Re-evaluation Decision RVD2020-08

Dichlorvos and Its associated end-use products

Final Decision

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Re-evaluation decision

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

Dichlorvos is a broad spectrum, non-systemic organophosphate insecticide used to manage various insect pests on greenhouse cucumbers, tomatoes and ornamentals, indoor and outdoor structural sites (for example, processing plants, storage facilities, theatres, animal buildings and various outdoor areas), and for mosquito control. Dichlorvos is applied indoors by hand sprayers, ultra-low volume applicators, and automatic foggers, and outdoors by ground equipment. It is also used in insecticide strips. Dichlorvos is registered for both commercial and domestic uses and currently registered products can be found in the Pesticide Label Search and in Appendix I.

The regulatory approach for the re-evaluation of dichlorvos was first presented in the Proposed Re-evaluation Decision PRVD2017-16, Dichlorvos,[1] which underwent a 90-day consultation period. The proposed decision is summarized below.

- Removal of use in mushroom houses as it was not supported by dichlorvos registrants for this re-evaluation.
- Cancellation of use:
    - Greenhouse tomato and cucumber, and greenhouse ornamentals (excluding greenhouse potted ornamentals)
    - Outdoor mosquito control
    - Outdoor residential living areas
    - Indoor pest strips (excluding areas that are unoccupied for a minimum of 4 months)
- Label Amendment:
    - Domestic class pest strip product is only allowed to be used in structures that are continuously unoccupied for at least 4 months (for example, cottages closed for the winter).
    - For use with automatic application equipment only and a 4-day restricted-entry interval with full ventilation for greenhouse potted ornamentals, tobacco storage, animal buildings, food processing plants, industrial plants, warehouses, and theaters.
    - Restriction on amount handled per day for tobacco storage, food processing plants, industrial plants, warehouses, and theaters (limited to 1.14 kg a.i./day).
    - Additional label statements to protect human health.
- Precautionary label statement to mitigate or reduce risks to bees, other insects, and aquatic habitats to protect the environment.

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

Health Canada received comments and information relating to the health and value assessments. Respondents are listed in Appendix II. These comments are summarized in Appendix III along with the responses by Health Canada. The comments and new data/information resulted in some revisions to the risk assessments (see Science Evaluation Update) which resulted in changes to the proposed regulatory decision as described in PRVD2017-16. A reference list of information used as the basis for the proposed re-evaluation decision is included in PRVD2017-16; further information used in the re-evaluation decision is listed in Appendix VI of this RVD.

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

Outcome of science evaluation

Following the consultation on the proposed re-evaluation decision, Health Canada revised the toxicology, occupational and residential risk assessments and/or risk mitigation based on the comments and information received. The revised assessment indicated that health risks from dichlorvos and its associated end-use products were not shown to be acceptable for certain uses of dichlorvos (such as spray and fogging application for certain crops/sites, and pest strip use in certain indoor areas) when used according to the label directions, or when additional mitigation measures are considered. As such, those uses are being cancelled.

Risk assessment for the commercial class pest strip product (for use in insect pheromone traps) did not required to be updated as risk was shown to be acceptable with mitigation measures in PRVD2017-16. For the remaining uses, value, health and environmental risks were shown to be acceptable, provided additional risk mitigation measures are implemented to protect human health. These include reclassifying some of the products from Commercial to Restricted class, and Domestic to Commercial class; restricting the sale and use of these indoor products to certified applicators only; and a provision of an information sheet to occupants of indoor treated sites. See the Risk Mitigation Measures for further details.

Regulatory decision for dichlorvos

Health Canada has completed the re-evaluation of dichlorvos. Under the authority of the *Pest Control Products Act*, Health Canada has determined that continued registration of some products containing dichlorvos is acceptable. An evaluation of available scientific information found that some uses of dichlorvos products meet current standards for protection of human health and the environment when used according to revised label directions. Therefore, label amendments to mitigate risks to the human health and environment, and label improvements to meet current standards are required for these uses.

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

However, spray and fogging application for certain crops/sites and pest strip use in certain indoor areas are cancelled since health risks are not shown to be acceptable when used according to the current conditions of registration, or when additional mitigation is considered. The risk mitigation measures are summarized below. No additional data are requested.

Risk mitigation measures

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

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

- Mushroom houses

Human health

To protect human health, the following risk-reduction measures are required for continued registration of dichlorvos in Canada.

Cancellation of use:

- Spray application to greenhouse crops (cucumbers, tomatoes and ornamentals), sheds, stables, barns, loafing sheds, pigpens, poultry houses, outdoor areas, and outdoor residential living areas
- Fogging application to dairies, piggeries and barns
- Fogging application for outdoor mosquito control
- Domestic class pest strip use in homes (including garages, attics, crawl spaces), animal and farm buildings, milk rooms, motels, restaurants, food processing plants, industrial and commercial locations, kennels, garbage storage areas and containers, and similar enclosed spaces, or any space that is occupied within 4 months of application

Label Amendment:

- For fogging application of the following indoor structures: tobacco storage, poultry houses, food processing plants, industrial plants, warehouses, theatres:
    - Change of classification from Commercial class to RESTRICTED class. The nature of the restriction is for sale to and use by certified applicators only.
    - For use with automated application equipment only.
    - Additional personal protective equipment (PPE) and full ventilation requirement.
    - A re-entry interval of 4 days.
- For the current domestic class pest strip product:
    - Change of classification from Domestic class to COMMERCIAL class.
    - For use only in cottages, cabins and trailers, unoccupied for at least 4 months following application. Not for use in occupied homes.

- For all indoor uses – Applicators are required to post and provide an information sheet to occupants of treated areas (to inform them of the product that was applied, the re-entry interval, symptoms of overexposure, and what to do if they experience these effects).
- For outdoor pest strip (in insect pheromone traps) – additional PPE and use limitations.
- Updated label statements are required to meet current label standards and to clarify use directions and mitigation measures.

Environment

The following precautionary label statement is required:

- A statement to inform the user that dichlorvos is toxic to aquatic organisms.

Next steps

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

- One (1) year of sale by registrant from the publication date of this decision document, followed by;
- One (1) year of sale by retailer from the last date of sale by registrant, followed by;
- One (1) year of permitted use from the last date of sale by retailer.

Other information

Any person may file a notice of objection[3] regarding this decision on dichlorvos within 60 days from the date of publication of this Re-evaluation Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides section of the Canada.ca website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service.

The relevant test data on which the decision is based (as referenced in PRVD2017-16 and this document) are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (hc.pmra.info-arla.sc@canada.ca).

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

Science evaluation update

1.0 Introduction

Dichlorvos is a broad spectrum, non-systemic organophosphate insecticide. Dichlorvos belongs to the Resistance Management Mode of Action group 1B, as classified by the Insecticide Resistance Action. It is used in agriculture, structures and outdoor areas to control various insect pests. The proposed re-evaluation decision was published in PRVD2017-16, Dichlorvos. Comments received regarding the health and value assessments and were considered, and the risk assessments were updated as appropriate.

2.0 Revised health risk assessment

2.1 Toxicology summary

The toxicology assessment for dichlorvos was previously conducted and summarized in PRVD2017-16. Comments were received from the registrant concerning various aspects of the assessment including the methods used in the conduct of the benchmark dose modelling, the selection of the oral toxicity study for the dermal risk assessment, the use of the 7-day oral toxicity study to establish the acceptable daily intake, and the application of chemical-specific adjustment factors for the risk assessment. In addition, a recently conducted 28-day dermal toxicity study performed with female Sprague-Dawley rats exposed to dichlorvos was submitted to Health Canada. Overall, the review of these comments and new data did not result in a change to the oral or inhalation reference values established for the human health risk assessment and outlined in the PRVD for dichlorvos. However, based on the results of the newly conducted 28-day dermal toxicity study, the dermal toxicology reference values for dichlorvos were updated. Detailed responses to comments and the updated toxicology reference values are presented in Appendix III. These updated toxicology reference values are considered protective of the health of all Canadians.

