Proposed Special Review Decision PSRD2019-02

Special Review of Naled and Its Associated End-use Product under subsection 17(1) of *Pest Control Products Act*

Consultation Document

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1.0 Introduction

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 (Canada, 2017a) based on the toxicology information submitted under section 12 of the *Pest Control Products Act*, following the re-evaluation of naled (Canada, 2004; and Canada, 2006).

Pursuant to subsection 18(4) of the *Pest Control Products Act*, the Health Canada has evaluated the aspects of concern that prompted the special review of pest control products containing 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).

In addition, Health Canada in 2015 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 (Canada, 2015). 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. The outcome of the evaluation of the special review of naled under subsection 17(2) of the *Pest Control Products Act* will be published separately.

The following sections outline the evaluation of the aspects of concern identified for the special review of naled under subsection 17(1) of the *Pest Control Products Act*.

2.0 Uses of Naled in Canada

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. It is not to be used in and around homes or other residential areas such as parks, school grounds, and playing fields. It is not for use by homeowners or other uncertified users. All currently registered pest control products containing naled are considered in this special review (Appendix I).

3.0 Aspects of Concern that Prompted the Special Review

The PMRA reviewed the submitted information under section 12 of the *Pest Control Products Act* (Appendix II), as well as information from the published scientific literature, and re-assessed the toxicological endpoints for naled in accordance with the current PMRA policies including the application of the *Pest Control Products Act* factor (for more details refer to Appendix III).

The revisions resulted in no changes or in non-significant changes to the reference values used for assessment of potential inhalation or dietary risks, respectively. However, the revised dermal endpoints are lower and the target margins of exposure (MOEs) are higher than that used for the re-evaluation of naled, and may affect the existing occupational assessments (Canada, 2004). Consequently, the following aspect of concern was identified for the special review under subsection 17(1) of the *Pest Control Products Act*:

- Human health
    - Potential occupational risk.

4.0 PMRA Evaluation of the Aspects of Concern that Prompted the Special Review

Following the initiation of the special review, the PMRA requested information related to the aspect of concern from provinces and other relevant federal government departments and agencies in accordance with subsection 18(2) of the *Pest Control Products Act*. No information was received.

In order to evaluate the aspect of concern for naled, the PMRA considered currently available relevant scientific information, which includes information submitted under section 12 of the *Pest Control Products Act* following the re-evaluation of naled, other toxicology data including the cholinesterase assays, and, use information submitted subsequently, as well as information considered for the re-evaluation of naled (Canada, 2004; and Canada, 2006).

4.1 Potential Occupational Risks

Based on the current use pattern of naled, there is a potential for exposure for workers mixing, loading, and applying the pest control product containing naled and for workers entering treated sites to conduct postapplication activities involving foliar contact (for example, pruning, thinning, harvesting or scouting).

Risk is estimated by comparing exposure estimates with the most relevant endpoint from toxicology studies to calculate an MOE. This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

This special review considers dermal and inhalation risks to workers resulting from the use of naled. While no revision was identified for the inhalation reference value, inhalation exposure results in brain cholinesterase inhibition at higher doses and thus, may contribute to the total effect of naled. Consequently, both dermal and inhalation risks to naled were considered for this special review. Further, given that dichlorvos is a transformation product of naled, the co-occurrence of naled and dichlorvos exposure for workers is considered likely. Both of these organophosphates share a common mechanism of toxicity, namely cholinesterase inhibition.

Accordingly, toxicological reference values for dichlorvos based on brain cholinesterase inhibition (Canada, 2017b) were considered relevant for the combined risk assessment. Toxicological reference values for use in the human health risk assessment for naled are presented in Appendix III.

4.1.1 Mixers/Loaders/Applicators

Based on the limit of two applications per year and the timing of application for outdoor uses, workers applying naled would generally have a short (<30 days) duration of exposure. Custom applicators may also have intermediate-term (up to several months) exposure for those crops with multiple applications. As greenhouse crops may have treatments year round, intermediate-/long-term duration of exposure may occur; however, since the number of applications is limited to three (including one post-harvest), exposure is likely to be short-/intermediate-term.

The PMRA assessed daily exposure for workers exposed to naled during mixing/loading (liquid formulation) and applying naled using different types of application equipment:

- groundboom (farmer and custom scenarios),
- airblast /tractor drawn mistblower/ ultra-low volume (ULV),
- aerial,
- handheld (manually pressurized handwand, backpack, mechanically pressurized handgun),
- automated fogger and mistblower,
- greenhouse vapor treatment to cold pipes, and
- handheld mistblower and handheld fogger equipment.

Dermal and inhalation exposure of mixers/loaders/applicators to naled

The PMRA calculated daily exposure using exposure data from the Agricultural Handler Exposure Task Force (AHETF) (for open cab airblast application) and the Pesticide Handlers Exposure Database (PHED) (for the remaining mixing/loading/application scenarios). The derived exposure estimates for mixers/loaders/applicators account for the current conditions of use as outlined in the pest control product labels.

The risk assessment under the current label directions is presented in Appendix IV.

For the following identified mixer/loader/applicator scenarios, the best available data were used:

- Fogging/mist blowing applications: Automated (stationary) fogger/mist blower mixing/loading exposure was estimated using PHED mixing/loading exposure data and applicator exposure was considered negligible. No data were available for workers using handheld mistblower or handheld fogger.
- Tractor-drawn mistblower or ultra-low volume (ULV) application for mosquito control: For outdoor scenarios, PHED closed cab airblast and AHETF open cab airblast data were used.

- Handheld sprayer to apply an insecticide to flying insects: PHED data for backpack, manually pressurized handwand, and mechanically pressurized handgun application were used.
- Vapour treatment (application using a squeeze bottle to cold pipes): Since no PHED or other data are available for this scenario, the backpack sprayer data was used.

Additional assumptions used to estimate daily exposure for workers mixing, loading, and applying naled included: label application rates (covering multiple pests), default or refined area treated per day (ATPD) values, and an 80 kg body weight.

Dermal and inhalation risks from exposure to naled were assessed using reference values summarized in Table 1 of Appendix III. While dermal and inhalation reference values for naled do not have the same toxicological endpoint, brain cholinesterase inhibition was observed via inhalation at a higher dose ($BMDL_{10}$ (benchmark dose lower confidence limit) of 1.254 µg/L or 0.35 mg/kg bw/day with a target MOE of 300). Therefore, a combined MOE approach was considered appropriate for assessing combined risks resulting from dermal and inhalation exposures to naled.

The risk assessment for mixers/loaders/applicators exposed to naled is presented in Appendix IV, Tables 4.1-4.5. Risk from dermal exposure of naled was higher than that from inhalation exposure for mixers/loaders/applicators. The calculated dermal, inhalation, and/or combined (dermal plus inhalation) MOEs did not meet the target MOE for all scenarios using the current PPE stated on the label. Based on this, the risks to all mixers/loaders/applicators from dermal and inhalation exposure to naled are not considered to be acceptable under current conditions of use.

Risks to mixers/loaders/applicators using handheld mistblower or fogger were not assessed due to the lack of exposure data for these types of application equipment. Considering that exposure is anticipated to be significant due to the characteristics of the spray, the risk to mixers/loaders applicators using this type of equipment is not considered to be acceptable.

Inhalation exposure to naled and dichlorvos during application

Naled is considered to be volatile; therefore, the use of AHETF and PHED data, which is based on generic exposures to non-volatile pesticides, may lead to the underestimation of inhalation exposure of naled to mixers/loaders/applicators. Furthermore, studies have shown that dichlorvos, a degradate of naled, and also a volatile substance, is detected in the air during application resulting in potential inhalation exposure to both naled and dichlorvos. Therefore, the PMRA conducted a supplemental exposure and risk assessment for mixers/loaders/applicators exposed via inhalation to both naled and dichlorvos during outdoor applications using the inhalation reference values for the combined assessments of naled and dichlorvos (Appendix III).

There are no chemical-specific data on file to determine the inhalation exposure to naled and dichlorvos during application. Therefore, the PMRA considered published scientific studies, in which air concentrations during and after naled application were measured; however, there were no studies directly measuring inhalation exposure to workers. The most suitable studies were conducted in California in vineyards and orange groves (CalEPA 1993, 1995). Both studies measured air concentrations of naled and dichlorvos from the field edge during airblast

application and up to approximately one hour after application was completed. These data are not a true representation of applicator exposure since the samples are taken from the field's edge and not in the field itself, and thus, are likely an underestimate of air concentration closer to the application sites. However, in the absence of better data, the field edge concentration data were used to estimate inhalation exposure to naled and dichlorvos during outdoor application.

The maximum air concentration of naled and the concurrent concentration of dichlorvos (6.3 $\mu g/m^3$ and 0.508 $\mu g/m^3$ respectively) from the 1995 CalEPA study were used in the risk assessment. Exposures were adjusted to account for a standard working day. This is likely an overestimate of exposure since mixing, loading, and applying activities may not necessarily require a full working day.

As the inhalation route of exposure for naled and dichlorvos (resulting from the use of naled) have the same toxicological endpoint for the combined assessment, but different points of departure (Appendix III), an aggregate risk index (ARI) was calculated. ARIs greater than or equal to one do not require risk mitigation. If the ARI is less than one, it does not necessarily mean that exposure will result in adverse effects. However, ARIs less than one require measures to mitigate (reduce) risk. For the individual inhalation exposures to naled and dichlorvos, as well as for the combined inhalation exposure to both chemicals, the calculated MOEs for outdoor workers mixers/loaders/applicators are greater than the target MOE and the ARI, indicating no concerns for inhalation exposure to naled and dichlorvos (Appendix IV, Table 4.6). On this basis, the potential risks to applicators from inhalation exposure to naled and dichlorvos is considered acceptable.

