	0.48	26	12.48	280	1800	270
Strawberries	0.95	26	25	140	910	140
Tomatoes	1.728	26	45	77	500	75
Ornamentals	0.324	26	8	410	2700	400
Alfalfa, clover, vetch – custom	1.9	200	380	34	80	31
Alfalfa, clover, vetch – custom	0.950	360	342	38	89	35
Alfalfa, clover, vetch – farmer	1.9	107	203	63	150	59
Alfalfa, clover, vetch – farmer	0.950	107	102	130	300	118
Rangeland, field areas, pastures (dairy cattle present) – custom	0.864	360	311	41	98	38
Rangeland, field areas, pastures (dairy cattle present) – custom	0.477	360	171	75	180	70
Rangeland, field areas, pastures (dairy cattle present) – farmer	0.864	107	92	140	330	129
Rangeland, field areas, pastures (dairy cattle present) – farmer	0.477	107	51	250	600	235
Peas, beans, lima beans – custom	1.9	200	380	34	80	31
Peas, beans, lima beans – custom	0.950	360	342	38	89	35
Peas, beans, lima beans – farmer	1.9	36	68	190	450	175
Peas, beans, lima beans – farmer	0.950	36	34	380	890	350
Broccoli, Brussels sprouts, cabbage, cauliflower – custom	1.9	26	49	260	620	242
Broccoli, Brussels sprouts, cabbage, cauliflower – custom	0.95	26	25	520	1200	484
Lettuce – custom	1.44	26	37	350	830	323
Lettuce – custom	0.95	26	25	520	1238	484
Onion – custom	0.48	26	12	1000	2500	958
Potatoes – custom	0.95	360	342	38	89	35

Crop	Application rate (kg a.i./ha)	ATPD (ha/day)[a]	Amount handled per day (kg a.i./day)	Dermal MOE[b,d]	Inhalation MOE[c,e]	Combined MOE[f]
PPE: Mid-level PPE + open M/L + open cab + respirator [g]						
Broccoli, Brussels sprouts, cabbage, cauliflower	1.9	26	49	70	460	68
Lettuce	1.44	26	37	92	600	90
Onion	0.48	26	12.48	280	1800	270
Strawberries	0.95	26	25	140	910	140
Tomatoes	1.728	26	45	77	500	75
Ornamentals	0.324	26	8	410	2700	400
Potatoes – farmer	0.95	85	81	160	380	148
Strawberries – custom	0.95	26	25	520	1200	484
Tomatoes – custom	1.728	26	45	290	680	266
Tomatoes – custom	0.95	26	25	520	1200	484
Sugar beet – custom	1.9	200	684	19	45	17
Sugar beet – farmer	1.9	107	203	63	150	59
Ornamentals	0.324	26	8	1500	3600	1420
Ornamentals	0.108	26	3	4600	11 000	4259

M/L = mix/load, ATPD = area treated per day, MOE = margin of exposure, PPE = personal protective equipment
Mid-level PPE= coveralls over a long-sleeved shirt, long pants and chemical-resistant gloves.
Max-level PPE = chemical-resistant coveralls over a long-sleeved shirt, long pants and chemical-resistant gloves.
[a] Values were refined based on the Census of Agriculture (Statistics Canada, 2011). When no suitable values were found, default ATPD were used. The current label limits workers using maximum rate of 2.2L/ha to 200ha/day. Farmer scenarios were removed from parts of this table since exposure and potential risk would be higher for custom application.
[b] Dermal exposure (mg/kg bw/day) = (dermal unit exposure × ATPD × application rate)/ body weight
[c] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure × ATPD × application rate)/body weight. 90% protection factor was used for the respirator to calculate inhalation exposure.
[d] Based on a $BMDL_{10}$ of 1.96 mg/kg bw/day from a rat 28-day dermal toxicity study, and a target MOE of 300.
[e] Based on a LOAEL of 0.065 mg/kg bw/day from a rat 90-day inhalation toxicity study, and a target MOE of 100.
[f] Combined MOE = $1/(1/MOE_{dermal}) + (1/MOE_{inhalation})$; based on a dermal $BMDL_{10}$ of 1.96 mg/kg bw/day, and a target MOE of 300 and an inhalation $BMDL_{10}$ of 0.35 mg/kg bw/day, and a target MOE of 300.
[g] Current PPE on the label states: Max-level PPE when applying to areas larger than 30 ha/day, Mid-level PPE if less than 30 ha/day + open M/L + respirator. Currently, respirator is only required for the applicator using an open cab.
Shaded cells indicate MOEs that are less than the target MOE.