2.2 Dietary exposure and risk assessment

Dietary risks were shown to be acceptable in PRVD2017-16. No comments specific to the dietary risk assessment were received. There were no changes to the dietary risk assessment.

2.3 Occupational and non-occupational exposure and risk assessment

In PRVD2017-16, risks were not shown to be acceptable for a number of uses. Therefore, cancellation was proposed for use on greenhouse tomatoes, cucumbers and ornamentals (excluding potted ornamentals), outdoor mosquito control, outdoor residential living areas and indoor pest strips (excluding areas that are unoccupied for a minimum of 4 months following application). Additionally, for the majority of the remaining uses, risk mitigation measures were proposed including re-entry and restricted-entry intervals, restriction of maximum amount handled per day, increased personal protective equipment (PPE) as well as additional label requirements.

During the PRVD consultation period, additional information was received from the registrant and grower groups, which were relevant to several aspects of the risk assessment. Additionally, the dermal toxicology reference values for dichlorvos were updated (see Section 2.1). These data and information were considered and incorporated, as appropriate, into the revised assessment. Health Canada's responses to specific comments are in Appendix III. Details regarding the revised occupational risk assessment are presented in Appendix IV.

Spray application – greenhouse crops

Dichlorvos is currently registered for foliar spray application only to greenhouse tomatoes, cucumbers and ornamentals. In PRVD2017-16, risks to mixer/loaders, applicators and any other workers present in the greenhouse during spray application to greenhouse crops were shown to be acceptable, provided that the application is conducted with automated application equipment without the presence of workers. This mitigation measure was proposed to address potential inhalation risk. In addition, cancellation was proposed in PRVD2017-16 for all crops (except potted ornamentals) due to unfeasible restricted-entry intervals (REIs). In response to PRVD2017-16, a number of stakeholders provided comments related to use pattern information, as well as applicator exposure details for these greenhouse crops. In particular, stakeholder comments, both written as well as during subsequent PMRA-stakeholder meetings, indicated that workers must be present in the greenhouse during spray application in order to move the automated spray cart from one row to the next. Therefore, the mitigation measure to not have workers present during spray application in greenhouses is not possible. As a result, this use is being cancelled.

Spray application – animal buildings

Dichlorvos is currently registered as a spray for use in sheds, stables, loafing sheds, pig pens, outdoor areas and poultry houses. In PRVD2017-16, risks to mixer/loaders, applicators and any other workers present during application in these commercial indoor structures were shown to be acceptable provided that the application be done with automated equipment without the presence of workers. Health Canada did not receive any comments regarding this mitigation measure. However, information from stakeholder consultations indicated that for greenhouses, it is not possible to have spray application without workers present. As no information was submitted for other areas, the same practice was assumed for animal buildings. Therefore, spray application for these uses will be cancelled.

Fogging application – animal buildings, tobacco storage, food processing plants, industrial plants, warehouses, theatres

Dichlorvos is currently registered for fogging application in the following commercial indoor structures: animal buildings, tobacco storage, food processing plants, industrial plants, warehouses and theatres. In PRVD2017-16, risks from fogging application to these buildings were shown to be acceptable, with a re-entry interval of 4 days; that is, workers or other individuals must not enter the treated site during application and during the restricted-entry interval of 4 days after the application is complete. In addition, the building must be fully ventilated before entry. These risk mitigation measures were proposed to address potential inhalation risks.

Comments were received indicating that, while fogging can be carried out without requiring a worker to be present in the building for the entire application period, workers may need to re-enter periodically to move the fogging equipment and/or remove the equipment within 4 days after treatment. Therefore, an assessment was conducted to determine potential risks for workers re-entering periodically and possible risk mitigation measures.

Risks were shown to be acceptable for workers entering the building to check, move or remove fogging equipment when they are wearing maximum PPE and a self-contained breathing apparatus (SCBA) respirator while in the building. Workers must only be present in the building being treated for a maximum of 1 hour per 24-hour period.

A 4-day re-entry interval was proposed in PRVD2017-16 for fogging in indoor structures. No comments relating to the feasibility of the mitigation measures were received during the public consultation period. Therefore, entry for workers into tobacco storage, food processing plants, industrial plants, warehouses, or theatres treated with dichlorvos is permitted only after 4 days following application and full ventilation has occurred.

For animal buildings, no comments were received during the public consultation period. However, based on previous stakeholder consultation, the 4-day restricted-entry interval was determined to be feasible for poultry houses only. As such, entry for workers and all other individuals into poultry houses treated with dichlorvos is permitted only after 4 days following application and full ventilation has occurred. Dichlorvos fogging application in all other animal buildings will be cancelled.

The re-entry interval, requirements for early re-entry, as well as the ventilation requirements must be communicated to all workers and other individuals who could potentially enter the building during and after application.

Label statements indicating that it is the responsibility of the applicator to communicate these requirements to the person-in-charge of the building will be required. In addition, the use of SCBA equipment is usually available only to specialized applicators who are trained in its use. For these reasons, dichlorvos products with this use will be required to be reclassified to RESTRICTED class with the nature of restriction being that dichlorvos is for sale to, and use by, certified applicators only. An information sheet will also be required to be presented to customers and posted at points of entry by the certified applicator upon application of dichlorvos. The information sheet provides information on the re-entry interval, the PPE (including SCBA) that is required for early entry before the re-entry interval has passed, ventilation requirements, and symptoms of overexposure.

Domestic class pest strip product

The current label allows the pest strip product to be used in a residential or a commercial area only if it is occupied for less than 4 hours/day. In PRVD2017-16, postapplication risks were not shown to be acceptable for this use scenario due to potential inhalation risks, thus, it was proposed for cancellation. No comments relating to the exposure assessment were received during the public consultation period and no additional information/data was provided to refine the risk assessment. Therefore, this use is being cancelled.

The pest strip can also be used in cottages, cabins and trailers if the area is unoccupied for 4 months following placement of strips. Due to the level of concern for potential inhalation risks if misuse occurs and a greater potential for misuse of a domestic class product, this product is required to be reclassified as a COMMERCIAL class product. The commercial applicator is required to present an information sheet to all customers who request use of the pest-strip product to inform them that the product can only be used in areas that are unoccupied for 4 months or longer. In addition, the information sheet will provide information on symptoms of overexposure.

3.0 Revised environmental risk assessment

No comments relating to the environmental risk assessment were received during the public consultation period for PRVD2017-16. Based on the remaining acceptable uses of dichlorvos, exposure to the environment is expected to be minimal. The environmental assessment has determined that the use of dichlorvos, and its associated end-use products, poses an acceptable risk to the environment when used in accordance with the revised label directions. However, based on the inherent toxicity of dichlorvos to aquatic organisms, demonstrated in laboratory toxicity studies, a precautionary label statement to advise users that dichlorvos is toxic to aquatic organisms is required.

4.0 Value assessment

As a broad spectrum, non-systemic organophosphate insecticide, dichlorvos has value for its consistent and effective control of a range of economically important insect pests on greenhouse crops, and indoor and outdoor structural sites. During consultation, a number of stakeholders emphasized the contribution of dichlorvos to greenhouse-grown cucumbers, tomatoes and ornamentals. Following the re-evaluation of dichlorvos, cancellation of certain uses/products are required, as the potential risks to human health risks are not shown to be acceptable. An assessment of the registered products indicated that suitable alternatives are available for the uses/products are being cancelled.

5.0 Conclusion of science evaluation

Based on the comments and information received during the PRVD consultation, Health Canada revised the health assessment for dichlorvos. Some health risks are not shown to be acceptable for certain uses of dichlorvos even with mitigation measures, thus, those uses are being cancelled. Some uses are shown to have acceptable risks when additional mitigation measures are considered.