Combined dermal and inhalation exposure to naled and dichlorvos

Since exposure to both naled and dichlorvos from inhalation and dermal sources contribute to a common toxicological effect (brain cholinesterase inhibition), the contribution from all sources should be combined for workers. Given that combined (dermal plus inhalation) risks for mixers/loaders/applicators from exposure to naled alone are unacceptable (Appendix IV, Tables 4.1-4.6), a combined risk assessment for workers from exposure to both naled and dichlorvos was not conducted at this time.

4.1.2 Postapplication Workers

The postapplication occupational risk assessment considers dermal and inhalation exposures to workers who enter treated sites to conduct postapplication activities involving foliar contact, such as outdoor and greenhouse crops. The postapplication assessment considers exposure to naled as well as dichlorvos resulting from the use of naled (when data are available).

For workers entering a treated site, restricted-entry intervals (REIs) are calculated to determine the minimum length of time required before workers can enter after application to perform tasks involving hand labour. An REI is the duration of time that must elapse in order to allow residues to decline to a level where there are no risks of concern for postapplication worker activities.

Dermal exposure for postapplication workers was estimated using updated activity-specific transfer coefficients (TCs) and dislodgeable foliar residues (DFRs).

Dislodgeable foliar residues (DFRs)

For outdoor crops, dermal exposure of postapplication workers to naled and dichlorvos is estimated using chemical-specific DFRs (Canada, 2004). The studies measured the dissipation of naled and its primary metabolite, dichlorvos, after two applications of 2.1 kg a.i./ha (as Dibrom 8 Emulsive) to cotton plants, broccoli, and orange trees. Each study was conducted at two American sites. The broccoli study also included an Ontario site. All three studies were evaluated to get a general understanding of the foliar dissipation of naled and dichlorvos in the field. In the studies, naled and dichlorvos DFRs declined rapidly and were below the limit of quantification after 72 hours with the exception of citrus in California.

The broccoli DFR results for Ontario were considered the most appropriate for assessing postapplication exposure to naled and dichlorvos. The chemical-specific DFRs were used on the following outdoor ground crops:

- Alfalfa, clover, and vetch;
- Peas, beans, and lima beans;
- Broccoli, Brussels sprouts, cabbage, and cauliflower;
- Outdoor lettuce;
- Onion;
- Potato;
- Strawberry;
- Tomato;
- Sugar beets; and
- Outdoor ornamentals
- Woodlands

Although broccoli may not be representative of some of the crops listed above, it is expected that because it is a waxy foliage crop it will not underestimate risk for crops with smooth or hairy foliage. In addition, the study was conducted in Ontario, which is representative of some of the geographic and climatic conditions of the naled use pattern. This is consistent with the approach that was taken in the previous naled re-evaluation (Canada, 2004 and Canada, 2006).

For indoor crops, there are no chemical-specific DFR studies available. Therefore, exposure was estimated using default DFRs that were calculated assuming 25% deposition of the application rate, with a 2.3% dissipation rate for greenhouse ornamentals, and no dissipation for greenhouse vegetables.

Transfer coefficient (TC)

A transfer coefficient (TC), usually expressed in units of cm^2 per hour, expresses the relationship between worker dermal exposure and dislodgeable residues. Transfer coefficients are specific to a given crop (and crop stage) and activity combination (for example, hand harvesting broccoli) and reflect standard agricultural work clothing worn by adult workers. Activity-specific TCs from the Agricultural Re-Entry Task Force (ARTF) were used.

4.1.2.1 Outdoor Crops

Based on the naled use pattern, there is potential for short- to intermediate-term postapplication exposure (dermal and inhalation) to naled and dichlorvos for workers entering treated fields.

There is potential for postapplication dermal exposure of workers to both naled and dichlorvos. Dermal exposure was estimated using chemical-specific DFRs (see above), standard TC values (ARTF), and assuming an 8-hour workday, 30% dermal absorption for dichlorvos (Canada, 2017b), and an 80-kg worker body weight. Since the dermal reference dose for naled was based on a dermal study, dermal absorption was not needed for naled. The dermal risks were calculated using the short-/intermediate-term dermal reference values for naled and dichlorvos (Appendix III). The combined risk from exposure to naled and dichlorvos was estimated using the ARI approach.

The dermal risk assessment for workers performing postapplication activities in outdoor crops is presented in Appendix V, Table 5.1. Target dermal MOEs and ARIs were met for all crops/sites at the 48-hour REI specified on the current label, with the exception of hand harvesting for brassica leafy vegetables. For this scenario, although the target MOE was not met for dermal exposure to dichlorvos, the risk is considered acceptable since the broccoli DFR data had no measurable amount of dichlorvos beyond 48 hours at any location. Therefore, it is recommended that the REI remain at two days for all crops and activities based on dermal exposure.

There is also potential for inhalation exposure to naled and dichlorvos for workers performing postapplication activities in crops treated with naled due to the volatility of naled and dichlorvos. The risk assessment was based on an ARTF study (Lamb et al., 1994) measuring dermal and inhalation exposures to naled and dichlorvos for workers harvesting in grape vineyards after three applications of Dibrom 8 Emulsive. Although grapes are not on the current label, the worker inhalation exposures measured in this study was considered to be representative of workers entering a treated field to conduct standard agricultural activities. Inhalation exposures (on day one) in the study were adjusted for a standard workday and default body weight. The postapplication inhalation assessment for workers exposed to naled and dichlorvos is presented in Appendix V, Table 5.2. Target inhalation MOEs for naled and dichlorvos were met. However, the combined ARI for exposure to both chemicals is less than one assuming air concentrations measured on day one. Taking into consideration that the current label REI is 48 hours, the combined inhalation risk to both naled and dichlorvos is considered acceptable.

4.1.2.2 Outdoor Farm Areas

Naled can be applied in /around outdoor farm areas such as rangeland, field areas, pastures, feedlots, corrals, and holding pens (dairy and beef cattle present). The postapplication dermal exposure of workers following such applications is expected to be low due to the limited direct contact with naled residues. Since dairy cattle may be present during spraying, some worker exposure is possible.

A 48-hour REI is currently required on the commercial end-use product label and workers are required to wear chemical-resistant gloves if animals are to be handled within 48 hours. Consequently, postapplication dermal risks to workers exposed to naled following applications

in/around outdoor farm areas are considered acceptable. The inhalation exposure following outdoor farm area applications is considered to be lower than exposure of workers entering treated sites (outdoor crops) to conduct postapplication activities. On this basis, the inhalation risk to workers following outdoor farm areas applications is considered acceptable.

4.1.2.3 Indoor Sites

Greenhouse crops

Dermal exposure to postapplication workers in greenhouses was estimated using agricultural TCs and default DFR assumptions in the absence of chemical-specific data for greenhouse DFRs. The dermal risks were calculated using the long-term dermal reference values for naled (Appendix III). The postapplication risk assessment for greenhouse workers is presented in Appendix V, Table 5.3. Target dermal MOEs are not met on the day of application for naled alone and calculated REIs that are required to meet the target MOE are not considered to be agronomically feasible. Consequently, the potential risks to postapplication greenhouse workers exposed to naled residues are not considered acceptable under current conditions of use. It should be noted, that in the absence of chemical-specific data, the dermal risk assessment for naled is based on assumptions for typical pesticides, which are considered to be non-volatile. Naled is volatile and compared to typical pesticides, a larger fraction would be expected to volatilize and not be available for dermal exposure from the foliage. Therefore, the assumptions used may not be appropriate and are likely over estimates of dermal exposure. However, there is no information available to refine the current risk assessment for greenhouse workers.

There is also a potential for inhalation exposure to naled and dichlorvos for workers performing postapplication activities in greenhouse crops due to the volatility of these compounds. At this time, greenhouse postapplication air concentration data for naled and dichlorvos are not available. Inhalation risks of concern for all indoor scenarios are expected based on 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.

Other indoor areas

There is a potential for postapplication exposure to workers re-entering indoor areas (poultry houses, pig pens, cider mills, livestock barns and wineries) which have been treated with naled. Postapplication exposure activities may vary from handling livestock, packaging stored items to cleaning activities. Due to the limit of applications to twice per year, exposure is likely to be short-term in duration.

The predominant route of exposure is expected to be inhalation due to the volatility of naled and dichlorvos. Although dermal exposure is possible, contact with potentially contaminated surfaces in structural sites is expected to be minimal; therefore, a quantitative dermal risk assessment was not conducted.

At this time, postapplication air concentration data are not available for indoor application sites. However, inhalation exposure risk is expected to occur based on the volatility of naled and dichlorvos. A worker exposure study (for example passive dosimetry, biomonitoring) or air concentration study is required for the indoor postapplication inhalation risk assessment.

4.1.3 Overall Conclusion for Occupational Risks

Based on the available information, the results of the occupational risk assessment indicate that:

- the risks to mixers/loaders/applicators (outdoor and indoor applications) as well as to postapplication workers indoors are not considered to be acceptable under the current conditions of use.

- the risks to postapplication workers outdoors are considered to be acceptable under current conditions of uses.

Consequently, all uses of naled are proposed to be cancelled as the occupational risks are not considered to be acceptable. A summary of the occupational risk assessment is presented in Appendix VI. Given the proposed cancellation of all uses, no further label amendments are proposed at this time.

No additional scientific data are being requested. However, during the consultation period, the registrants may consider submission of further data and risk management options for naled that could be used to address the uncertainties in the assessment and to refine the risk assessment. These data and information are identified in Section 7.0 of this Proposed Special Review Decision.