Table 2 Mixer/loader/applicator exposure and risk assessment of naled by aerial application

Crop	Rate (kg a.i./ha) [g]	ATPD (ha/day)[a]	Amount handled per day (kg a.i./day)	Dermal MOE[b,d]	Inhalation MOE[c,e]	Combined MOE[f]
Aerial M/L closed (Max-level PPE) [h]						
Potatoes	0.950	240	228	89	210	82
Tomatoes	0.950	200	190	110	250	110
Corrals, pastures,	0.275	222	61	330	770	310

Crop	Rate (kg a.i./ha) [g]	ATPD (ha/day)[a]	Amount handled per day (kg a.i./day)	Dermal MOE[b,d]	Inhalation MOE[c,e]	Combined MOE[f]
holding pens, (dairy and beef cattle present)	0.110	222	24	830	1900	770
Alfalfa, clover, vetch	1.900	200	380	53	120	49
	0.950	400	380	53	120	49
Rangeland, field areas, pastures (dairy cattle present)	0.864	222	192	110	250	98
	0.477	222	106	190	450	180
Livestock pastures, feed lots, pastures (dairy cattle present)	0.275	222	61	330	770	310
	0.110	222	24	830	1900	770
Peas, beans, lima beans	1.900	200	380	53	120	49
	0.950	400	380	53	120	49
Aerial applicator. Baseline PPE: single layer, no gloves						
Potatoes	0.950	240	228	260	2400	250
Tomatoes	0.950	200	190	310	2800	300
Corrals, pastures, holding pens, (dairy and beef cattle present)	0.275	222	61	960	8800	940
	0.110	222	24	2400	22000	2400
Alfalfa, clover, vetch	1.900	200	380	150	1400	150
	0.950	400	380	150	1400	150
Rangeland, field areas, pastures (dairy cattle present)	0.864	222	192	310	2800	300
	0.477	222	106	560	5100	550
Livestock pastures, feed lots, pastures (dairy cattle present)	0.275	222	61	960	8800	940
	0.110	222	24	2400	22 000	2400
Peas, beans, lima beans	1.900	200	380	150	1400	150
	0.950	400	380	150	1400	150

M/L = mix/load, ATPD = area treated per day, MOE = margin of exposure, PPE = personal protective equipment
Max-level PPE = chemical-resistant coveralls over a long-sleeved shirt, long pants and chemical-resistant gloves.
Baseline PPE = long-sleeved shirt, long pants and chemical-resistant gloves unless otherwise indicated.
[a] ATPD values were refined based on the National Agricultural Aviation Association (NAAA, 2004). The current label limits workers using maximum rate of 1.9 kg a.i./ha to treat only 200 ha/day.
[b] Dermal exposure (mg/kg bw/day) = (dermal unit exposure × ATPD × application rate)/ body weight
[c] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure × ATPD × application rate)/ body weight. 90% protection factor was used for the respirator to calculate inhalation exposure.
[d] Based on a $BMDL_{10}$ of 1.96 mg/kg bw/day from a rat 28-day dermal toxicity study, and a target MOE of 300.
[e] Based on a LOAEL of 0.065 mg/kg bw/day from a rat 90-day inhalation toxicity study, and a target MOE of 100.
[f] Combined MOE = $1 / (1/MOE_{dermal}) + (1/MOE_{inhalation})$; based on a dermal $BMDL_{10}$ of 1.96 mg/kg bw/day, and a target MOE of 300 and an inhalation $BMDL_{10}$ of 0.35 mg/kg bw/day, and a target MOE of 300.
[g] Some crops have application rates that vary; this may depend on the insect targeted. Maximum and minimum application rates are presented here.
[h] Label states "The field crew and the mixer/loaders must wear chemical-resistant gloves, coveralls and goggles or face shield during mixing/loading, cleanup and repair. Follow the more stringent label precautions in cases where the operator precautions exceed the label recommendations on the existing groundboom label." Also "All applications must use closed mixing/loading systems".
Shaded cells indicate MOEs that are less than the target MOE

Table 3 Mixer/loader/applicator exposure and risk assessment of naled by handheld application

Equipment	Crop	Max rate (kg a.i./L)[a]	ATPD (L/day)[b]	Amount handled per day (kg a.i./day)	Dermal exposure[c] (mg/kg bw/day)	Inhalation exposure[d] (mg/kg bw/day)	Dermal MOE[e]	Inhalation MOE[f]	Combined MOE[g]
PPE: Mid-level PPE									
MPHW	Strawberries	0.0095	150	1.4	1.31E-02	8.05E-04	150	81	110
	In and around dairy barns, livestock barns, pig pens, poultry houses	0.0026	150	0.4	3.58E-03	2.20E-04	550	290	400
	Cider mills, wineries	0.0052	150	0.8	7.17E-03	4.41E-04	270	150	200
	Outdoor ornamentals	0.00108	150	0.2	1.49E-03	9.15E-05	1300	710	980
Backpack	Strawberries	0.0095	150	1.4	4.63E-02	1.11E-03	42	59	37
	In and around dairy barns, livestock barns, pig pens, poultry houses	0.0026	150	0.4	1.27E-02	3.03E-04	150	210	140
	Cider mills wineries	0.0052	150	0.8	2.53E-02	6.05E-04	77	110	68
	Outdoor ornamentals	0.00108	150	0.2	5.26E-03	1.26E-04	370	520	330
PPE: Max-level PPE + respirator									
MPHW	Strawberries	0.0095	150	1.4	1.24E-02	8.05E-05	160	810	153