Risk mitigations include the cancellation of spray application to greenhouse crops (cucumbers, tomatoes and ornamentals), sheds, stables, barns, loafing sheds, pigpens, poultry houses, outdoor areas, and outdoor residential living areas; fogging application to dairies, piggeries and barns, outdoor mosquito control; and domestic class pest strip use in homes (including garages, attics, crawl spaces), animal and farm buildings, milk rooms, motels, restaurants, food processing plants, industrial and commercial locations, kennels, garbage storage areas and containers, and similar enclosed spaces, or any space that is occupied within 4 months of application.

Label Amendment:

- For fogging application of the following indoor structures: tobacco storage, poultry houses, food processing plants, industrial plants, warehouses, theatres:
    - Change of classification from Commercial class to RESTRICTED class. The nature of the restriction is for sale to and use by certified applicators only.
    - For use with automated application equipment only.
    - Additional PPE and full ventilation requirement.
    - A re-entry interval of 4 days.
- For the current domestic class pest strip product:
    - Change of classification from domestic class to COMMERCIAL class.
    - For use only in cottages, cabins and trailers, unoccupied for at least 4 months following application. Not for use in occupied homes.
- For all indoor uses – Applicators are required to post and provide an information sheet to occupants of treated areas (to inform them of the product that was applied, the re-entry interval, symptoms of overexposure, and what to do if they experience these effects).
- For outdoor pest strip (in insect pheromone traps) – additional PPE and use limitations.
- A precautionary statement on the label to inform the user that dichlorvos is toxic to aquatic organisms.
- Updated label statements are required to meet current label standards and to clarify use directions and mitigation measures.

List of abbreviations

AChE	acetyl cholinesterase
ADI	acceptable daily intake
AHETF	Agricultural Handlers Exposure Task Force
a.i.	active ingredient
ARfD	acute reference dose
ARTF	Agricultural Re-Entry Task Force
ATPD	area treated per day
BChE	brain cholinesterase
BMD	benchmark dose
BMDL	benchmark dose lower confidence limits
bw	bodyweight
CAF	composite assessment factor
ChE	cholinesterase
CR	chemical-resistant
CSAF	chemical-specific adjustment factor
DFR	dislodgeable foliar residue
GLP	good laboratory practices
IC_{50}	half maximal inhibitory concentration
i.p.	intraperitoneal
IR	inhalation rate
k_i	bimolecular rate constant
k_p	phosphorylation constant
kg	kilogram(s)
m^3	cubic meter
mg	milligram(s)
M/L	mixer/loader
MOE	margin of exposure
NOAEL	no observed adverse effect level
PCPA	*Pest Control Product Act*
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PoD	point of departure
PPE	personal protective equipment
PRVD	Proposed Re-evaluation Decision Document
REI(s)	Restricted-entry interval(s)
RVD	Re-evaluation Decision Document
SCBA	self-contained breathing apparatus
TC	transfer coefficient
TTR	turf transferable residue
ULV	ultra low-volume sprayer
WHO	World Health Organization
wk(s)	week(s)
ULV	ultra low volume
USEPA	Environmental Protection Agency

♂	males
♀	females
↑	increased
↓	decreased

Appendix I Registered dichlorvos products in Canada[1]

Registration number	Registrant	Product name	Formulation type	Guarantee (Dichlorvos)
Technical Active Ingredient				
19723	AMVAC Chemical Corporation	Dichlorvos (DDVP) Technical	Liquid	96%
Commercial Class End-Use Products				
11819	Gardex Chemicals Ltd.	Gardex Vapona Insecticide Industrial Fogging Solution	Emulsifiable concentrate or emulsion	4.65%
16476	Gardex Chemicals Ltd.	Gardex Vapona-20 ULV Concentrate	Emulsifiable concentrate or emulsion	20%
19680	Premier Tech Brighton Ltd.	Pro Professional DDVP-20 Ultra-Low Volume Insecticide	Solution	20%
21222	Aberdeen Road Company	Hercon Vaportape II Insecticidal Strips	Slow-release generator	10%
21824	Plus	Dichlorvos Plus #1 Ready to Use Insecticide	Solution	1.8%
23915[2]	Loveland Products Canada Inc.	DDVP 20% Insecticide	Emulsifiable concentrate or emulsion	20%
Domestic Class End-Use Product				
22027	Scotts Canada Ltd.	Ortho Home Defense Max No-Pest Insecticide Strip	Slow-release generator	19.2%

[1] as of 24 January 2020, excluding discontinued products or products with a submission for discontinuation

[2] Product to be cancelled based on updated health risk assessment

Appendix II List of respondents to PRVD2017-16

List of respondents' affiliations in terms of comments submitted in response to PRVD2017-16

Category	Respondent
registrant	AMVAC Chemical Corporation
grower group	Canadian Horticulture Council (CHC)
grower group	Ontario Greenhouse Vegetable Growers (OGVG)
grower group	Flowers Canada Growers Inc.
general public	private individual

Appendix III Comment(s) and response(s)

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

1.0 Comment(s) related to the health risk assessment

Health Canada received comments from the technical registrant, Canadian Horticultural Council, Flowers Canada Growers Inc., Ontario Greenhouse Vegetable Growers and a member of the public.

1.1 Comments related to toxicology

Registrant Comment - Chronic Point-of-Departure (PMRA# 2844667):

Health Canada proposed an acceptable daily intake (ADI) of 0.0001 mg/kg bw/day based on benchmark dose modeling (BMD) of brain cholinesterase inhibition from an oral (gavage) 7-day repeat-dose cholinesterase inhibition study in postnatal day (PND) 18 and adult rats.[4] Specifically, Health Canada calculated a $BMDL_{10}$ (lower limit of a 10% decline in brain cholinesterase) of 0.011 mg/kg bw/day and applied a standard 100-fold uncertainty factor. The registrant contends that this 7-day repeat-dose cholinesterase inhibition study had a small sample size (5 rats/sex/dose level) and was too short in duration to be used for setting a chronic endpoint, as the steady state for cholinesterase inhibition would only be expected to be established after 15 days. Therefore, BMD analyses were performed by the registrant on three additional repeat-dose oral toxicity studies that measured brain cholinesterase activity. These additional repeat-dose toxicity studies involving adult animals were:

- 13-week oral (gavage) toxicity study in rats (PMRA# 2541047–2541050)[5;]
- 28-day oral (gavage) immunotoxicity study in rats (PMRA# 2844666);
- 52-week oral (capsule) toxicity study in dogs (PMRA# 2930502).

In considering the most appropriate BMD_{10} and $BMDL_{10}$ for the risk assessment of dichlorvos, the registrant noted that the 7-day rat and 52-week dog studies have small sample sizes with only 4–5 animals/group. In addition, the registrant noted the short duration of the 7-day study and that steady state for cholinesterase inhibition is usually considered to be established at or after 15 days of daily doses for determining a chronic toxicity endpoint. It was also noted that the immunotoxicity study was the most recently conducted study, tested 10 female rats, included 28 days of repeated oral administration, and demonstrated the lowest variability among control animals. Since there were no sex-related differences noted throughout the database for dichlorvos, the use of only female animals was considered acceptable by the registrant.