5.0 Incident Reports

The PMRA incident reporting database was searched for human incident reports related to the identified aspect of concern for naled. As of 17 May 2017, there was one human incident.

The reported incident occurred in the United States and was classified as major. According to the report, the subject was exposed to a significant quantity of a concentrated naled product when a hose exploded from an airplane tank and the product splashed onto his eyes and face from under a face shield. The initial symptoms experienced by the subject were tongue swelling and erythema. He was hospitalized and aggressively treated for organophosphate toxicosis. The incident was considered related to the reported pesticide exposure. The circumstances of exposure reported in the incident relate to equipment failure. Therefore, no additional risk mitigation measures were identified as a result of this incident.

6.0 Proposed Special Review Decision for Naled

Evaluation of available relevant scientific information related to the aspect of concern, indicates that the risk to postapplication workers for outdoor applications of naled is considered to be acceptable under the current conditions of use.

However, the occupational risk to workers mixing, loading and applying naled (outdoor and indoor applications), as well as to post application workers in indoor areas is not considered to be acceptable under the current label directions.

On this basis, Health Canada, under the authority of the *Pest Control Products Act*, is proposing to cancel the current registration of pest control products containing naled for sale and use in Canada pursuant to subsection 21(2) of the *Pest Control Products Act*.

This proposed special review decision is a consultation document.[1] The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (please see contact information on the cover page of this document).

7.0 Additional Data that May Help Address Uncertainties and Refine the Assessments

No additional scientific data are being requested. However, during the consultation period, the registrants and other stakeholders may consider submitting the following information that may address uncertainties in the available information database of naled and support refined risk assessment. In addition, stakeholders may consider providing information on risk management options for naled (for example, additional PPE, engineering control).

The evaluation of any additional data would be based on the scientific merit and relevance to the risk assessment. While additional data may reduce uncertainty in the risk assessment, continued registration of any uses would be based on the acceptability of risk assessed using a science-based approach.

All studies would need to include consideration of both naled and dichlorvos (degradate of naled). When using biomonitoring studies (DACO 5.5 or 5.7) suitable human pharmacokinetic data is required to adequately characterise the pharmacokinetics in humans.

Greenhouse (non-food crops: roses and cut flowers) (food crops: cucumbers, tomatoes, eggplant, peppers):

1. DACO 5.9 DFR data (greenhouse vegetable and a smooth ornamental crop),
2. DACO 5.10 Ambient air samples and dissipation data following a greenhouse application and continued until the residues are below Limit of detection (breathing zone samples are preferable),
3. DACO 5.6/5.7 Post application passive dosimetry/biological monitoring (this could replace DACO 5.9 and DACO 5.10 above, if both dermal and inhalation exposure are considered),
4. DACO 5.4/5.5 Vapour treatment: Mixing/Loading/Applying (M/L/A) passive dosimetry/biological monitoring (if this application method is required) (include both dermal and inhalation exposure).

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

Other Indoor Areas (poultry houses, cider mills, livestock barns, wineries):

1. DACO 5.10 Ambient air samples and dissipation data following an indoor application and continued until the residues are below LOD (breathing zone samples are preferable),
2. DACO 5.4/5.5 Handheld mistblower MLA passive dosimetry/biological monitoring (if this equipment is required indoors) (include both dermal and inhalation exposure).

Outdoor Crops:

1. DACO 5.4/5.5 Handheld mistblower M/L/A passive dosimetry/biological monitoring (if this equipment is required outdoors) (include both dermal and inhalation exposure)
2. DACO 5.4/5.5 M/L/A passive dosimetry/biological monitoring (for any application scenario that is required but has not been shown to have acceptable risk)

8.0 Next Steps

Before making a special review decision on naled, the PMRA will consider all comments received from the public in response to this consultation document. A science-based approach will be applied in making a final decision. The PMRA will then publish a special review decision document, which will include the decision, the reasons for it, a summary of the comments received on the proposed decision, and the PMRA's response to these comments.

Appendix I Registered Products Containing Naled as of 23 January 2019

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

Appendix II Studies Submitted by the Registrant under Section 12 of the Pest Control Products Act

Following the re-evaluation of naled, the PMRA received the following studies under section 12 of the *Pest Control Products Act*

PMRA Document Number	Reference
1266791 and 1266792	Naled: Data Evaluation Record of a Developmental Neurotoxicity Study. United States Environmental Protection Agency, Health Effects Division, Office of Pesticide Programs, Arlington, Virginia, U.S.A. August 31, 2005.
1297649 and 1297650	Naled: Developmental Neurotoxicity Study in Rats, Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, U.K., Laboratory Study Number: RR0882. October 8, 2003. DACO 4.5.12.
1847170	Naled: Repeat Dose Cholinesterase Inhibition Study in Pre-weaning and Young Adult Rats, Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, U.K., Laboratory Study Number: KR1489. October 22, 2003. DACO 4.5.12.
1847172	Naled: Acute Cholinesterase Inhibition Study in Rats, Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, U.K., Laboratory Study Number: AR7139. June 25, 2002. DACO 4.5.12.
1847173	Naled: Acute Cholinesterase Inhibition Study in Pre-weaning Rats, Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, U.K., Laboratory Study Number: AR7146. October 24, 2003. DACO 4.5.12.

Appendix III Updated Toxicology Reference Values for Use in Human Health Risk Assessment for Naled

Health Canada re-assessed the toxicological endpoints and overall reference values for naled based on the information submitted under section 12 of the *Pest Control Products Act* (see below), and in consideration of the detailed review of the toxicology database for naled that was included in the Proposed Acceptability for Continued Registration, PACR2004-33 *Re-evaluation of Naled* (Canada, 2004).

Pursuant to subsection 17(1) of the *Pest Control Products Act*, Health Canada initiated a special review of naled (Canada, 2017a) based on the review of the toxicology information submitted under section 12 of the *Pest Control Products Act*, following the re-evaluation of naled (Canada, 2004; and Canada, 2006). The aspect of concern for this special review is relevant to human health (potential occupational risks).

In addition, Health Canada, in 2015, 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 due to for human health and environmental concerns (Canada, 2015). The aspects of concern identified for this 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 will publish separately the outcome of the evaluation of the special review of naled under subsection 17(2) of the *Pest Control Products Act*.

The toxicological reference values considered in both of these special reviews for naled (under subsections 17(1) and 17(2)), are outlined below.

Summary of Section 12 Data

Due to study limitations, results of the developmental neurotoxicity study in rats, submitted under section 12 of the *Pest Control Products Act*, did not resolve concerns identified during the re-evaluation (Canada, 2004) regarding potential sensitivity of the young. These limitations included highly variable motor activity data and the lack of brain morphometric data in the low and mid-dose level offspring. Decreases in sub-session motor activity, peak auditory startle, and brain weights, as well as changes in brain morphometrics, were seen in offspring at dose levels that did not cause maternal toxicity; however, cholinesterase measurements in this study were lacking. Available data suggest that cholinesterase inhibition would be occurring in the dams at the dose levels producing effects in the young.

Review of the submitted cholinesterase inhibition studies confirmed the nervous system as the target for toxicity of naled. In the acute and repeat-dose oral comparative cholinesterase inhibition studies, erythrocyte and brain cholinesterase inhibition were noted in juvenile and adult rats. Sensitivity of the young was evident in both the acute and repeat-dose studies based on cholinesterase inhibition. Benchmark dosing analysis confirmed that juvenile rats were more sensitive to the effects of naled compared to adults and that brain cholinesterase was more sensitive to inhibition than erythrocyte cholinesterase. With acute dosing, juvenile rats were up to twofold and threefold more sensitive than adults regarding brain and erythrocyte cholinesterase inhibition, respectively. With repeated dosing, juvenile rats were up to twofold more sensitive than adults for both brain and erythrocyte cholinesterase inhibition. Evidence in

the database suggested a durational effect on cholinesterase inhibition, with long-term oral exposure to naled in rats resulting in greater cholinesterase inhibition when compared to studies of shorter duration. Benchmark dose analysis indicated brain cholinesterase inhibition occurred at approximately fourfold lower dose levels in the rat 2-year study compared to the 7-day study.

Pest Control Products Act Hazard Characterization

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

With respect to the completeness of the toxicity database as it pertains to the exposure of and toxicity to infants and children, extensive data were available for naled. The database contains the standard complement of required studies including oral developmental toxicity studies in rats and rabbits and an oral multi-generation reproductive toxicity study in rats. Pursuant to the last review (Canada, 2004), a developmental neurotoxicity study and several comparative cholinesterase assays in juvenile and young adult rats were submitted and reviewed.

With respect to concerns relevant to the assessment of risk to infants and children, the prenatal developmental toxicity studies in rats and rabbits gave no indication of increased susceptibility of fetuses following in utero exposure. In a reproductive toxicity study, pup survival was reduced, but only at a dose level resulting in parental mortality. The number of pups born per litter in the second generation was reduced at a lower dose level but data from the rat chronic toxicity study indicated that significant toxicity, including inhibition of cholinesterase, would be expected in the parental animals at this dose level. Although developmental and multi-generation studies did not indicate an increased sensitivity of the young, the assessment of cholinesterase inhibition was lacking in these studies.

Results of the developmental neurotoxicity study did not resolve concerns regarding potential sensitivity of the young due to study limitations. However, sensitivity of the directly-dosed young was noted in several comparative cholinesterase assays. Effects on cholinesterase activity levels in the indirectly-dosed young were not assessed following in utero or via lactation exposure; therefore, it is not known whether the young are sensitive via these pathways as well. In absence of these data, it is assumed that these subpopulations (fetuses and nursing pups) would demonstrate at most, a comparable degree of sensitivity to that observed in directly-dosed young animals. Therefore, the use of cholinesterase inhibition in the directly-dosed young animal as the point of departure for risk assessment is expected to address concerns relating to indirect exposures.