Equipment	Crop	Max rate (kg a.i./L) [a]	ATPD (L/day) [b]	Amount handled per day (kg a.i./day)	Dermal exposure [c] (mg/kg bw/day)	Inhalation exposure [d] (mg/kg bw/day)	Dermal MOE [e]	Inhalation MOE [f]	Combined MOE [g]
PPE: Mid-level PPE									
	In and around dairy barns, livestock barns, pig pens, poultry houses	0.0026	150	0.4	3.38E-03	2.20E-05	580	2900	559
	Cider mills, wineries	0.0052	150	0.8	6.76E-03	4.41E-05	290	1500	280
	Outdoor ornamentals	0.00108	150	0.2	1.40E-03	9.15E-06	1400	7100	1300
Backpack	Strawberries	0.0095	150	1.4	3.61E-02	1.11E-04	54	590	53
	In and around dairy barns, livestock barns, pig pens, poultry houses	0.0026	150	0.4	9.88E-03	3.03E-05	200	2100	200
	Cider mills wineries	0.0052	150	0.8	1.98E-02	6.05E-05	99	1100	97
	Outdoor ornamentals	0.00108	150	0.2	4.11E-03	1.26E-05	480	5200	470
MPHG	Strawberries	0.0095	1000	9.5	2.17E-01	1.79E-03	9	36	9
	In and around dairy barns, livestock barns, pig pens, poultry houses	0.0026	1000	2.6	5.94E-02	4.91E-04	33	130	32
	Cider mills, wineries	0.0052	1000	5.2	1.19E-01	9.82E-04	17	66	16

Equipment	Crop	Max rate (kg a.i./L)[a]	ATPD (L/day)[b]	Amount handled per day (kg a.i./day)	Dermal exposure[c] (mg/kg bw/day)	Inhalation exposure[d] (mg/kg bw/day)	Dermal MOE[e]	Inhalation MOE[f]	Combined MOE[g]
PPE: Mid-level PPE									
	Outdoor ornamentals	0.00108	1000	1.1	2.47E-02	2.04E-04	79	320	76

ATPD = area treated per day, MOE = margin of exposure, MPHW = manually pressurized hand wand, MPHG = mechanically pressurized hand gun, PPE = personal protective equipment, Max = maximum
Mid-level PPE = coveralls over a long-sleeved shirt, long pants and chemical-resistant gloves
Max-level PPE = chemical-resistant coveralls over a long-sleeved shirt, long pants and chemical-resistant gloves.
[a] Application rates in kg a.i./L were calculated: application rate (kg a.i./ha) / spray volume (100 – 300 L/ha as stated on the label)
[b] Default value of 150 L/day was used for MPHW and backpack. A maximum value of 1000 L/day was used for MPHG as stated on the current label.
[c] Dermal exposure (mg/kg bw/day) = (dermal unit exposure × ATPD × application rate)/body weight
[d] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure × ATPD × application rate)/body weight. 90% protection factor was used for the respirator to calculate inhalation exposure.
[e] Based on a $BMDL_{10}$ of 1.96 mg/kg bw/day from a rat 28-day dermal toxicity study, and a target MOE of 300.
[f] Based on a LOAEL of 0.065 mg/kg bw/day from a rat 90-day inhalation toxicity study, and a target MOE of 100.
[g] Combined MOE = 1 / ($1/MOE_{dermal}$) + ($1/MOE_{inhalation}$); based on a dermal $BMDL_{10}$ of 1.96 mg/kg bw/day, and a target MOE of 300 and an inhalation $BMDL_{10}$ of 0.35 mg/kg bw/day, and a target MOE of 300.
Shaded cells indicate MOEs that are less than the target MOE.

Table 4 Mixer/loader/applicator exposure and risk assessment of naled by airblast/tractor drawn mistblower [a] application

Site	Rate (kg a.i./ha)	ATPD (ha/day)[b]	Amount handled per day (kg a.i./day)	Dermal MOE[c,f]	Inhalation MOE[d,e,g]	Combined MOE[h]
PPE: Mid-level PPE + open M/L + respirator + open cab						
ULV: Livestock pastures, feed lots, pastures (dairy cattle present)	0.275	1200	330	0	16	0
ULV: Woodland	0.275	500	137.5	0	39	0
Airblast: Outdoor ornamentals	0.324	20	6.5	7	830	7
PPE: Max-level PPE + Closed M/L + respirator + CR hat for application + open cab						
Airblast: Outdoor ornamentals	0.324	20	6.5	210	870	200
PPE: Closed M/L (Max-level PPE + respirator) + closed cab (Mid-level PPE)						
Airblast: Outdoor ornamentals	0.324	20	6.5	1100	2400	1000
ULV: Livestock pastures, feed lots, pastures (dairy cattle present)	0.275	1200	330	22	48	20
ULV: Woodland	0.275	500	138	52	110	48

M/L = mix/load, A = apply, ATPD = area treated per day, MOE = margin of exposure, PPE = personal protective equipment, CR = chemical-resistant
Mid-level PPE = coveralls over a long-sleeved shirt, long pants and chemical-resistant gloves
Max-level PPE = chemical-resistant coveralls over a long-sleeved shirt, long pants and chemical-resistant gloves.
[a] When the label states mistblower, AHETF airblast exposure data is used. Results from handheld mistblower can be found in Table 4.5.
[b] Specific ATPD values were not available. The default ATPD for airblast applications was used for tractor drawn mistblower/airblast. Where the target pest is adult mosquitos, ULV treatment was included with an ATPD of 1200 ha/day. (Although airblast equipment would not necessarily be used to treat for adult mosquitoes, data were not available for mosquito control equipment. Airblast equipment was considered most similar.) Current label limit for woodlands "For areas less than 500 ha only".
[c] Dermal exposure (mg/kg bw/day) = (dermal unit exposure × ATPD × application rate)/body weight
[d] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure × ATPD × application rate)/body weight.
[e] 90% protection factor was used for the respirator, where indicated.
[f] Based on a $BMDL_{10}$ of 1.96 mg/kg bw/day from a rat 28-day dermal toxicity study, and a target MOE of 300.
[g] Based on a LOAEL of 0.065 mg/kg bw/day from a rat 90-day inhalation toxicity study, and a target MOE of 100.
[h] Combined MOE = 1 / ($1/MOE_{dermal}$) + ($1/MOE_{inhalation}$); based on a dermal $BMDL_{10}$ of 1.96 mg/kg bw/day and a target MOE of 300, and an inhalation $BMDL_{10}$ of 0.35 mg/kg bw/day and a target MOE of 300.
Shaded cells indicate MOEs that are less than the target MOE.