[4] 2003. Dichlorvos: Repeat Dose Cholinesterase Inhibition Study in Pre-weaning and Young Adult Rats. DACO 4.8. (PRVD2017-16, PMRA# 2502260)

[5] 1993. A Subchronic (13 week) Neurotoxicity Study of Dichlorvos in Rats, Volume 1 to 4. DACO 4.5.13. (PRVD2017-16, PMRA# 2541047–2541050)

The registrant also indicated that Health Canada did not provide any information on the BMD analysis that was performed. Missing information was noted to include the software used, the guidance that was followed, and details on the models used for specific BMD fits. The United States Environmental Protection Agency (USEPA) BMDS software was used by the registrant to estimate BMD_{10}s and $BMDL_{10}$s for brain cholinesterase inhibition for all the available repeat oral dose studies and USEPA guidance on BMD modeling was followed to select the best-fitting model for each dataset. The registrant-calculated BMD_{10}s ranged from 0.37 mg/kg bw/day (PND 18 males in the 7-day rat study) to 2.4 mg/kg bw/day (females in the 13-week rat study). The corresponding $BMDL_{10}$s were 0.30 mg/kg bw/day and 1.6 mg/kg bw/day, respectively. These values are substantially higher than the $BMDL_{10}$ of 0.011 mg/kg bw/day estimated by Health Canada using the EFSA methodology. A BMD analysis of the study by the registrant using the USEPA BMDS software yielded a $BMDL_{10}$ of 0.69 mg/kg bw/day, which is more than twice the $BMDL_{10}$ from the 7-day study. Therefore, the registrant contends that the $BMDL_{10}$ of 0.30 mg/kg bw/day from the 7-day study and calculated using the USEPA BMDS software represented a very conservative basis for risk assessment.

Health Canada response

Health Canada used brain cholinesterase inhibition to establish the reference values for dichlorvos, as it was found to be the most sensitive indicator of toxicity throughout the database. These studies and BMD analyses are listed in Table 1. Health Canada concluded that significant variation in the cholinesterase data of different age groups in the 7-day oral cholinesterase inhibition study[6] precluded a meaningful determination of age-related sensitivity. As such, the brain cholinesterase inhibition data for both age groups (PND 18 and adult rats) were combined to calculate a $BMDL_{10}$ as it was considered appropriate to combine the data since there was no evidence of age-related sensitivity found for cholinesterase inhibition or any other endpoint. By combining these two age groups for the BMD analysis, the sample size for the 7-day comparative cholinesterase study increased to 10 rats/sex, the same number of animals tested in the immunotoxicity study used by the registrant. In examining the other available toxicity studies that measured cholinesterase activity, there were additional issues that precluded their use for the reference values for dichlorvos. In the 13-week oral toxicity study in rat, it was unclear how the registrant calculated a single $BMDL_{10}$ value for brain cholinesterase from the regional brain data provided; nonetheless, the registrant's $BMDL_{10}$ value of 1.6 mg/kg bw/day was higher than the $BMDL_{10}$ calculated by Health Canada for the acute neurotoxicity study that was used to establish the Acute Reference Dose, thus rendering it unusable for an ADI. Regarding the 52-week oral study in dog, only the cerebrum was sampled. Furthermore, it is Health Canada's practice to use the most sensitive (and relevant) species for risk assessment, which, in the case of dichlorvos, is the rat.

Although the registrant commented on the general time to steady state for cholinesterase inhibition, no data were provided to support dichlorvos-specific time to steady state. In addition, Health Canada notes that the establishment of an ADI is intended to address all repeat-dose dietary scenarios, which is not limited to chronic exposure. Therefore, results of the 7-day study are relevant for an ADI, as it represents the most sensitive study in the database for cholinesterase inhibition. Steady-state inhibition should be achieved with repeated dosing in

[6] 2003. Dichlorvos: Repeat Dose Cholinesterase Inhibition Study in Pre-weaning and Young Adult Rats. DACO 4.8. (PRVD2017-16, PMRA# 2502260)

principle; however, the influence of sampling time on the results cannot be completely dismissed. Neither the immunotoxicity nor the 13-week rat studies indicated the sampling time, while the 52-week dog study sampling time was 3 hours postdose. The time-to-peak inhibition was determined to be 1 hour for dichlorvos, which was the sampling time in the 7-day study.

In the conduct of the benchmark dose modelling, Health Canada chose the EFSA BMD guidance and Proast software over the USEPA BMDS guidance and software because it allowed for the analysis of individual animal data on the log scale. In addition, the EFSA BMD guidance and software allow one to avoid the use of hard parameter constraints and minimize the need for specification testing. Additionally, for dichotomous outcomes, it allows the use of model averaging. Although the EFSA methodology was critiqued and deemed conservative by the registrant, it should be noted that the issues regarding the use of constraints in the USEPA software (the main difference between the methodologies) have been acknowledged by the USEPA in their most recent BMDS user guide. Specifically, the guide indicates that the "EPA plans to continually improve and expand the BMDS system. Plans include…adding covariate analysis tools and Bayesian models and model averaging methods for continuous response data to further alleviate issues and uncertainties associated with data selection, bounding frequentist model parameters and assisting the user with selecting a 'best' model".

In summary, the registrant has not provided any supported rationale to indicate that 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 combined ages in the 7-day cholinesterase inhibition study will continue to be used for the human health risk assessment of dichlorvos.

Table 1 Summary of PMRA BMD analyses for brain cholinesterase inhibition in specific toxicity studies

Study	Age (sample size)	Dosing duration	Sex	Region of brain sampled	BMD_{10} ($BMDL_{10}$)
13-week oral toxicity study[7]	Adult rats (10/sex)	13 weeks	Combined	Olfactory Region	7.14 (1.02)
				Cerebellum	14.43 (4.68)
				Hippocampus	4.67 (0.362)
				Cerebral Cortex	3.21 (0.19)
				Brain Stem	5.61 (1.20)
				Midbrain	10.19 (3.00)
7-day oral cholinesterase study (PMRA# 2502260)	PND 18 rats (5/sex)	7 days	Males	Whole Brain[b]	0.018 (0.002)
			Females		0.014 (0.001)
	Adult rats (5/sex)		Males		0.246 (0.013)
			Females		0.534 (0.092)
	Combined ages[a] (10/sex)		Males		0.062 (0.011)
			Females		0.120 (0.028)
28-day immunotoxicity study (PMRA# 2844666)	Adult rats (10 ♀)	28 days	Females	Whole Brain	0.763 (0.486)
52-week oral toxicity study (PMRA# 2930502)	Adult dogs (4/sex)	52 weeks	Males	Cerebrum	0.490 (0.112)
			Females		0.848 (0.565)

[a] Data from both age groups were combined for BMD analysis by Health Canada due to significant variation in the cholinesterase data that precluded a meaningful determination of age-related sensitivity.

[7] 2003. Dichlorvos: Repeat Dose Cholinesterase Inhibition Study in Pre-weaning and Young Adult Rats. DACO 4.8. (PRVD2017-16, PMRA# 2502260)

[b] Slight differences in values were obtained between analyses performed in 2015 and 2018 due to minor updates to the Proast software; however, after rounding, these differences were not considered to be of any consequence. As a result, the values from 2015 were retained for risk assessment.

Registrant comment - Chemical-specific adjustment factors (CSAF) for dichlorvos

The registrant submitted information to support a reduction of the intra- and inter-species toxicodynamic uncertainty factors that were used in Health Canada's human health risk assessment of dichlorvos (PRVD2017-16). To justify the reduction of the toxicodynamic uncertainty factors, the registrant provided:

A. A study characterizing the inhibition kinetics of dichlorvos on human and rat erythrocyte acetylcholinesterase (AChE) (PMRA# 2875288);
B. A computational modelling study comparing the experimentally-determined 3D structure of human AChE to the predicted structure of rat AChE in complex with a variety of OP ligands (PMRA# 2875289);
C. A summary document calculating the CSAF for dichlorvos based on the outcomes of the inhibition kinetics and computational modelling studies (PMRA# 2844668).