In summary, with regards to the *Pest Control Products Act* factor, the toxicity data are considered complete and the overall level of concern is low. This conclusion is based on the nature and level of concern for the cholinesterase endpoint and the fact that, for certain risk assessments, the endpoint was established from data on the sensitive subpopulation.

Where the endpoint from the sensitive subpopulation was not used in the risk assessment, the application of other uncertainty factors addressed residual concerns for potential sensitivity of the young as noted above. Accordingly, the *Pest Control Products Act* factor was reduced to onefold on the basis of these considerations.

Acute Reference Dose (ARfD)

General Population (including females 13 to 49 years of age, infants and children)

To estimate acute dietary risk (1 day), the acute cholinesterase study in rats was selected for risk assessment. A benchmark dose lower confidence limit for a 10% response (BMDL) of 5.9 mg/kg bw was determined in male post-natal (PND) 22 pups based on inhibition of brain cholinesterase activity. This value was selected as it is based on the most sensitive endpoint in the database following a single exposure, is derived from a susceptible subpopulation (that is, the young), and is protective of other neurological and systemic effects. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the PCPA Hazard Characterization Section, the *Pest Control Products Act* factor was reduced to onefold, thus the composite assessment factor (CAF) is 100.

The ARfD is calculated according to the following formula:

$$\text{ARfD (General Population)} = \frac{BMDL_{10}}{CAF} = \frac{5.9 \text{ mg/kg bw}}{100} = 0.06 \text{ mg/kg bw}$$

The ARfD was considered protective of all populations including infants and children.

Acceptable Daily Intake (ADI)

General Population (including females 13 to 49 years of age, infants and children)

To estimate risk from repeat dietary exposure, the 7-day cholinesterase study in rats was selected for risk assessment. A $BMDL_{10}$ of 0.67 mg/kg bw/day was determined in male PND12 pups based on inhibition of brain cholinesterase activity. Uncertainty factors of 10-fold for interspecies extrapolation as well as 10-fold for intraspecies variability were used to derive the ADI. Although adult brain cholinesterase inhibition BMD_{10} values were lower (0.81 mg/kg bw/day) after 2 years of oral exposure than after 7 days of exposure (2.90/3.47 mg/kg bw/day [♂/♀]), the chronic study was not used for the point of departure as it did not assess the most sensitive subpopulation. Accordingly, an additional threefold uncertainty factor for duration was applied to the selected point of departure. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to onefold, thus the composite assessment factor (CAF) is 300.

The ADI is calculated according to the following formula:

$$\text{ADI (General Population)} = \frac{BMDL_{10}}{CAF} = \frac{0.67 \text{ mg/kg bw/day}}{300} = 0.002 \text{ mg/kg bw/day}$$

This ADI is considered protective of all populations including pregnant women, infants and children.

Toxicology Reference Values for Occupational and Residential Risk Assessments

For **short- and intermediate-term dermal exposures**, the 28-day dermal toxicity study in rats was selected for risk assessment. A $BMDL_{10}$ of 1.96 mg/kg bw/day was determined in rats based on inhibition of brain cholinesterase activity. Studies demonstrated that direct oral exposure of the young to naled resulted in greater sensitivity compared to adult animals. Since the 28-day dermal toxicity study was conducted in adults, there was uncertainty whether this sensitivity would also be manifested via the dermal route. In addition, there is uncertainty as to whether the fetus or nursing infant would also be sensitive as a result of an indirect exposure via the mother. This was a concern because the population, including workers, could include pregnant or lactating women. Given the lack of appropriate dermal data to address sensitivity or data to assess the potential sensitivity of the fetus or nursing offspring, an additional threefold factor, in the form of a database deficiency, was considered appropriate to protect the young. The magnitude of this factor was considered appropriate taking into account the relative sensitivity of the young, compared to adults, following direct oral exposure to naled. Therefore, the target MOE was 300, accounting for standard uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability and the extra 3-fold uncertainty factor for database deficiency for concerns relating to sensitivity of the young. For residential scenarios, the *Pest Control Products Act* factor was reduced to onefold as discussed in the *Pest Control Products Act* Hazard Characterization section.

For **long-term dermal exposures**, the 28-day dermal toxicity study in rats was selected. A $BMDL_{10}$ of 1.96 mg/kg bw/day was determined in rats based on inhibition of brain cholinesterase activity. Studies demonstrated that direct oral exposure of the young to naled resulted in greater sensitivity compared to adult animals. Since the 28-day dermal toxicity study was conducted in adults, there was uncertainty whether this sensitivity would also be manifested via the dermal route. In addition, there is uncertainty as to whether the fetus or nursing infant would also be sensitive as a result of an indirect exposure via the mother. This was a concern because the population, including workers, could include pregnant or lactating women. Given the lack of appropriate dermal data to address sensitivity or data to assess the potential sensitivity of the fetus or nursing offspring, an additional uncertainty factor, in the form of a database deficiency, was considered appropriate to protect the young. Given that long-term direct oral exposure of rats to naled resulted in a lower effective dose for cholinesterase inhibition when compared to studies of shorter duration, an additional factor for the durational consideration was also applied. Therefore, an additional 10-fold database deficiency factor was applied to address both the potential sensitivity of the young and concerns related to the increased toxicity with increased duration of dosing. The target MOE selected was 1,000, accounting for standard uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability and the extra 10-fold uncertainty factor for database deficiencies.

For **short-, intermediate- and long-term inhalation exposures**, the 90-day inhalation toxicity study in rats was selected. A lowest observed adverse effect concentration (LOAEC) of 0.23 µg/L, equivalent to a lowest observed adverse effect level (LOAEL) of 0.065 mg/kg bw/day, was selected based on clinical signs and nasal pathology likely attributed to the irritant properties of naled. Inhibition of cholinesterase activity occurred at a higher dose level than the clinical signs

and nasal pathology in this study. An additional uncertainty factor for lack of a no observed adverse effect concentration (NOAEC) was not applied as the nature and severity of findings at the LOAEC suggested the LOAEC was at the threshold of toxicity. No additional factor was applied for concerns relating to sensitivity of the young as sensitivity was not anticipated for a local irritant response. For occupational exposures, a target MOE of 100 was selected, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. These values were considered to be protective of all worker populations including women who may be pregnant or nursing. For residential scenarios, the *Pest Control Products Act* factor was reduced to onefold as discussed in the *Pest Control Products Act* Hazard Characterization section.

Cancer Assessment

There was no evidence of carcinogenicity in mice or rats; therefore, a cancer risk assessment was not required for naled.

Aggregate Assessment

Short-term Aggregate

For short-term aggregate risk assessment of the general population, including pregnant women, infants and children, the selected toxicological endpoint was brain cholinesterase inhibition. For oral exposure, the $BMDL_{10}$ of 0.67 mg/kg bw/day was determined based on inhibition of brain cholinesterase activity in the 7-day comparative cholinesterase study. The target MOE was 100 since this endpoint was derived from data obtained from the sensitive subpopulation and the study duration was appropriate for use in a short-term exposure scenario. For dermal exposure, the $BMDL_{10}$ of 1.96 mg/kg bw/day was selected based on brain cholinesterase inhibition from the 28-day dermal toxicity study in rats. A target MOE of 300 was selected which includes a 10-fold uncertainty factor for interspecies extrapolation, 10-fold uncertainty factor for intraspecies variability and a 3-fold database uncertainty factor for concerns relating to sensitivity of the young as this sensitive subpopulation was not assessed by the dermal route. For inhalation exposure, the $BMDL_{10}$ of 1.254 µg/L, approximately equivalent to 0.35 mg/kg bw/day, was selected based on brain cholinesterase inhibition in the 90-day inhalation toxicity study in rats. The target MOE was 300, which includes a 10-fold uncertainty factor for interspecies extrapolation, 10-fold uncertainty factor for intraspecies variability, and a 3-fold database uncertainty factor for concerns relating to sensitivity of the young as this sensitive subpopulation was not assessed by the inhalation route. For residential scenarios, the *Pest Control Products Act* factor was reduced to onefold as discussed in the *Pest Control Products Act* Hazard Characterization section.

Cumulative Assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Naled belongs to a group of chemicals classified as organophosphates. Organophosphates have a common mechanism of toxicity wherein they all possess the ability to interact with the cholinesterase enzyme ultimately leading to neurotoxicity. Given that dichlorvos is a transformation product of naled, endpoints to assess the co-exposure to naled and dichlorvos were selected (see below) for assessment under

subsection 17(2) of the *Pest Control Products Act*, to be published separately. Upon completion of the re-evaluation of the individual chemicals in the organophosphate group, it will be determined whether a cumulative effects assessment is necessary for the entire group of organophosphates and, if so, this will be performed with all relevant chemicals of the common mechanism group.

Non-Occupational Assessment for Cumulative Exposure to Naled and Dichlorvos

Given that dichlorvos is a transformation product of naled, the co-occurrence of naled and dichlorvos exposure needs to be considered. Both of these organophosphates share a common mechanism of toxicity, namely cholinesterase inhibition. Accordingly, endpoints based on brain cholinesterase inhibition were considered relevant for this assessment.

For an acute risk assessment to address co-exposure to naled and dichlorvos in food and drinking water, acute oral comparative cholinesterase studies were available for both compounds, with inhibition of brain cholinesterase activity noted as the common effect. The selected studies and $BMDL_{10}$ values were the same as those selected for the ARfD and are presented in Tables 1 and 2. Target MOE values were consistent with those selected for the naled and dichlorvos risk assessments and are considered to be protective of all populations.