Table 5 Mixer/loader/applicator exposure and risk assessment of naled by handheld mistblower/fogger[a] application

Site	Rate (kg a.i./L)	ATPD (L/day)[b]	Amount handled per day (kg a.i./day)	Dermal MOE[c,e]	Inhalation MOE[d,f]	Combined MOE[g]
PPE: Max-level PPE + open M/L + respirator						
Livestock pastures, feed lots, pastures (dairy cattle present)	0.0100	150	1.50	3	1	2
	0.0060	150	0.90	5	2	3
In and around dairy barns, livestock barns, pig pens, poultry houses	0.0026	150	0.39	12	3	7
Cider mills, wineries	0.0026	150	0.39	12	3	7
Outdoor ornamentals	0.001080	150	0.162	30	8	18

M/L = mix/load, ATPD = area treated per day, MOE = margin of exposure, PPE = personal protective equipment
Max-level PPE = chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves and a chemical-resistant hood.
[a] When the label states mistblower or space spray, it was assumed that handheld mistblower/fogger could be used as application equipment.
[b] Default ATPD was used.
[c] Dermal exposure (mg/kg bw/day) = (dermal unit exposure × ATPD × application rate)/body weight. Unit exposure data is from Testman 2015 [PMRA# 2905452].
[d] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure × ATPD × application rate)/body weight. Unit exposure data is from Theouvenin 2016.
[e] Based on a $BMDL_{10}$ of 1.96 mg/kg bw/day from a rat 28-day dermal toxicity study, and a target MOE of 300.
[f] Based on a LOAEL of 0.065 mg/kg bw/day from a rat 90-day inhalation toxicity study, and a target MOE of 100.
[g] Combined MOE = 1 / ($1/MOE_{dermal}$) + ($1/MOE_{inhalation}$); based on a dermal $BMDL_{10}$ of 1.96 mg/kg bw/day and a target MOE of 300, and an inhalation $BMDL_{10}$ of 0.35 mg/kg bw/day and a target MOE of 300.
Shaded cells indicate MOEs that are less than the target MOE.

Table 6 Mixer/loader/applicator exposure and risk assessment of naled by fogger and vapour application

Site	Rate	ATPD[a]	Amount handled per day (kg a.i./day)	Dermal MOE[b,d]	Inhalation MOE[c,e]	Combined MOE[f]
PPE: Max-Level PPE + respirator + CR gloves for all equipment						
Indoor areas (poultry houses, pig pens, cider mills, livestock barns, wineries) – fogger/mistblower (**automated**)[g,h]	0.119 kg a.i. /ha	0.022 ha	0.0026	2.30E+06	32000000	2300000
Greenhouse (food and non-food) – fogger (**automated**) [h,i]	0.00012 kg a.i. /m^2	28000 m^2	3.4	1800	25000	1800
Greenhouse –vapour treatment [j]	0.000086 kg a.i. /m^3	50000 m^3	4.3	18	310	18

ATPD = area treated per day, MOE = margin of exposure, PPE: personal protective equipment, CR: chemical-resistant

Max-level PPE = chemical-resistant coveralls over a long-sleeved shirt, long pants and chemical-resistant gloves.

[a] Indoor space spray and greenhouse vapour treatment area treated per day is based on data-call in information for dichlorvos. Greenhouse fogger area treated per day is based on Statistics Canada, 2011 data for greenhouse vegetables.

[b] Dermal exposure (mg/kg bw/day) = (dermal unit exposure × ATPD × application rate)/body weight

[c] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure × ATPD × application rate)/body weight. 90% protection factor was used for the respirator to calculate inhalation exposure for the vapour treatment.

[d] Based on a $BMDL_{10}$ of 1.96 mg/kg bw/day from a 28-day rat dermal toxicity study, and a target MOE of 300.

[e] Based on a LOAEL of 0.065 mg/kg bw/day from a 90-day rat inhalation toxicity study, and a target MOE of 100.

[f] Combined MOE = 1 / $(1/MOE_{dermal}) + (1/MOE_{inhalation})$; based on a dermal $BMDL_{10}$ of 1.96 mg/kg bw/day and a target MOE of 300, and an inhalation $BMDL_{10}$ of 0.35 mg/kg bw/day and a target MOE of 300.

[g] The application rate for indoor areas was based on: application rate (0.0026 kg a.i./L) × spray volume (45.8 L/ha). The label does not specify fogger or mistblower application equipment for this site; however, Health Canada has received use pattern information that fogging application is conducted in these use sites. The spray volume was based on the pest treated to obtain similar coverage as from airblast. Automated fogger was assessed as mix/load exposure only.