Registrant comment - Inhibition kinetics of DDVP on human and rat erythrocyte acetylcholinesterase (PMRA# 2875288):

A report characterizing the inhibition kinetics of dichlorvos on acetylcholinesterase from erythrocytes of human and rat origin was submitted. Although brain acetylcholinesterase is the target of dichlorvos, the registrant stated that the acetylcholinesterase of erythrocytes was the same gene product as neural acetylcholinesterase; therefore, comparison of the kinetic parameters from human and rat erythrocytes would be useful in addressing the interspecies uncertainty factor applied in the health risk assessment. To accomplish this, erythrocyte "ghost" cell membranes were isolated from blood samples as the source of acetylcholinesterase. These samples were collected from 18 individual human samples (adults: 16–60 years, juveniles: 10–13 years and cord blood samples) and 6 pooled rat samples (of unknown strain and age). The inhibition kinetic constants for each of the blood samples for the dichlorvos inhibition of acetylthiocholine hydrolysis by rat and human acetylcholinesterase were determined and presented.

Health Canada response

Health Canada agrees with the registrant that the toxicodynamic component of the interspecies uncertainty factor could be lowered if no significant differences were observed between human and rat enzymes. However, sufficient information was not provided by the registrant to support their proposal. Key missing information and/or concerns are indicated below:

- No data were provided for the results of the positive control (paraoxon) inhibition of acetylcholinesterase-catalyzed acetylthiocholine hydrolysis, nor was a comparison provided of the positive control results to the known kinetic parameters of paraoxon, which is required to demonstrate proper experimental control.
- No information was provided to demonstrate the absence of tissue-specific differences between erythrocyte and neural AChE (such as comparison of gene expression levels, alternative splicing, post-translational modifications or oligomeric assembly).

- No information was provided to demonstrate the kinetic equivalence of acetylcholinesterase-catalyzed hydrolysis of acetylthiocholine relative to hydrolysis of acetylcholine.
- The registrant stated that the averages for the human bimolecular rate constants were not statistically significantly different by ANOVA across different age groups (adult, child and fetal), and sexes, but did not present details of the calculations.
- According to the registrant, there were no differences in kinetic constants across different ethnicities but no statistical analysis was provided to support this statement.
- Only three different ethnicities were represented by the human samples. Also, when disaggregating by age, ethnicity, or sex, the sample sizes for humans were: 4 female, 6 male, 8 sex not specified, 4 fetal, 6 child (1–16 years) and 8 adult. Information was not provided to demonstrate the sufficiency of three ethnicities and 4–8 samples in each age and sex category to characterize the diversity of the human population.
- Information relating to the quality and purity of the erythrocyte "ghost" cell membrane samples was not provided.
- An explanation of how the data resulting from pooled rat samples were analyzed relative to the data resulting from individual human samples was not provided.
- The substrate concentration at which preliminary range-finding studies for inhibitor concentration were carried out was not indicated.
- Acetylcholinesterase was incubated with dichlorvos prior to substrate addition and inhibition quantification, while in vivo, the enzyme encounters inhibitor and substrate simultaneously. The relevance of this pre-incubation with inhibitor was not discussed.
- It was unclear if the test substance, obtained from Sigma Chemical Co., was equivalent to the dichlorvos technical grade active ingredient manufactured by the registrant.
- Errors associated with each individual kinetic parameter were not reported.
- A high degree of variation was observed across the range of values obtained for all inhibition kinetic parameters, with coefficients of variation ranging from 17.9–64.5%. No explanation was given as to why experimental data with such a high degree of experimental variation would be considered valid.
- None of the parameters of human or rat acetylcholinesterase were significantly different at the significance level of $p<0.05$, which may be due to the high degree of variation in the dataset.
- The mean *ki* (bimolecular rate constant) values that were summarized and presented by the registrant did not match the actual means of the data that were presented in the table.
- From the limited data presented by the registrant, the range of *ki* values are similar but the range of k_p (phosphorylation constant) values were ~twofold lower for the human AChE enzyme than for the rat AChE enzyme. No explanation or discussion was provided by the registrant regarding the relevance of the lower k_p and K_I (dissociation constant) values observed for the human enzyme compared to the rat enzyme.

Given all of these concerns and uncertainties, the information provided by the registrant is insufficient to conclude that a high degree of similarity exists in the inhibition kinetics of dichlorvos between human and rat acetylcholinesterase enzymes.

B. Registrant comment - Computational modelling study comparing experimentally-determined 3D structure of human AChE to the predicted structure of rat AChE in complex (PMRA# 2875289):

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. 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.

Health Canada response

In examining the submitted computational modelling information, Health Canada noted the following uncertainties and concerns:

- Information on the identity, quality and quantity of protein sequences used to generate the alignments demonstrating percent identity between AChE rat and mouse enzymes were not provided, thus making 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.
- No experimentally-determined X-ray crystallographic 3D structure exists for rat AChE; the mouse 3D acetylcholinesterase structure was used with *in silico* mutagenesis to build the predicted rat 3D AChE structure, on the basis of 98.2% amino acid identity between mouse and rat AChE.
- Validation of the physiological relevance of docking studies used to simulate covalent enzyme modification were not provided.
- Any allosteric sites involved in the modulation of catalysis or inhibition were not compared between human and rat enzymes, which would be necessary to demonstrate structural similarity between the enzymes.
- Docking studies are typically used to model reversible binding interactions; the validity of using docking studies to simulate covalent enzyme modification is unknown.
- The similarity between the experimentally-determined human acetylcholinesterase structure and the predicted rat acetylcholinesterase structure generated through computational modelling was high. The similarity was also high between human and rat enzymes for predicted interactions with dichlorvos across various stages of inhibition. However, some differences were predicted to exist between rat and human acetylcholinesterase enzymes for dichlorvos bound in the transition state; the significance of these differences is uncertain given the resolution of the crystal structures used to create these models.

The computational modelling predictions support the likelihood of a high degree of similarity between human and rat acetylcholinesterase; however, this information should be considered supplemental since predictions cannot replace an experimentally-determined X-ray crystallographic structure of rat acetylcholinesterase. Therefore, Health Canada concluded that the information provided by the registrant for the computational modelling is insufficient to unequivocally demonstrate the structural similarity of human and rat AChE enzymes in complex with dichlorvos.

C. Registrant comment - Chemical-specific adjustment factors (CSAF) for dichlorvos based on the outcomes of the inhibition kinetics and computational modelling studies (PMRA# 2844668):

The registrant provided a document summarizing the results of the inhibition kinetics and computational modelling studies, and used these results to calculate a chemical-specific adjustment factor for the risk assessment of dichlorvos. In the World Health Organization (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 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 total uncertainty factor should be 19 rather than the value of 100 used by Health Canada.

Health Canada response

Health Canada contends that, based on the deficiencies and uncertainties noted with the registrant provided information indicated above, a CSAF for dichlorvos could not be supported. In addition to the limitations discussed under responses to registrant comments A and B, the following deficiencies and uncertainties were also noted:

- Sufficient data were not provided to demonstrate that the animal and human populations are appropriate and comparable according to the WHO guidance on estimating CSAFs.
- A statistical report comparing kinetic constants for rat and human enzymes was absent.
- The registrant stated that the inhibition kinetic parameters would be used to calculate the CSAF. However, an IC_{50} value was used instead. The use of IC_{50} values instead of kinetic constants to calculate a CSAF was insufficiently justified.
- No methodology or raw data relating to the determination of IC_{50} values were provided. Health Canada disagrees with the registrant's opinion that the IC_{50} may be a more reliable value for calculation of CSAFs. IC_{50} is a relative value that depends on concentrations of enzyme, substrate and inhibitor along with other experimental conditions, which were not indicated by the registrant.
- Since kinetic constants, such as k_i and K_I, are intrinsic thermodynamic properties for an enzyme with respect to a specific inhibitor, they are more appropriate for calculation of CSAFs.

Based on the concerns and uncertainties discussed above, Health Canada concluded that the registrant-provided data are insufficient to conclude similarity of acetylcholinesterase enzymes across the human population. In addition, given there was no demonstrated comparability of

AChE inhibition kinetics between human and rat populations, no discussion to demonstrate how the data resulting from pooled rat samples were analyzed relative to the data resulting from individual human samples, the absence of statistical comparison of kinetic constants for rat and human enzymes, and no demonstration of erythrocyte "ghost" membrane sample purity or quality in the in vitro studies, the data are insufficient to conclude similarity of human and rat acetylcholinesterase enzymes.