For short-term risk assessment of co-exposures to naled and dichlorvos from food, drinking water and residential (incidental oral and dermal) exposures, the relevant duration of exposure is for a period of up to one month, and inhibition of brain cholinesterase was the common toxic effect. The most relevant studies for this assessment were route-specific for naled (7-day oral, 28-day dermal and 90-day inhalation toxicity studies) with $BMDL_{10}$ values identified in Table 1. For dichlorvos, in the absence of suitable short-term inhalation and dermal toxicity studies, a 7-day oral cholinesterase inhibition study in rats was considered appropriate for the oral, dermal and inhalation components of this risk assessment as presented in Table 2. Target MOE values were consistent with those selected for the route-specific risk assessments and are considered to be protective of all populations.

For long-term risk assessment of co-exposures to naled and dichlorvos from food and drinking water exposures, inhibition of brain cholinesterase activity was the common toxic effect for both compounds. The selected studies and $BMDL_{10}$ values were the same as those selected for the ADI and are presented in Tables 1 and 2, for naled and dichlorvos, respectively. Target MOE values were consistent with those selected for the naled and dichlorvos-specific risk assessments and are considered to be protective of all populations.

Updated toxicological reference values for use in the human health risk assessment for naled are summarized in Table 1. Toxicological reference values for use in the health risk assessment for dichlorvos (Canada, 2017b) are summarized in Table 2.

Table 1 Studies Submitted by the Registrant Under Section 12 of the *Pest Control Products Act*

Study/Species	Purity of Test Material/Dose Level/Results/Effects
Acute Oral (gavage) Cholinesterase Study Sprague-Dawley Rats Non-guideline PMRA No. 1847172	**$BMD_{10}/BMDL_{10}$ for BChE = 21.64/10.64 mg/kg bw (♂); 12.73/10.11 mg/kg bw (♀) (for 'half-brain' section)** **$BMD_{20}/BMDL_{20}$ for EChE = 25.83/10.06 mg/kg bw (♂); 44.45/7.319 mg/kg bw (♀)** 25 mg/kg bw: ↓ EChE activity (recovery by Day 8), ↓ BChE activity in cerebellum, cortex and half-brain sections (recovery not assessed because samples were not analyzed); 100 mg/kg bw: ↓ EChE activity (recovery by Day 15), ↓ BChE activity (in all brain sections, no recovery observed by Day 8; recovery observed at Day 15 for hippocampus (♀), remainder (♀), half-brain (♂); recovery not observed: cerebellum, cortex, hippocampus (♂), remainder (♂) and half brain (♀)).
Acute Oral (gavage) Cholinesterase Study Wistar Rats Non-guideline PMRA No. 1847173	**Pre-Weanling (8 days old)** **$BMD_{10}/BMDL_{10}$ for BChE = 8.954/6.773 mg/kg bw (♂); 7.744/6.422 mg/kg bw (♀)** **$BMD_{20}/BMDL_{20}$ for EChE = 22.2/15.99 mg/kg bw (♂); 40.11/21.07 mg/kg bw (♀)** ≥25 mg/kg bw: ↓ BChE activity; ↓ EChE activity (♂); 100 mg/kg bw: ↑ mortality (2♂ and 2♀), clinical signs (pallor); ↓ EChE activity (♀). **Pre-Weanling (15 days old)** **$BMD_{10}/BMDL_{10}$ for BChE = 7.958/5.972 mg/kg bw (♂); 13.44/6.763 mg/kg bw (♀)** **$BMD_{20}/BMDL_{20}$ for EChE = 21.8/7.923 mg/kg bw (♂); 27.23/9.216 mg/kg bw (♀)** ≥25 mg/kg bw: ↓ EChE and BChE activity; 100 mg/kg bw: clinical signs (slight tremors, ↓ activity). **Pre-Weanling (22 days old)** **$BMD_{10}/BMDL_{10}$ for BChE = 7.983/5.871 mg/kg bw (♂); 8.956/6.845 mg/kg bw (♀)** **$BMD_{20}/BMDL_{20}$ for EChE = 16.25/7.507 mg/kg bw (♂); 12.81/3.33 mg/kg bw (♀)** ≥25 mg/kg bw: ↓ EChE and BChE activity; 100 mg/kg bw: clinical signs (moderate tremors, ↓ activity).

Study/Species	Purity of Test Material/Dose Level/Results/Effects
7-Day Oral (gavage) Cholinesterase Study Wistar Rats Non-guideline PMRA No. 1847170	**Pre-Weanling (12 days old)** **BMD_{10}/$BMDL_{10}$ for BChE = 2.091/0.6709 mg/kg bw/day (♂); 2.355/1.869 mg/kg bw/day (♀)** **BMD_{20}/$BMDL_{20}$ for EChE = 3.975/2.705 mg/kg bw/day (♂); 4.229/2.653 mg/kg bw/day (♀)** ≥0.4 mg/kg bw/day: ↓ EChE activity (♀); ≥2.0 mg/kg bw/day: ↓ BChE activity; ≥10 mg/kg bw/day: ↓ EChE activity (♂); 30 mg/kg bw/day: EChE activity not assessed. **Adult (42 days old)** **BMD_{10}/$BMDL_{10}$ for BChE = 3.331/2.573 mg/kg bw/day (♂); 4.128/2.988 mg/kg bw/day (♀)** **BMD_{20}/$BMDL_{20}$ for EChE = 6.105/3.763 mg/kg bw/day (♂); 21.17/4.067 mg/kg bw/day (♀)** ≥10 mg/kg bw/day: ↓ EChE and BChE activity; 30 mg/kg bw/day: EChE activity not assessed. **Sensitivity of the young.**
Oral (gavage) Developmental Neurotoxicity Wistar rats PMRA Nos. 1297649 and 1297650	**Maternal** No treatment-related effects at HDT (10 mg/kg bw/day) **Offspring** ≥2 mg/kg bw/day: ↓ motor activity (F_1♂ PNDs 14 and 18; high variability in data without statistical significance); 10 mg/kg bw/day: alterations in brain morphometric measurements on PNDs 12 and 63 (PND12: ↑ thickness of dorsal cortex, ↑ width of dentate gyrus and hippocampus in ♂, ↓ length of dentate gyrus in hippocampus in ♀; PND 63: ↑ length from midline and of dentate gyrus in hippocampus in ♂, ↑ width of dentate gyrus in hippocampus in ♀), ↓ mean auditory startle reflex peak amplitude in ♂ at PNDs 23 and 61; ↓ absolute brain wt (♀). **Study considered supplemental.**

Table 2 Toxicological Reference Values for Use in the Human Health Risk Assessment for Naled

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[a] or Target MOE
Acute dietary - general population, combined[b] acute	Acute oral cholinesterase in rats	$BMDL_{10}$ = 5.9 mg/kg bw Decreased BChE activity	100
	ARfD = 0.06 mg/kg bw		
Repeated dietary - general population, combined[b] long-term	7-day oral cholinesterase in rats	$BMDL_{10}$ = 0.67 mg/kg bw/day Decreased BChE activity	300
	ADI = 0.002 mg/kg bw/day		
Short- and intermediate-term dermal	28-day dermal in rats	$BMDL_{10}$ = 1.96 mg/kg bw/day Decreased BChE activity	300
Long-term dermal	28-day dermal in rats	$BMDL_{10}$ = 1.96 mg/kg bw/day Decreased BChE activity	1000
Inhalation, all durations	90-day inhalation in rats	LOAEL = 0.065 mg/kg bw/day Clinical signs and nasal pathology	100
Aggregate short-term, Co-exposure[b]	Oral: 7-day oral cholinesterase in rats Dermal: 28-day dermal in rats Inhalation: 90-day inhalation in rats	$BMDL_{10}$ = 0.67 mg/kg bw/day $BMDL_{10}$ = 1.96 mg/kg bw/day $BMDL_{10}$ = 1.254 µg/L (~0.35 mg/kg bw/day) Common endpoint: Decreased BChE activity	100 300 300
Cancer	No evidence of oncogenicity		

[a] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments; $BMDL_{10}$ – benchmark dose level for 10% change; BChE- brain cholinesterase; ARfD – acute reference dose; ADI – acceptable daily intake; LOAEL – lowest observed adverse effect level

[b] Co-exposure refers to risk assessments for co-occurrence of naled with dichlorvos

Table 3 Toxicological Reference Values for Use in Health Risk Assessment for Dichlorvos (Canada, 2017b)

Exposure Scenario	Endpoint	Study	CAF[a] or Target MOE
Acute Dietary combined[d] (all populations)	$BMDL_{10}$ = 1.4 mg/kg bw (BChE inhibition)	Two Acute Oral Cholinesterase Inhibition Studies - neonate and young adult Rats	100
	ARfD = 0.014 mg/kg bw		
Chronic Dietary combined[d] (all populations)	$BMDL_{10}$ = 0.011 mg/kg bw (BChE inhibition)	7-day Repeat-dose Oral Cholinesterase Inhibition Study - PND 18 and 48 rats	100
	ADI = 0.0001 mg/kg bw/day		
Dermal[b], all durations	$BMDL_{10}$ = 0.011 mg/kg bw (BChE inhibition)	7-day Repeat-dose Oral Cholinesterase Inhibition Study - PND 18 and 48 rats	100

Exposure Scenario	Endpoint	Study	CAF[a] or Target MOE
Inhalation[c], all durations	$BMDL_{10}$ = 0.011 mg/kg bw (BChE inhibition)	7-day Repeat-dose Oral Cholinesterase Inhibition Study - PND 18 and 48 rats	100
Aggregate short-term, co-exposure[d]	Oral, dermal, and inhalation: $BMDL_{10}$ = 0.011 mg/kg bw (BChE inhibition)	7-day Repeat-dose Oral Cholinesterase Inhibition Study - PND 18 and 48 rats	100
Cancer Oral, Dermal and Inhalation	Dichlorvos is an in vitro mutagen and clastogen; however, the overall weight of evidence suggested that it is neither mutagenic nor clastogenic in vivo. The available evidence is insufficient to rule out the possibility that dichlorvos may be carcinogenic. Although a data gap remains in the dichlorvos database with respect to carcinogenicity, there is a large margin (~40,000) between the proposed reference values for repeat-exposure and the lowest dose resulting in tumours in the available dichlorvos studies.		