[h] Fogger assessed as stationary equipment (mix/load exposure only) as per label instructions.

[i] Greenhouse crops refer to cucumbers, tomatoes, eggplants, peppers, and roses and cut flowers.

[j] Vapour application assessed as backpack with max PPE and respirator.

Shaded cells indicate MOEs that are less than the target MOE.

Table 7 Postapplication dermal exposure and risk assessment for greenhouse crops for naled

Crop (Application Type)	Activity	Rate [a]	TC (cm^2/hr) [b]	Naled DFR_0 ($\mu g/cm^2$) [c]	Dermal MOE [d, e] (Target = 300)	REI required to meet target MOE[f]
Roses and cut flowers (Fog)	Harvesting (hand), pruning, disbudding	0.121 g a.i./m^2	4000	3.03	2	259
	All other activities		230		28	118

Roses and cut flowers (Vapour Treatment)	Harvesting (hand), pruning, disbudding	0.01728 g a.i./m^2	4000	0.43	11	163
	All other activities		230		197	21
Eggplant, pepper (Fog)	All activities except postharvest	0.121 g a.i./m^2	1400	3.03	5	207
	Postharvest [g]		640		10	168
Cucumber, tomato, eggplant, pepper (Vapour Treatment)	All activities except postharvest	0.01728 g a.i./m^2	1400	0.43	32	111
	Postharvest [g]		640		71	72

TC = Transfer coefficient, DFR = Dislodgeable Foliar Residue, MOE = margin of exposure, REI = Restricted-entry Interval

[a] Fogging rate was provided as g a.i./m^2. Vapour treatment rate was provided in g a.i./m^3 which was converted to g a.i./m^2 by dividing by the typical greenhouse height of 5 m.

[b] The TC values are from PRO2014-02, except for postharvest activities, see below.

[c] DFR_0 is the expected DFR on the day of application. The DFR values are based on the PMRA standard (SPN2014-02).

[d] Dermal exposure (mg/kg bw/day) = DFR (ug/cm^2) × TC (cm^2/hr) × work duration (8 hr) / BW (80 kg)

[e] Based on a $BMDL_{10}$ of 1.96 mg/kg bw/day from a rat 28-day dermal toxicity study, and a target MOE of 300.

[f] Based on the revised standard DFR dissipation of 2% per day.

[g] Based on the revised TC for postharvest applications based on response to comments.

Shaded cells indicate MOEs that are less than the target MOE.

Appendix V Environmental risk assessment

Table 1 Ecological water modelling fate input parameters for naled and dichlorvos

Parameter	Naled	Dichlorvos	Transformation fraction
Molecular weight (g/mol)	380.84	220.98	NA
Vapour pressure (mm Hg) at 20°C	1.95E-3	1.2E-2	NA
Solubility (mg/L) in distilled water	1	15000	NA
Henry's law constant (unitless)	3.95E-2	9.51E-6	NA
Photolysis half-life (d) at 38°N latitude	0.98[a]	Stable	1
Hydrolysis half-life (d) at pH 7	0.64	5.19	0
Kd (L/kg)	1.6	0.3	NA
Soil half-life (d) at 25°C	1	19.3	0
Aerobic aquatic half-life (d) at 25°C	0.26[a]	0.42	0.13
Anaerobic aquatic half-life (d) at 25°C	0.14[a]	23.5	1
Air diffusion coefficient (cm^2/d)	4870	4870	NA
Heat of Henry (J/mol)	59000	59000	NA

[a] Reported as "stable" in PSRD2019-03.

Table 2 Revised endpoints for aquatic risk assessment of naled and its major transformation product, dichlorvos

Organism	Species	Exposure	Toxicity value [µg a.i./L]	Uncertainty factor
Naled				
Freshwater invertebrates	Water flea *Daphnia pulex*	96-h EC_{50}	0.35	2
Estuarine/marine invertebrates	Shrimp *Palaemon macrodactylus*	96-h LC_{50}	8.13	2
Dichlorvos				
Freshwater fish	Reported in PSRD2019-03: Lake trout *Salvelinus namaycush*	96-h LC_{50}	Incorrectly reported as 0.183; corrected to 183	10
	Used for revised assessment: Cutthroat trout[a] Salmo clarkia	96-h LC_{50}	170	10

[a] Previously reported in PRVD2017-16, Dichlorvos. This is not a new data point but became the most sensitive endpoint when the value for lake trout was corrected.
NOTE: Other assessment endpoints were reported in PSRD2019-03.