Overall, Health Canada concludes that the data provided by the registrant are insufficient to allow for any reduction in the toxicodynamic components of the intra- and interspecies uncertainty factors for dichlorvos below the default uncertainty factor.

Registrant comment - Refine the dermal point of departure (PoD) based on the results from a new 28-day dermal toxicity study (PMRA# 3003814):

The registrant suggested that the PoD used for the dermal risk assessment in the PRVD, which was derived from a 7-day oral toxicity study, be replaced with that from a newly submitted 28-day dermal toxicity study (PMRA# 3003818). The registrant stated that although there was no evidence of local toxicity in this study, there was statistically significant erythrocyte and brain cholinesterase inhibition at the highest dose tested (10 mg/kg bw/day). The registrant derived a $BMDL_{10}$ for brain cholinesterase inhibition of 0.67 mg/kg bw/day from the new study, and suggested that it be used as the PoD for dermal risk assessment. They noted that this value represents a direct measurement of repeated-dose dermal toxicity, and is considerably higher than the value used previously by Health Canada, 0.011 mg/kg bw/day from an oral toxicity study with a 30% dermal absorption factor.

Health Canada response

In 2017, Health Canada did not have a suitable repeat-dose dermal toxicity study available for establishing toxicology reference values for the short-, intermediate- and long-term dermal exposure scenarios, nor for the dermal component of the aggregate risk assessment for dichlorvos. An 8-day dermal cholinesterase inhibition study in the guinea pig was considered supplemental due to the lack of details on the application method and the histopathological examination performed. A 117-day dermal cholinesterase inhibition study in the rat was also considered insufficient as animals were dosed only once every 72 hours, and a 10-day dermal toxicity study in the monkey was outdated and did not establish a NOAEL. In the absence of a suitable dermal toxicity study, the 7-day oral cholinesterase inhibition study in neonatal and young adult rats was deemed appropriate for use in establishing the PoD for the dermal risk assessments. A $BMDL_{10}$ of 0.011 mg/kg bw/day was derived from this study for brain cholinesterase inhibition in combined PND 18 and 48 male rats. It was considered appropriate to combine the data from the two age groups as there was no evidence of age-related sensitivity found for cholinesterase inhibition or any other endpoint. Standard uncertainty factors of 10-fold for intraspecies variability and 10-fold for interspecies extrapolation were applied, resulting in a target margin of exposure (MOE) of 100. For residential scenarios the *Pest Control Products Act* factor (PCPA factor) was reduced to onefold as discussed in the *Pest Control Products Act* Hazard Characterization section of the PRVD. Since an oral study was used for the dermal risk assessment of dichlorvos, a dermal absorption factor of 30% was applied to the $BMDL_{10}$ value of 0.011 mg/kg bw/day.

In 2019, Health Canada received a 28-day dermal toxicity study conducted in female Sprague-Dawley rats. The treatment-related findings for this study are presented in Table 2. Based on decreased forelimb grip strength and urine volume noted at the mid-dose level, a NOAEL of 1.0 mg/kg bw/day was selected for systemic toxicity in this study. Decreased brain cholinesterase was observed at the highest dose level. In an effort to further refine the endpoints relating to brain cholinesterase activity, a benchmark dose analysis was performed resulting in a $BMDL_{10}$ of 1.2 mg/kg bw/day and a BMD_{10} of 4.8 mg/kg bw/day for brain cholinesterase inhibition in females.

With the review of the recently conducted 28-day dermal toxicity study, Health Canada has determined that the 7-day oral cholinesterase inhibition study is no longer the most appropriate study to establish the dermal toxicology reference values for the risk assessment of dichlorvos. The 28-day dermal toxicity study was performed by the relevant route of exposure and examined the most sensitive parameter (brain cholinesterase). Further, there was no evidence of increased toxicity with increased duration of dosing in the toxicology database, and with the use of a dermal study, a dermal absorption factor is not required. Therefore, 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 follows:

For short-, intermediate- and long-term dermal occupational and residential risk assessments, the $BMDL_{10}$ of 1.2 mg/kg bw/day derived for brain cholinesterase inhibition in female rats from the 28-day dermal toxicity study was considered appropriate. Standard uncertainty factors of 10-fold for intraspecies variability and 10-fold for interspecies extrapolation were applied, resulting in a target MOE of 100. For residential scenarios, the PCPA factor was reduced to onefold as discussed in the *Pest Control Products Act* Hazard Characterization section of the PRVD. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and unborn children of exposed women.

For aggregate assessments of all durations, the toxicology endpoint selected for aggregation was brain cholinesterase inhibition. For the dermal component of the aggregate risk assessment, the $BMDL_{10}$ of 1.2 mg/kg bw/day from the 28-day dermal toxicity study with a target MOE of 100 was selected. For the oral and inhalation routes, the PoD and target MOE remain the same as in the PRVD: the $BMDL_{10}$ of 0.011 mg/kg bw/day from the 7-day oral cholinesterase inhibition study with a target MOE of 100. The PCPA factor for all routes was reduced to onefold as discussed in the *Pest Control Products Act* Hazard Characterization section of the PRVD. These updated toxicology reference values are presented in Table 3.

Table 2 Summary of 28-day dermal toxicity study in female Sprague-Dawley rats exposed to dichlorvos

Study type/animal/PMRA#	Study results
28-Day Dermal Toxicity Study Sprague-Dawley rats (♀) PMRA# 3003818	NOAEL (systemic toxicity) = 1.0 mg/kg bw/day **$BMDL_{10}$ for BChE inhibition = 1.2 mg/kg bw/day** **≥3.0 mg/kg bw/day:** ↓ urine volume and forelimb grip strength **10 mg/kg bw/day:** ↑ incidence of eschar and slight to well-defined erythema, ↑ phosphorus, ↓ hind limb grip strength, ↑ thyroid/parathyroid weight, ↓ BChE activity.

Table 3 Toxicology reference values for use in the health risk assessment for dichlorvos

Exposure scenario	Study	Point of departure and endpoint	CAF[a] or target MOE
Acute Dietary (all populations)	Two Acute Oral ChE Inhibition Studies - neonate and young adult rats	$BMDL_{10}$ = 1.4 mg/kg bw (BChE inhibition)	100
ARfD = 0.014 mg/kg bw			
Chronic Dietary (all populations)	7-day Repeat-dose Oral ChE Inhibition Study - PND 18 and 48 rats	$BMDL_{10}$ = 0.011 mg/kg bw/day (BChE inhibition)	100
ADI = 0.0001 mg/kg bw/day			
Dermal Short-, Intermediate- and Long-term	28-day Dermal Toxicity Study - rats	$BMDL_{10}$ = 1.2 mg/kg bw/day (BChE inhibition)	100
Inhalation[b] Short-, Intermediate- and Long-term	7-day Repeat-dose Oral ChE Inhibition Study - PND 18 and 48 rats	$BMDL_{10}$ = 0.011 mg/kg bw/day (BChE inhibition)	100
Incidental Oral, Short-term	7-day Repeat-dose Oral ChE Inhibition Study - PND 18 and 48 rats	$BMDL_{10}$ = 0.011 mg/kg bw/day (BChE inhibition)	100
Aggregate Short-, Intermediate- and Long-term, Oral, Dermal and Inhalation[b]	Oral and Inhalation: 7-day Repeat-dose Oral ChE Inhibition Study - PND 18 and 48 rats Dermal: 28-day Dermal Toxicity Study - rats	Common endpoint: BChE inhibition Oral and Inhalation: $BMDL_{10}$ = 0.011 mg/kg bw/day Dermal: $BMDL_{10}$ = 1.2 mg/kg bw/day	100 100
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.		