$BMDL_{10}$ – benchmark dose level for 10% change; BChE – brain cholinesterase; PND – post-natal day

[a] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments.

[b] Since an oral NOAEL was selected, a 30% dermal absorption was used for route-to-route extrapolation

[c] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used for route-to-route extrapolation

[d] Co-exposure refers to risk assessments for co-occurrence of naled with dichlorvos

Appendix IV Mixer/Loader/Applicator Risk Assessment According to Current Label Directions

Table 4.1 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 Exposure[b] (mg/kg bw/day)	Inhalation Exposure[c] (mg/kg bw/day)	Dermal MOE[d]	Inhalation MOE[e]	Combined MOE[f]
PPE: Mid-level PPE + open M/L + open cab + respirator [g]								
Broccoli, Brussels sprouts, cabbage, cauliflower	1.9	26	49	3.32×10^{-2}	1.58×10^{-4}	59	410	57
Lettuce	1.425	26	37	2.49×10^{-2}	1.19×10^{-4}	79	550	77
Onion	0.48	26	12.48	8.39×10^{-3}	3.99×10^{-5}	230	1600	227
Strawberries	0.95	26	25	1.66×10^{-2}	7.9×10^{-5}	120	820	115
Tomatoes	1.728	26	45	3.02×10^{-2}	1.44×10^{-4}	65	450	63
PPE: Maximum-level PPE + open M/L + open cab + respirator [g]								
Alfalfa, clover, vetch	1.9	200	380	2.27×10^{-1}	1.22×10^{-3}	9	53	8
Rangeland, field areas, pastures (dairy cattle present)	0.864	360	311	1.86×10^{-1}	9.95×10^{-4}	11	65	10
Peas, beans, lima beans	1.9	200	380	2.27×10^{-1}	1.22×10^{-3}	9	53	8
Potatoes	0.95	360	342	2.05×10^{-1}	1.09×10^{-3}	10	59	9
Sugarbeet	1.9	200	380	2.27×10^{-1}	1.22×10^{-3}	9	53	8

M/L = mixing/loading, ATPD = area treated per day, MOE = margin of exposure, PPE = personal protective equipment

[a] Default ATPD values were used for custom applicators. Farmer values were refined based on the Census of Agriculture (Statistics Canada, 2011) however they were not presented here since there is unacceptable risk for custom applicators. Label limits workers using maximum rate of 2.2 L end-use product/ha to treat only 200 ha/day.

[b] Dermal exposure (mg/kg bw/day) = (dermal unit exposure × ATPD × maximum application rate)/ body weight (80 kg)

[c] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure × ATPD × maximum application rate)/ body weight (80 kg)

[d] Based on a short- and intermediate-term $BMDL_{10}$ of 1.96 mg/kg bw/day, and a target MOE of 300 for the dermal endpoint

[e] Based on a LOAEL of 0.065 mg/kg bw/day, and a target MOE of 100 for the inhalation endpoint

[f] Combined MOE = 1 / (1/MOE dermal) + (1/MOE inhalation); based on a dermal $BMDL_{10}$ of 1.963 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: Maximum-level PPE when applying to areas larger than 30 ha/day, Mid-level PPE if less than 30 ha/day, open mixing/loading plus respirator. Shaded cells indicate MOEs that are less than the target MOE.

Table 4.2 Mixer/Loader/Applicator Exposure and Risk Assessment of Naled by Aerial Application

Crop	Application Rate (kg a.i./ha)[a]	ATPD (ha/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]
Aerial with closed M/L (maximum-level PPE + respirator) [h]								
Potatoes	0.950	240	228	2.21×10^{-2}	3.14×10^{-4}	89	210	88
Tomatoes	0.950	200	190	1.84×10^{-2}	2.61×10^{-4}	110	250	106
Corrals, pastures, holding pens, (dairy and beef cattle present)	0.275	222	61	5.91×10^{-3}	8.39×10^{-5}	330	770	329
Alfalfa, clover, vetch	1.900	200	380	3.68×10^{-2}	5.23×10^{-4}	53	120	53
Rangeland, field areas, pastures (dairy cattle present)	0.864	222	192	1.86×10^{-2}	2.64×10^{-4}	110	250	105
Livestock pastures, feed lots, pastures (dairy cattle present)	0.275	222	61	5.91×10^{-3}	8.39×10^{-5}	330	770	329
Peas, beans, lima beans	1.900	200	380	3.68×10^{-2}	5.23×10^{-4}	53	120	53
Aerial applicator. Baseline PPE: single layer, no gloves								
Potatoes	0.950	240	228	2.75×10^{-2}	2.00×10^{-4}	71	330	68
Tomatoes	0.950	200	190	2.29×10^{-2}	1.66×10^{-4}	85	390	82
Corrals, pastures, holding pens, (dairy and beef cattle present)	0.275	222	61	7.37×10^{-3}	5.34×10^{-5}	266	1200	256
Alfalfa, clover, vetch	1.900	200	380	4.59×10^{-2}	3.33×10^{-4}	43	200	41
Rangeland, field areas, pastures (dairy cattle present)	0.864	222	192	2.32×10^{-2}	1.68×10^{-4}	85	390	81
Livestock pastures, feed lots, pastures (dairy cattle present)	0.275	222	61	7.37×10^{-3}	5.34×10^{-5}	266	1200	256
Peas, beans, lima beans	1.900	200	380	4.59×10^{-2}	3.33×10^{-4}	43	200	41

M/L = mixing/loading, ATPD = area treated per day, MOE = margin of exposure, PPE = personal protective equipment

[a] Some crops have application rates that vary; this may depend on the insect targeted. The maximum rate is presented here.

[b] ATPD values were mostly refined. The label limits workers using maximum rate of 1.9 kg a.i./ha to treat only 200 ha/day.

[c] Dermal exposure (mg/kg bw/day) = (dermal unit exposure × ATPD × maximum application rate)/ body weight (80 kg)

[d] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure × ATPD × maximum application rate)/ body weight (80 kg)

[e] Based on a short- and intermediate-term $BMDL_{10}$ of 1.96 mg/kg bw/day, and a target MOE of 300 for the dermal endpoint
[f] Based on a LOAEL of 0.065 mg/kg bw/day, and a target MOE of 100 for the inhalation endpoint
[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
[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 ground boom label." also "All applications must use closed mixing/loading systems". Therefore, the PPE for groundboom was applied here.
Shaded cells indicate MOEs that are less than the target MOE.

Table 4.3 Mixer/Loader/Applicator Exposure and Risk Assessment of Naled by Handheld Application

Equipment	Crop	Application 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	1.31×10^{-2}	8.05×10^{-4}	150	81	110
	In and around dairy barns, livestock barns, pig pens, poultry houses	0.0026	150	0.4	2.58×10^{-3}	2.20×10^{-4}	550	290	407
	Cider mills, wineries	0.0052	150	0.8	7.17×10^{-3}	4.41×10^{-4}	270	150	200
	Outdoor ornamentals	0.00108	150	0.2	1.49×10^{-3}	9.15×10^{-5}	1300	710	980
Backpack	Strawberries	0.0095	150	1.4	4.63×10^{-2}	1.11×10^{-3}	42	59	37
	In and around dairy barns, livestock barns, pig pens, poultry houses	0.0026	150	0.4	1.27×10^{-2}	3.03×10^{-4}	150	210	140
	Cider mills, wineries	0.0052	150	0.8	2.53×10^{-2}	6.05×10^{-4}	80	110	70
	Outdoor ornamentals	0.00108	150	0.2	5.26×10^{-3}	1.26×10^{-4}	370	520	330

PPE: Maximum-level PPE + respirator									
MPHG	Strawberries	0.0095	1000	9.5	2.17×10^{-1}	1.79×10^{-3}	10	36	9
	In and around dairy barns, livestock barns, pig pens, poultry houses	0.0026	1000	2.6	5.94×10^{-2}	4.91×10^{-4}	30	130	32
	Cider mills, wineries	0.0052	1000	5.2	1.19×10^{-1}	9.82×10^{-4}	20	66	16
	Outdoor ornamentals	0.00108	1000	1.1	2.47×10^{-2}	2.04×10^{-4}	80	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

[a] Application rates in kg a.i./L were calculated: application rate (kg a.i/ha) / spay 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 label.