Table 3 Risk quotients (RQ) for aquatic invertebrates (freshwater (FW) acute and chronic; marine (SW) acute) using modelled EECs (4-d and 21-d) for naled resulting from runoff (80 cm water body) – maximum yearly application rate for various use sites/crops for Dibrom Insecticide (Naled; 2 × 1890 g a.i./ha, 7-d interval)

Crop/region	4-d EEC / 96-h[a] FW EC_{50} (µg a.i./L)		21-d EEC / 21-d[b] FW NOEC (µg a.i./L)		4-d EEC/ 96-h[c] SW LC_{50} (µg a.i./L)		21-d EEC / 21-d[d] SW NOEC (µg a.i./L)	
	EEC	RQ	EEC	EEC	EEC	RQ	EEC	RQ
Broccoli/BC	0.27	1.5	0.053	0.5	0.27	0.07	0.053	0.2
Cabbage/BC	0.26	1.4	0.051	0.5	0.26	0.06	0.051	0.2
Cabbage/ON	2.2	12	0.45	5	2.2	0.5	0.45	1
Cabbage/QC	2.1	12	0.40	4	2.1	0.5	0.40	1
Cabbage/Atlantic	6.0	33	1.3	13	6.0	1.5	1.3	4

[a] FW 96-h EC_{50} = 0.35 µg a.i./L ÷ 2 = 0.18 µg a.i./L, *Daphnia pulex*

[b] FW 21-d NOEC = 0.098 µg a.i./L, *Daphnia magna*

[c] SW 96-h LC_{50} = 8.13 µg a.i./L ÷ 2 = 4.07 µg a.i./L, *Palaemon macrodactylus*

[d] SW 21-d NOEC = 0.33 µg a.i./L, *Americamysis bahia*

NOTES: EEC = Estimated Environmental Concentrations, Risk $quotient_{acute}$ = [EEC / (toxicity endpoint ÷ 2)], where 2 is the uncertainty factor for aquatic invertebrates

Table 4 Risk quotients (RQ) for freshwater aquatic invertebrates (acute 48-h and chronic) using modelled EECs for dichlorvos resulting from runoff (80 cm water body) – maximum and minimum yearly application rates for various use sites/crops for Dibrom Insecticide (applied as naled; 7-d interval)

Crop/region	1-d / 48-h[a] EC_{50} (µg a.i./L)		21-d / 21-d NOEC[b] (µg a.i./L)	
	EEC	RQ	EEC	RQ
Highest application rate (2 × 1890 g/ha/year)				
Highest for all crops	1.5	43	0.15	26
Cabbage and Broccoli maximum rate (2 × 945 g/ha/year)				
Broccoli/BC	0.027	<1	0.002	0.3
Cabbage/BC	0.024	<1	0.003	0.5
Cabbage/ON	0.37	10	0.030	5
Cabbage/QC	0.21	6	0.020	3
Cabbage/Atlantic	0.64	18	0.057	10
Onion maximum rate (2 × 477 g/ha/year)				
Onion/BC	0.035	1	0.003	0.5
Onion/Prairie	0.24	7	0.022	4
Onion/ON	0.32	9	0.024	4
Onion/QC	0.25	7	0.022	4
Onion/Atlantic	0.38	11	0.082	14
Lettuce maximum rate (2 × 1440 g/ha/year)				
Lettuce/BC	0.11	3	0.010	2
Lettuce/Prairie	0.73	21	0.066	11
Lettuce/ON	0.98	28	0.071	12
Lettuce/QC	0.75	21	0.066	11
Lettuce/Atlantic	1.2	34	0.25	43
Lettuce minimum rate (2 × 945 g/ha/year)				
Lettuce/BC	0.070	2	0.007	1

Crop/region	1-d / 48-h[a] EC_{50} (µg a.i./L)		21-d / 21-d NOEC[b] (µg a.i./L)	
	EEC	RQ	EEC	RQ
Lettuce/Prairie	0.48	14	0.043	7
Lettuce/ON	0.64	18	0.047	8
Lettuce/QC	0.49	14	0.043	7
Lettuce/Atlantic	0.76	22	0.16	28
Livestock pasture maximum rate (2 × 274.8 g/ha/year)	0.002 to 0.10	<1 to 3	0.001 to 0.011	0.2 to 2
Feedlots maximum rate (2 × 274.8 g/ha/year)	0.033 to 0.33	1 to 9	0.004 to 0.041	0.7 to 7
Livestock pasture minimum rate (2 × 109.8 g/ha/year)	0.001 to 0.042	≤ 1	0.001 to 0.005	≤ 1
Feedlots minimum rate (2 × 109.8 g/ha/year)	0.013 to 0.13	<1 to 4	0.002 to 0.016	0.3 to 3

[a] 48-h EC_{50} = 0.07 µg a.i./L ÷ 2 = 0.035 µg a.i./L, *Daphnia magna*; most sensitive of FW invertebrate endpoints

[b] 21-d NOEC = 0.0058 µg a.i./L, *Daphnia magna*

NOTES: EEC = Estimated Environmental Concentration, Risk $\text{quotient}_{\text{acute}}$ = [EEC / (toxicity endpoint ÷ 2)], where 2 is the uncertainty factor for aquatic invertebrates, Endpoints for marine/estuarine aquatic invertebrates are less sensitive than freshwater toxicity values for dichlorvos; RQs for acute and chronic endpoints were < 1 and were not reported here.