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

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

1.2 Comments related to occupational and residential exposure

1.2.1 Comment relating to calculation of exposure and risk

Comment

The registrant provided a re-estimation of exposure and risk based on their suggested toxicology point of departure and margin of exposure (MOE).

Health Canada response

As noted in Section 1.1 (Comments Related to Toxicology), the toxicology reference values for the occupational and residential risk assessment were not revised, with the exception of the reference value for the dermal risk assessment. As a result, the dermal risk assessments have been updated accordingly (see Appendix IV). However, the overall risk outcomes did not change due to potential inhalation risks.

1.2.2 Comments relating to use information

Comment

Comments were received regarding the current use pattern of dichlorvos on greenhouse tomatoes and cucumbers, which is typically applied only for postharvest cleanup or to control high pest pressure. Typical postharvest application of dichlorvos in greenhouses by automated or robotic sprayer was described. While a 4-day REI is not feasible in regular cropping season, growers indicated this REI would be acceptable in the context of a fall postharvest cleanup or high pest pressure application, rather than cancelling greenhouse uses entirely.

Health Canada response

The comments submitted during the consultation period and further stakeholder consultation indicated that the use of automated or robotic sprayers required that at least two workers be present in the greenhouse to operate the sprayer. However, PRVD2017-16 indicated that use of dichlorvos in greenhouses could be permitted provided that “Individuals MUST not be present in the entire enclosed area during application.”

The information Health Canada received during the consultation period indicated that it is not possible to use spray equipment without the presence of workers, thereby rendering the proposed risk mitigation unfeasible. Therefore, all spray uses in greenhouses will be cancelled.

Comment

Comments were received stating that the exposure duration used for the risk assessment of dichlorvos use on greenhouse tomatoes and cucumbers should be less than long-term, the duration assumed in PRVD2017-16. It was indicated that growers do not typically use dichlorvos in regular cropping situations due to the long preharvest interval and REI, as well as due to potential effects to biocontrols and crop yields.

For these reasons, crops are treated with dichlorvos only at postharvest or in response to high pest pressure. Postharvest treatment is typically done once in the fall, even if there are multiple cropping cycles per year (such as for cucumbers).

Health Canada response

This information is useful in determining the most common use pattern of dichlorvos for risk assessment. However, the re-evaluation of dichlorvos is based on current label directions, which can be interpreted as regular applications during the crop season. Postharvest treatment is not a use on the label. Furthermore, for regular applications during the growing season, the exposure

duration would be long-term. However, as the toxicology reference values for dermal and inhalation exposures are identical for short- to long-term exposure to dichlorvos, and since exposure is estimated on a per day basis, the risk assessment outcome would be the same, regardless of whether short-term or long-term exposure is assumed. Based on the current risk assessment, greenhouse uses are to be cancelled as risk was not shown to be acceptable since application with spray equipment requires workers to be present during application.

Comment

Flowers Canada Growers Inc. suggested that some farmers could accept modified registered crops, fewer applications, longer intervals between applications, and/or lower application rates (where efficacious) for cut flowers if it would help preserve the use.

Health Canada response

While Health Canada has considered this information and revised the risk assessment for cut flowers, applicator risks were still not shown to be acceptable for spray foliar applications. Therefore, this use is being cancelled based on worker risks during spray application.

1.2.3 Comments relating to agricultural re-entry task force (ARTF), including transfer coefficients (TC) and dislodgeable foliar residues (DFR)

Comment

Flowers Canada Growers Inc. commented that the default TC used for hand harvesting cut flowers (Gcf, 4000 cm^2/hour) and default DFR data assumptions often contribute to regulatory decisions that identify occupational concerns for cut flowers.

Health Canada response

For the dichlorvos greenhouse assessment, the default DFR values were not required, since a chemical-specific study was available, (Manninen et al., 1996). This study was used to assess postapplication dermal exposures from activities involving greenhouse ornamentals, cucumbers and tomatoes.

As there was no chemical-specific exposure study available for dichlorvos, standard transfer coefficients were used for all postapplication tasks. For more information on estimating worker postapplication exposure, please refer to Health Canada's regulatory proposal PRO2014-02 *Updated Agricultural Transfer Coefficients for Assessing Occupational Postapplication Exposure to Pesticides*. For specific information regarding the cut flower TC, please refer to the response to the related comment below. Pesticide companies are encouraged to contact Health Canada for direction on the generation of data to support a pesticide registration.

However for dichlorvos, as discussed above, risks were not shown to be acceptable for workers during spray application of dichlorvos to greenhouses. Therefore, this use is being cancelled for all crops.

Comment

Flowers Canada Growers Inc. commented that Health Canada should consider financially assisting the study of the accuracy of the default TCs and DFR data presently used in risk assessments.

Health Canada response

In order to support the registration of a currently registered pesticide, companies intending to sell a pest control product in Canada are responsible for generating and submitting detailed information for evaluation by Health Canada. Companies must provide all the scientific studies necessary for Health Canada to determine whether the risk from the use of the product is acceptable to human health. Health Canada uses the best available data to conduct the re-evaluations of pesticides and makes regulatory decisions accordingly. Pesticide companies are encouraged to contact Health Canada regarding the generation data to support a pesticide registration.

Comment

Flowers Canada Growers Inc. expressed concern over the suitability of the use of the Brouwer et al., 1992 study for use in the establishment of the cut flower hand harvesting TC. Namely, the study was generated over 25 years ago, outside of Canada, using chemicals not currently registered in Canada, on crops not grown in Canada (cut roses), in what appears to be non-GLP accredited facilities. Additionally, the comment highlights production practice differences between cut roses and cut flower crops grown in Canada as well as a qualitative description of the extent of postapplication exposure resulting from these activities.

Health Canada response

Health Canada's TC for harvesting cut flowers (cluster Gcf) was based on data from three available studies (Brouwer et al., 1992; Schneider, et al., 2002; and ARF055). These three studies represent a number of cut flower crops, and active ingredients, thus capturing a range of variables. This is the best data currently available to determine postapplication exposure for cut flowers. As noted in the comment above, pesticide companies have the option of generating more specific or relevant data.

Comment

Flowers Canada Growers Inc. commented that regulatory decisions are made using ARTF proprietary data that provides no transparency to stakeholders who may wish to evaluate the scientific reliability of these decisions.

Health Canada response

As stated above, companies must submit detailed information and data for Health Canada to determine if risks are acceptable to allow for the registration of a pesticide. This includes an evaluation of the health and safety of workers who enter sites previously treated with a pesticide in order to conduct activities such as harvesting and pruning. To address this data requirement, the ARTF was formed. Rather than providing chemical-specific studies for all pesticides for all

crops for all activities, ARTF conducted and purchased studies to generate a database of generic agricultural re-entry transfer coefficients that would be applicable to all crop/activity scenarios. The technical registrant for dichlorvos is a member of the ARTF, and as such, has provided this data to Health Canada in order to conduct postapplication worker exposure and risk assessments for all agricultural dichlorvos uses. Health Canada's review of the studies and determination of the transfer coefficients are presented in Regulatory Proposal PRO2014-02 Updated Agricultural Transfer Coefficients for Assessing Occupational Postapplication Exposure to Pesticides. Confidential test data are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). Alternatively, stakeholders can consider contacting ARTF or the technical registrant to request this information. Health Canada encourages stakeholders to contact the ARTF or the technical registrant regarding the data, including the adequacy of the data, used to support a registration.

Comment

Flowers Canada Growers Inc. commented that all ARTF-generated data relating to ornamental crops was derived with the surrogate chemical, malathion, which is very rarely used in production. It is difficult for growers to accept that ARTF results would be replicated with alternate active ingredients.