[c] Dermal exposure (mg/kg bw/day) = (dermal unit exposure × ATPD × maximum application rate)/ body weight (80 kg)

[d] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure × ATPD × maximum application rate)/ body weight (80 kg)

[e] Based on a short- and intermediate-term $BMDL_{10}$ of 1.96 mg/kg bw/day, and a target MOE of 300 for the dermal endpoint

[f] Based on a LOAEL of 0.065 mg/kg bw/day, and a target MOE of 100 for the inhalation endpoint

[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 4.4 Mixer/Loader/Applicator Exposure and Risk Assessment of Naled by Airblast/Tractor Drawn Mistblower/ULV[a] Application

Site	Application Rate (kg a.i./ha)	ATPD (ha/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								
Airblast: Livestock pastures, feed lots, pastures (dairy cattle present)	0.275	20	5.5	2.36×10^{-1}	7.34×10^{-4}	8	89	8
ULV: Livestock pastures, feed lots, pastures (dairy cattle present)	0.275	1200	330	1.42×10^{-1}	4.41×10^{-2}	0	1	0
Airblast: Woodland	0.275	20	5.5	2.36×10^{-1}	7.34×10^{-4}	8	89	8
ULV: Woodland	0.275	500	137.5	5.90×10^{-0}	1.84×10^{-2}	0	4	0
Outdoor ornamentals	0.324	20	6.5	2.78×10^{-1}	8.65×10^{-4}	7	75	7

M/L = mixing/loading, A = apply, ATPD = area treated per day, MOE = margin of exposure, PPE = personal protective equipment,

[a] When the label states mistblower, PHED and/or AHETF airblast data is used. There is no data for handheld mistblower.

[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. Label limitation to woodlands = maximum of 500 ha.

[c] Dermal exposure (mg/kg bw/day) = (dermal unit exposure × ATPD × maximum application rate)/ body weight (80 kg)

[d] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure × ATPD × maximum application rate)/ body weight (80 kg)

[e] Based on a short- and intermediate-term $BMDL_{10}$ of 1.96 mg/kg bw/day, and a target MOE of 300 for the dermal endpoint

[f] Based on a LOAEL of 0.065 mg/kg bw/day, and a target MOE of 100 for the inhalation endpoint

[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 4.5 Mixer/Loader/Applicator Exposure and Risk Assessment of Naled by Fogger and Vapour Application

Site	Application Rate	ATPD[a]	Amount handled per day (kg a.i./day)	Dermal Exposure[b] (mg/kg bw/day)	Inhalation Exposure[c] (mg/kg bw/day)	Dermal MOE[d]	Inhalation MOE[e]	Combined MOE[f]
PPE: Maximum-level PPE + respirator for all equipment								
Indoor areas (poultry houses, pig pens, cider mills, livestock barns, wineries) – fogger/mistblower (**automated**)[gh]	0.119 kg a.i. /ha	0.022 ha	0.0026	9.53×10^{-7}	5.24×10^{-9}	2.10×10^{6}	1.20×10^{7}	2.00×10^{6}
Indoor areas (poultry houses, pig pens, cider mills, livestock barns, wineries) – fogger/mistblower (handheld)	There is no data available to assess this use.							
Greenhouse (food and non-food) – fogger (**automated**) [hi]	0.00012 kg a.i. /m^2	28000 m^2	3.36	1.22×10^{-3}	6.72×10^{-6}	1600	9700	1556
Greenhouse –vapour treatment [j]	0.000086 kg a.i. /m^3	50000 m^3	4.3	1.09×10^{-1}	2.10×10^{-4}	18	310	18

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

[a] Indoor space spray and greenhouse vapour treatment area treated per day is based on data-call in information for dichlorvos (PMRA, 2016b). Greenhouse fogger area treated per day is based on the Census of Agriculture (Statistics Canada, 2011) for greenhouse vegetables.

[b] Dermal exposure (mg/kg bw/day) = (dermal unit exposure × ATPD × maximum application rate)/ body weight (80 kg)

[c] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure × ATPD × maximum application rate)/ body weight (80 kg). 90% protection factor was used for the respirator to calculate inhalation exposure for the vapour treatment.

[d] Based on a short- and intermediate-term $BMDL_{10}$ of 1.96 mg/kg bw/day, and a target MOE of 300 for the dermal endpoint

[e] Based on a LOAEL of 0.065 mg/kg bw/day, and a target MOE of 100 for the inhalation endpoint

[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 space spray could be interpreted many ways. Since the PMRA received a confirmation that fogger was being used in a poultry house, this scenario was expanded to include additional application equipment. The spray volume was based on the pest treated to obtain similar coverage as from airblast. Automated fogger was assessed as mixing/loading exposure only. Although this use was assessed for potential human exposure, it is not necessarily a viable option.

[h] Greenhouse fogger assessed as stationary (mixing/loading exposure only) as per label instructions.

[i] Greenhouse crops refer to cucumbers, tomatoes, eggplant, pepper, and roses and cut flowers

[j] Vapour application assessed using backpack data from PHED.

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

Table 4.6 Applicator Outdoor Supplemental Inhalation Exposure and Risk Assessment

	Air Concentration[a] (µg/m^3)	Inhalation Exposure[b] (mg/kg bw/day)	MOE[c]	MOE [d] for ARI	ARI (naled and dichlorvos) [e]
Naled	6.30	0.000630	103	556	1.00
Dichlorvos	0.508	0.0000508	217	217	

MOE= margin of exposure, ARI = aggregate risk index

[a] Maximum air concentration value for naled and concurrent dichlorvos sample from Cal EPA, 1995

[b] Inhalation exposure = air concentration × inhalation rate × exposure time / body weight (80 kg)

[c] Based on a LOAEL of 0.065 mg/kg bw/day and a target MOE of 100 for naled and a $BMDL_{10}$ of 0.011 mg/kg bw/day and a target MOE of 100 for dichlorvos

[d] Based on a $BMDL_{10}$ of 0.35 mg/kg bw/day and a target MOE of 300 for naled and a $BMDL_{10}$ of 0.011 mg/kg bw/day and a target MOE of 100 for dichlorvos both based on a common endpoint of decreased BChE activity (Canada, 2017b)

[e] ARI = $1/((\text{target } MOE_{NAL}/MOE_{NAL}) + (\text{target } MOE_{DVP}/MOE_{DVP}))$; NAL – naled, DVP – dichlorvos

Appendix V Postapplication Worker Risk Assessment

Table 5.1 Postapplication Dermal Exposure and Risk Assessment for Outdoor Applications of Naled (48hrs after application)

Crop	Activity	TC (cm^2/hr)[b]	Application Rate (kg a.i./ha)	Naled DFR ($\mu g/cm^2$)[c]	Naled Dermal Exposure (mg/kg/day)[d]	Naled Dermal MOE[e]	Dichlorvos DFR ($\mu g/cm^2$)[c]	Dichlorvos Dermal Exposure (mg/kg/day)[d]	Dichlorvos Dermal MOE[f]	ARI (naled and dichlorvos)[g]
Outdoor ornamentals	Cut flowers	4000	0.019	0.0002	8.02×10^{-5}	24000	0.0001	1.67×10^{-5}	660	6
	Irrigation (hand-set)	1750	0.019	0.0002	3.51×10^{-5}	30000	0.0001	7.29×10^{-6}	1500	13
	All other activities	230	0.019	0.0002	4.61×10^{-6}	230000	0.0001	9.58×10^{-7}	11000	96
Onion	Weeding, hand	4400	0.48	0.0003	1.31×10^{-4}	8100	0.0002	2.71×10^{-5}	410	4
	Irrigation (hand set)	1750	0.48	0.0003	5.20×10^{-5}	20000	0.0002	1.08×10^{-5}	1000	9
	Scouting, plant thinning	1300	0.48	0.0003	3.86×10^{-5}	28000	0.0002	8.02×10^{-6}	1400	12
Potato	Irrigation (hand set)	1750	0.95	0.0006	1.03×10^{-4}	10000	0.0004	2.14×10^{-5}	510	4
	Roguing	1100	0.95	0.0006	6.47×10^{-5}	16000	0.0004	1.34×10^{-5}	820	7
	Scouting	210	0.95	0.0006	1.24×10^{-5}	86000	0.0004	2.56×10^{-6}	4300	37
	Hand weeding	70	0.95	0.0006	4.12×10^{-6}	260000	0.0004	8.55×10^{-7}	13000	113
Strawberry	Harvesting, hand	1100	0.95	0.0006	6.47×10^{-5}	16000	0.0004	1.34×10^{-5}	820	7
	Transplanting	230	0.95	0.0006	1.35×10^{-5}	79000	0.0004	2.81×10^{-6}	3900	34
	Scouting	210	0.95	0.0006	1.24×10^{-5}	86000	0.0004	2.56×10^{-6}	4300	37
	Weeding, canopy management	70	0.95	0.0006	4.12×10^{-6}	260000	0.0004	8.55×10^{-7}	13000	113
Lettuce	Irrigation (hand set)	1750	1.425	0.0009	1.54×10^{-4}	13000	0.0006	3.24×10^{-5}	340	3
	Harvesting, hand	1100	1.425	0.0009	9.70×10^{-5}	20000	0.0006	2.04×10^{-5}	540	5
	Transplanting	230	1.425	0.0009	2.03×10^{-5}	97000	0.0006	4.26×10^{-6}	2600	24
	Scouting	210	1.425	0.0009	1.85×10^{-5}	110000	0.0006	3.89×10^{-6}	2800	27
	Thinning, weeding, hand	70	1.425	0.0009	6.18×10^{-6}	320000	0.0006	1.30×10^{-6}	8500	80