Table 5 Hectares grown of various crops listed in naled use pattern, 2018 (Statistics Canada)

Province	Broccoli	Brussels sprouts	Cabbage	Regular cabbage	Cauliflower	Dry onions	Lettuce
British Columbia	243	176	462	196	89	134	221
Alberta	74	2	143	142	12	461	11
Saskatchewan	23	4	37	34	6	9	4
Manitoba	108	0	108	88	138	219	19
Ontario	1946	279	2603	1380	486	2408	193
Quebec	1869	146	2265	1866	971	2124	3359
New Brunswick	23	4	45	43	4	6	4
Newfoundland and Labrador	7	1	45	42	4	3	5
Nova Scotia	255	14	123	115	73	218	97
Prince Edward Island	22		80	79		42	17

Table 6 Summary of dichlorvos and naled detections in Canadian surface water (2005–2017)

Chemical	Province	# of samples	# of detections	% detection	Concentration (ug/L)	
					Max Detection	LOD
Dichlorvos	AB	2052	0	0	0	0.005–0.068
	BC	61	32	52[1]	0.0004	0.000001–0.0004
	ON	1015	1	<0.1	0.00143	0.0002–1
	QC	5436	8	<0.1	0.52	0.02–0.05
Dichlorvos Total		8564	41	<0.1	0.52	1

Naled	AB	665	0	0	0	0.03–0.15
	BC	61	31	50[1]	0.002	0.0001–0.002
	NS	8	0	0	0	0.0014
	ON	484	0	0	0	0.03
	PEI	7	0	0	0	0.001
Naled Total		1225	31	<0.1	0.00207	0.15

[1] Limit of detection is very low, resulting in a high detection frequency

Appendix VI Summary of risk mitigation measures related to the aspects of concern

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

1.0 Label amendments relating to the health risk assessment

Label Amendments for TECHNICAL and COMMERCIAL CLASS END-USE PRODUCTS CONTAINING NALED

Based on the toxicology assessments, both of the technical and commercial class product label text must be expanded and/or standardized as follows:

1.1 Under TOXICOLOGICAL INFORMATION section:

Naled is a cholinesterase inhibitor. Typical symptoms of overexposure to cholinesterase inhibitors include headache, nausea, dizziness, sweating, salivation, runny nose and eyes. This may progress to muscle twitching, weakness, tremor, incoordination, vomiting, abdominal cramps and diarrhea in more serious poisonings. A life-threatening poisoning is signified by loss of consciousness, incontinence, convulsions and respiratory depression with a secondary cardiovascular component. Treat symptomatically. If exposed, plasma and red blood cell cholinesterase tests may indicate degree of exposure (baseline data are useful). Atropine, only by injection, is the preferable antidote. Oximes, such as Pralidoxime Chloride, may be therapeutic if used early; however, use only in conjunction with atropine. In cases of severe acute poisoning, use antidotes immediately after establishing an open airway and respiration. With oral exposure, the decision of whether to induce vomiting or not should be made by an attending physician.

Label amendments for COMMERCIAL CLASS END-USE PRODUCTS CONTAINING NALED

1.2 On the principle panel:

DO NOT apply in residential areas. Residential areas are defined as any use site where bystanders including children could be exposed during or after application. This includes in and around homes, schools, public buildings or any other areas where the general public including children could be exposed.

1.3 Under DIRECTIONS FOR USE section:

Remove use directions for the following uses that are cancelled:

- beans (dry or field), lima beans, peas (processing), alfalfa, clover, vetch, potato, sugar beets
- aerial application to field tomatoes
- rangeland, field areas and pastures (grasshopper treatment)

- all greenhouse crops
- in and around dairy barns, livestock barns, pig pens, poultry houses, cider mills, wineries
- woodland
- all mistblower treatments

1.4 Under DIRECTIONS FOR USE section - ACCEPTABLE COMMERCIAL USES FOR NALED table and HUMAN HEALTH PRECAUTIONS section:

DO NOT apply using handheld mistblower/fogger.

DO NOT apply using Ultra Low Volume (ULV) equipment.

DO NOT apply by air, unless otherwise specified in the crop-specific use directions.

1.5 Under HUMAN HEALTH PRECAUTIONS section:

Apply only when the potential for drift beyond the area to be treated is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

DO NOT use in greenhouses or any other indoor structures.

DO NOT allow the pilot to mix or load chemicals to be loaded onto the aircraft.

1.6 Under PROTECTIVE CLOTHING AND EQUIPTMENT section:

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

Follow the personal protective equipment, engineering controls, and restriction requirements for the appropriate mixer/loader and applicator scenario as described in the table below:

Application Equipment	**Personal Protective Equipment and Engineering Controls**		
	Mixer/Loader/Clean-up and Repair	**Applicator**	**Maximum Amount of Product Handled per Day** [3]
Groundboom	**Closed mixing/loading** system is required.[1] Wear chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes.	**Open cab:** Wear chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. Wear a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides, or a NIOSH-approved canister approved for pesticides during open cab application.	(25 kg a.i. to be reported as a product equivalent value by the registrant)
		Closed cab[2]**:** Wear a long-sleeved shirt, long pants,	(40 kg a.i. to be reported as a product equivalent value by the registrant)

Application Equipment	Personal Protective Equipment and Engineering Controls		
	Mixer/Loader/Clean-up and Repair	**Applicator**	**Maximum Amount of Product Handled per Day** [3]
		socks and shoes. Gloves are not required within a closed cab.	
Airblast	**Closed mixing/loading** system is required.[1] Wear chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes.	**Open cab:** Wear chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes. Wear chemical-resistant headgear. Chemical-resistant headgear includes Sou'Wester hat, chemical-resistant rain hat or large-brimmed waterproof hat and hood with sufficient neck protection. Wear a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides, or a NIOSH-approved canister approved for pesticides during open cab application.	(4.4 kg a.i. to be reported as a product equivalent value by the registrant)
		Closed cab[2]: Wear a long-sleeved shirt, long pants, socks and shoes. Gloves are not required within a closed cab.	(16 kg a.i. to be reported as a product equivalent value by the registrant)
Aerial	**Closed mixing/loading** system is required.[1] Wear chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes.	Wear long-sleeved shirt, long pants, socks and shoes.	(62 kg a.i. to be reported as a product equivalent value by the registrant)
Backpack and Mechanically Pressurized Handgun	Wear chemical-resistant coveralls with a chemical-resistant hood over long-sleeved shirt, long pants, chemical-resistant gloves, socks, chemical-resistant footwear and a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NOSH-approved canister approved for pesticides.		(0.3 kg a.i. to be reported as a product equivalent value by the registrant)
Manually Pressurized Handwand	Wear chemical-resistant coveralls with a chemical-resistant hood over long-sleeved shirt, long pants, chemical-resistant gloves, socks, chemical-resistant		(0.7 kg a.i. to be reported as a product equivalent value by the registrant)

Application Equipment	Personal Protective Equipment and Engineering Controls		
	Mixer/Loader/Clean-up and Repair	Applicator	Maximum Amount of Product Handled per Day [3]
	footwear and a respirator with a NIOSH-approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NOSH-approved canister approved for pesticides.		

[1] A closed mix/load 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.

[2] A closed cab 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.

[3] These restrictions are in place to minimize exposure to individual workers. Application may need to be performed over multiple days or using multiple workers.

1.7 Under RESTRICTED-ENTRY INTERVAL (REI) section:

DO NOT enter or allow worker entry into treated areas to perform postapplication activities during the restricted-entry interval (REI) of 48 hours.

1.8 Under AERIAL APPLICATION INSTRUCTIONS - Operator Precautions section:

Do not allow the pilot to mix or load chemicals to be loaded onto the aircraft.

2.0 Label amendments relating to the environmental risk assessment

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

Label amendments for TECHNICAL PRODUCTS CONTAINING NALED

2.1 Under ENVIRONMENTAL PRECAUTIONS section:

TOXIC to aquatic organisms.

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

2.2 Under DISPOSAL section:

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

Label amendments for COMMERCIAL CLASS END-USE PRODUCTS CONTAINING NALED

2.3 Under ENVIRONMENTAL PRECAUTIONS section:

Toxic to birds.

TOXIC to aquatic organisms. Observe buffer zones specified under DIRECTIONS FOR USE.

TOXIC to bees. Minimize spray drift to reduce harmful effects on bees in habitats close to the application site. Avoid application during the crop blooming period. If applications must be made during the crop blooming period, restrict applications to the evening when most bees are not foraging. Avoid applications when bees are foraging in the treatment area in ground cover containing blooming weeds. To further minimize exposure to pollinators, refer to the complete guidance "Protecting Pollinators during Pesticide Spraying – Best Management Practices" on the Health Canada website (www.canada.ca/pollinators).

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 filter strip between the treated area and the edge of the water body.

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

2.4 Under DIRECTIONS FOR USE section:

To protect pollinators, follow the instructions regarding bees in the Environmental Precautions section.

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.

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

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

Apply only by fixed-wing or rotary aircraft equipment which has been functionally and operationally calibrated for the atmospheric conditions of the area and the application rates and conditions of this label.

Label rates, conditions and precautions are product specific. Read and understand the entire label before opening this product. Apply only at the rate recommended for aerial application on this label. Where no rate for aerial application appears for the specific use, this product cannot be applied by any type of aerial equipment.

Ensure uniform application. To avoid streaked, uneven or overlapped application, use appropriate marking devices.

2.5 Under USE PRECAUTIONS section:

Apply only when meteorological conditions at the treatment site allow for complete and even crop coverage. Apply only under conditions of good practice specific to aerial application as outlined in the National Aerial Pesticide Application Manual, developed by the Federal/Provincial/Territorial Committee on Pest Management and Pesticides.

2.6 Under PRODUCT SPECIFIC PRECAUTIONS section:

Application of this specific product must meet and/or conform to the following:

Volume: Apply the recommended rate in a minimum spray volume of 10 litres per hectare.

2.7 Under SPRAY BUFFER ZONES section:

A spray buffer zone is NOT required for uses with hand-held application equipment permitted on this label.

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

Method of application	Crop		Spray Buffer Zones (metres) Required for the Protection of:			
			Freshwater Habitat of Depths:		Estuarine/Marine Habitat of Depths:	
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m
Field sprayer	Outdoor ornamentals		10	4	1	1
	Onion (bulb or seed only)		10	5	1	1
	Strawberry		20	10	1	1
	Lettuce		25	10	2	1
	Tomato		30	15	2	1
	Broccoli, Brussels sprouts, cabbage, cauliflower		35	15	3	1
Airblast	Outdoor ornamentals	Early growth stage	40	35	10	4
		Late growth stage	30	25	5	2
Aerial	Livestock pastures, pastures (dairy cattle present), corrals, feedlots, holding pens	Fixed wing	500	250	50	25
		Rotary wing	250	100	30	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 on the Pesticides portion of the Canada.ca website.

2.8 Under STORAGE section:

Store this product away from food or feed.

References

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List of studies/information submitted by registrant

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