Crop	Activity	TC (cm^2/hr)[b]	Application Rate (kg a.i./ha)	Naled DFR ($\mu g/cm^2$)[c]	Naled Dermal Exposure (mg/kg/day)[d]	Naled Dermal MOE[e]	Dichlorvos DFR ($\mu g/cm^2$)[c]	Dichlorvos Dermal Exposure (mg/kg/day)[d]	Dichlorvos Dermal MOE[f]	ARI (naled and dichlorvos)[g]
Tomato	Irrigation (hand set)	1750	1.728	0.0011	1.87×10^{-4}	5700	0.0007	3.89×10^{-5}	280	2
	Harvesting, tying, training (hand)	1100	1.728	0.0011	1.18×10^{-4}	9000	0.0007	2.44×10^{-5}	450	4
	Transplanting	230	1.728	0.0011	2.46×10^{-5}	43000	0.0007	5.11×10^{-6}	2200	19
	Scouting	210	1.728	0.0011	2.25×10^{-5}	47000	0.0007	4.66×10^{-6}	2400	21
	Pruning, weeding (hand)	70	1.728	0.0011	7.49×10^{-6}	140000	0.0007	1.55×10^{-6}	7100	62
Alfalfa, vetch, clover, beans (dry), lima beans, peas (processing)[a]	Irrigation (hand set)	1750	1.90	0.0012	2.06×10^{-4}	5200	0.0008	4.27×10^{-5}	260	2
	Scouting	1100	1.90	0.0012	1.29×10^{-4}	8200	0.0008	2.69×10^{-5}	410	4
Brassica leafy vegetables (Broccoli, Brussels sprouts, cabbage, cauliflower)	Harvesting (hand)	5150	1.90	0.0012	6.06×10^{-4}	1800	0.0008	1.26×10^{-4}	87	0.8
	Weeding (hand)	4400	1.90	0.0012	5.18×10^{-4}	2100	0.0008	1.07×10^{-4}	100	0.9
	Scouting	4000	1.90	0.0012	4.70×10^{-4}	2300	0.0008	9.77×10^{-5}	110	0.96
	Irrigation (hand set)	1750	1.90	0.0012	2.06×10^{-4}	9500	0.0008	4.27×10^{-5}	260	2
	Cabbage: scouting, hand harvesting, mechanically assisted harvesting	1300	1.90	0.0012	1.53×10^{-4}	13000	0.0008	3.18×10^{-5}	350	3
	Transplanting	230	1.90	0.0012	2.71×10^{-5}	39000	0.0008	5.62×10^{-6}	2000	17
Sugar beet	Harvesting (hand)	1100	1.90	0.0012	1.29×10^{-4}	15000	0.0008	2.69×10^{-5}	410	4
	Scouting	210	1.90	0.0012	2.47×10^{-5}	79000	0.0008	5.13×10^{-6}	2100	18
	Weeding, thinning	70	1.90	0.0012	8.23×10^{-6}	240000	0.0008	1.71×10^{-6}	6400	56
Woodlands [h]	Irrigation (hand set)	1750	0.275	0.0002	2.98×10^{-5}	66000	0.00000024	1.27×10^{-8}	860000	215
	Harvesting (Christmas trees)	1400	0.275	0.0002	2.38×10^{-5}	82000	0.00000024	1.02×10^{-8}	1000000	267
	Scouting,	580	0.275	0.0002	9.87×10^{-6}	200000	0.00000024	4.22×10^{-9}	2600000	650

Crop	Activity	TC (cm^2/hr)[b]	Application Rate (kg a.i./ha)	Naled DFR ($\mu g/cm^2$)[c]	Naled Dermal Exposure (mg/kg/day)[d]	Naled Dermal MOE[e]	Dichlorvos DFR ($\mu g/cm^2$)[c]	Dichlorvos Dermal Exposure (mg/kg/day)[d]	Dichlorvos Dermal MOE[f]	ARI (naled and dichlorvos)[g]
	shaping, hand pruning									
	Transplanting	230	0.275	0.0002	3.92×10^{-6}	500000	0.00000024	1.67×10^{-9}	6600000	1626
	Grading, tagging, weeding	100	0.275	0.0002	1.70×10^{-6}	1200000	0.00000024	7.27×10^{-10}	150000000	3896

TC = Transfer coefficient, DFR = Dislodgeable Foliar Residue, MOE = margin of exposure, ARI = Aggregate Risk Index

[a] Forage crop TCs were used a surrogate for vetch and clover TCs

[b] The TC values are from the ARTF. The TC value for maximum foliage density was considered as a worst-case scenario for the risk assessment.

[c] The DFR values are based on a broccoli study (Canada, 2004) following a 48-hour REI.

[d] Dermal exposure (mg/kg bw/day) = DFR ($\mu g/cm^2$) × TC (cm^2/hr) × work duration (8 hr) / body weight (80kg)

[e] Based on a short- and intermediate-term $BMDL_{10}$ of 1.96 mg/kg bw/day, and a target MOE of 300

[f] Based on a short- and intermediate-term $BMDL_{10}$ of 0.011 mg/kg bw/day, and a target MOE of 100. A dermal absorption value of 30% was used (Canada, 2017b)

[g] ARI = 1 / (Target MOE_{NAL} / MOE_{NAL}) + / (Target MOE_{DVP} / MOE_{DVP})

[h] Woodlands may include Christmas tree plantations and tree nurseries.

Table 5.2 Postapplication Outdoor Inhalation Worker Exposure and Risk Assessment

Chemical	Exposure (μg/4hr)[a]	Exposure (μg/hr)	Duration (hr/day)	Body weight (kg)	Exposure (mg/kg/day)[b]	Inhalation MOE[c,d]	Inhalation MOE for ARI[e] (↓BChE)	ARI (Naled and Dichlorvos)[f]
Naled	9.77	2.44	8	80	0.000244	266	1430	0.9
Dichlorvos	2.32	0.58	8	80	0.00058	190	190	

MOE= margin of exposure; ARI = Aggregate Risk Index

[a] Inhalation exposure to naled and dichlorvos as determined in Lamb et al, 1994

[b] Inhalation exposure (mg/kg/day) = [exposure (μg/hr) × duration (hr/day)]/body weight (kg)

[c] Naled is based on an all duration-term LOAEL of 0.065 mg/kg bw/day, and a target MOE of 100

[d] Dichlorvos is based on an all duration-term $BMDL_{10}$ of 0.011 mg/kg bw/day, and a target MOE of 100

[e] Based on a $BMDL_{10}$ of 0.35 mg/kg bw/day and a target MOE of 300 for naled and a $BMDL_{10}$ of 0.011 mg/kg bw/day and a target MOE of 100 for dichlorvos both based on a common endpoint of decreased BChE activity (Canada, 2017b)

[f] ARI = 1 / (Target MOE_{NAL} / MOE_{NAL}) + / (Target MOE_{DVP} / MOE_{DVP})

Table 5.3 Postapplication Dermal Exposure and Risk Assessment for Greenhouse Crops

Crop (Application Type)	Activity	Application Rate[a]	TC (cm^2/hr)[b]	Naled DFR_0 ($\mu g/ cm^2$)[c]	Dermal MOE[d,e] (Target = 1000)	REI required to meet target MOE
Roses and cut flowers (Fog)	Harvesting (hand), pruning, disbudding	0.121 g a.i./m^2	4000	5.60	1	303
	All other activities		230		15	180
Roses and cut flowers (Vapour Treatment)	Harvesting (hand), pruning, disbudding	0.01728 g a.i./m^2	4000	0.80	6	219
	All other activities		230		107	97
Cucumber, tomato, eggplant, pepper (Fog)	All activities	0.121 g a.i./m^2	1400	6.05	16	NA [f]
Eggplant, pepper (Vapour Treatment)	All activities	0.01728 g a.i./m^2	1400	0.86	2	NA [f]

TC = Transfer coefficient, DFR = Dislodgeable Foliar Residue, MOE = margin of exposure, NA = not applicable

[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 the ARTF

[c] DFR_0 is the expected DFR on the day of application. The DFR values are defaults

[d] Dermal exposure (mg/kg bw/day) = DFR ($\mu g/cm^2$) × TC (cm^2/hr) × work duration (8 hr) / body weight (80kg)

[e] Based on a long term $BMDL_{10}$ of 1.96 mg/kg bw/day, and a target MOE of 1000

[f] Given the data on hand it is not possible to extrapolate beyond the day of application

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

Appendix VI Occupational Risk Assessment Summary

Scenario	Mixer/Loader/Applicator	Postapplication
Groundboom	Risks are not acceptable for all scenarios (alfalfa, clover, vetch, peas, beans, lima beans, broccoli, Brussels sprouts, cabbage, cauliflower, lettuce, onion, potatoes, strawberries, tomatoes, sugarbeet, rangeland, field areas, and pastures)	Risks are acceptable following the 48 hour REI.
Aerial	Risks are not acceptable for all scenarios (potatoes, tomatoes, alfalfa, clover, vetch, peas, beans, lima beans, corrals, pastures, holding pens, rangeland, field areas and feed lots)	Risks are acceptable following the 48 hour REI.
Mistblower (airblast)	Risks are not acceptable for all outdoor areas (livestock pastures, feed lots, dairy pastures, woodland, ornamentals)	Risks are acceptable following the 48 hour REI.
Mistblower (tractor-drawn ULV)	Risks are not acceptable for all outdoor areas (livestock pastures, feed lots, dairy pastures, and woodland)	Risks are acceptable following the 48 hour REI.
Mistblower (Handheld) Indoor/Outdoor	No data to assess.	Risks are acceptable following the 48 hour REI outdoors. No data to assess inhalation exposure in indoor scenarios.
Handheld Sprayer (Outdoor)	Risks are not acceptable for all scenarios (strawberries, ornamentals, around dairy barns, pig pens)	Risks are acceptable following the 48 hour REI.
Handheld Sprayer (Indoor)	Risks are not acceptable for all scenarios (in and around dairy bans, livestock barns, pig pens, and poultry houses)	No data to assess inhalation exposure in indoor scenarios. Dermal risk is not acceptable for all greenhouse workers.
Fogger (Automated) Indoor	Risks are acceptable with use of automated stationary fogger.	
Fogger (Handheld) Indoor/Outdoor	No data to assess.	
Vapour treatment Greenhouse	Risks are not acceptable for all crops (cucumbers, tomatoes, eggplant, pepper, roses and cut flowers)	

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