Health Canada response

As noted in Regulatory Proposal PRO2014-14 Updated Agricultural Transfer Coefficients for Assessing Occupational Postapplication Exposure to Pesticides, as part of the data development process, ARTF conducted an analysis of the "genericness" of transfer coefficients, that is the applicability of studies conducted with one chemical for use in assessing exposures for a different chemical. The early work performed in establishing TCs demonstrated that postapplication exposure was primarily a function of the degree of body immersion in treated foliage and that it could be used as a generic tool for estimating exposures to workers based on a chemical-specific DFR dissipation curve. Regulatory experience in the use of TCs has demonstrated this to be valid for conventional pesticides whose physical and chemical properties fall within a similar range, and where dislodgeable foliar residues are neither very low nor very high. For most conventional pesticides, TCs can be used generically between different active ingredients; however, DFR and TTR data are chemical-specific. This process is considered a reasonable method for assessing exposure while saving time and resources associated with conducting passive dosimetry or biological monitoring exposure studies for all proposed pesticide registrations and registration reviews, including the multitude of scenarios and uses therein.

As noted above, Health Canada encourages stakeholders to contact the technical registrants regarding the data, including the adequacy of the data, used to support a registration.

Comment

Flowers Canada Growers Inc. provided details on the differences in production practices between commonly produced cut flower crops grown in Canada.

Health Canada response

This is useful information. Further information that could be provided in order to inform future risk assessments would be an analysis of how these activities relate to the activities used to derive the transfer coefficients that Health Canada currently uses for cut flowers (for example, potential impact on transfer coefficients as described in Regulatory Proposal PRO2014-02, *Updated Agricultural Transfer Coefficients for Assessing Occupational Postapplication Exposure to Pesticides*).

Based on the current risk assessment, greenhouse uses are to be cancelled as risk was not shown to be acceptable since application with spray equipment requires workers to be present during application.

1.2.4 Comments relating to greenhouse risk assessment

Comment

Canadian Horticulture Council 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 concentration. 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. However, greenhouse uses are to be cancelled due to applicator (both dermal and inhalation) risks identified during spray application.

Comment

Canadian Horticulture Council provided details regarding typical sizes and volumes of greenhouses were provided.

Health Canada response

The data provided in the comment were reflected in the risk assessment presented in PRVD2017-16.

1.2.5 Comment relating to PPE for postapplication workers

Comment

Flowers Canada Growers Inc. commented that Health Canada should consider that workers do utilize PPE after pesticide application when harvesting cut flowers.

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 (see below).

Before Health Canada can estimate risk to workers wearing gloves or other PPE, 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), a number of other available studies suggest that exposure may actually increase when gloves are worn (Brouwer, 2000; Boman et al., 2005; Garrigou et al., 2011; Graves et al., 1995; Keifer, 2000; Rawson et al., 2005).

Health Canada is currently participating in a working group that includes grower and industry representatives. The purpose of the working group is to a) investigate the potential use of PPE (specifically 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.

2.0 Comment(s) related to the environmental risk assessment

No comments were received on the environmental risk assessment.

3.0 Comment(s) related to the value assessment

3.1 Greenhouse vegetables

Comment

Comments from the Canadian Horticultural Council and Ontario Greenhouse Vegetable Growers were received in response to the proposed cancellation of dichlorvos on greenhouse vegetables. The value of the use of dichlorvos, particularly for end-of-cycle crop cleanup was detailed.

Health Canada response

The PMRA recognizes the value of dichlorvos to the production of greenhouse cucumbers and tomatoes. However, the health risk to workers is not shown to be acceptable, and therefore, this use is cancelled. There are a number of alternative active ingredients to control aphid and whitefly pests in greenhouse vegetables.

3.2 Greenhouse ornamentals

Comment

Comments from the Canadian Horticultural Council and Flowers Canada Growers Inc. were received in response to the proposed cancellation of dichlorvos on greenhouse ornamentals (excluding greenhouse potted ornamentals). The value of the use of dichlorvos to the greenhouse ornamental growers in Canada was detailed, including the control of Western Flower Thrips (*Frankliniella occidentalis*).

Health Canada response

While Health Canada recognizes the value of dichlorvos to the production of greenhouse ornamentals, the health risk to workers is not shown to be acceptable, and therefore, this use is cancelled. There are a number of alternative active ingredients to control aphid and whitefly pests in greenhouse ornamentals, including greenhouse potted ornamentals. It is also noted that dichlorvos is not currently registered for the control of thrips in greenhouse ornamentals.

Appendix IV Revised commercial mixer/loader/applicator risk assessment for fogging of commercial indoor structures

Site	Application equipment[a]	PPE[b]	Application rate (mg a.i./m^3)	ATPD[c] (m^3)	Dermal exposure[d] (mg/kg bw)	Dermal MOE[e]	Inhalation exposure[f] (mg/kg bw)	Inhalation MOE[g]	Combined MOE[h]
Tobacco Storage	Automated fogger/ULV	Baseline, respirator[i] + early re-entry PPE[j], if needed	66.0	21000	1.0×10^{-3}	1180	1.1×10^{-5}	1050	560
Food processing plants, industrial plants, warehouses, theatres		Max PPE, respirator[i] + early re-entry PPE[j], if needed	33.0	350000	3.7×10^{-3}	330	1.9×10^{-5}	590	210
Dairies, piggeries, poultry houses, barns	Automated fogger	Baseline, respirator[i] + early re-entry PPE, if needed	17.4	610	7.8×10^{-6}	154600	9.4×10^{-6}	1170	1160

ATPD = area treated per day, CR = chemical-resistant, MOE = margin of exposure, PPE = personal protective equipment, ULV = ultra low-volume sprayer

[a] Exposure scenario assumes closed M/L+ 1 hour early re-entry applicator exposure.

[b] Baseline PPE: Long pants, long-sleeved shirt, CR gloves, socks and shoes; Max PPE: CR coveralls over a long-sleeved shirt, long pants, CR gloves, socks and CR footwear; early re-entry PPE: Max PPE + self-contained breathing apparatus (SCBA).

[c] ATPD values are based on data call-in information received from registrants and stakeholders.

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

[e] Based on a short, intermediate, long-term $BMDL_{10}$ of 1.2 mg/kg bw/day from a 28-day dermal toxicity study in rats, and a target MOE of 100.

[f] Inhalation exposure includes total inhalation from mixing/loading + 1 hour early re-entry applicator exposure. Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure × ATPD × maximum application rate)/80 kg body weight. Inhalation exposure for early re-entry scenario was based on data from Manninen *et al*., 1996.

[g] Based on a short, intermediate, long-term $BMDL_{10}$ of 0.011 mg/kg bw/day from a 7-day repeat dose oral cholinesterase inhibition study in rats, and a target MOE of 100. Default mixing/loading inhalation unit exposure values may underestimate inhalation exposure to dichlorvos in some scenarios.

[h] Combined MOE = 1/(1/Dermal MOE)+(1/Inhalation MOE).

[i] 90% protection factor was used for the respirator.

[j] 99.9% protection factor was used for the SCBA respirator.

Appendix V Label amendments for products containing dichlorvos

The label amendments presented below do not include all label requirements for individual end-use products such as standard 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 label statements provided below.

The required label amendments are outlined below. Product specific label improvements and amendments will be communicated to registrants following publication of the RVD.

A. GENERAL AMENDMENTS

Cancellation of Product:

- Registration No. 23915 is cancelled

Cancellation of Use:

All label directions related to these uses must be removed from end-use product label.

- Domestic class pest strip use in homes (including garages, attics, crawl spaces), animal and farm buildings, milk rooms, motels, restaurants, food processing plants, industrial and commercial locations, kennels, garbage storage areas and containers, and similar enclosed spaces
- Greenhouse cucumbers, tomatoes and ornamentals
- Fogging to dairies, piggeries and barns
- Mushroom houses
- Outdoor mosquito control
- Outdoor residential living areas
- Spray application to sheds, stables, barns, loafing sheds, pigpens, outdoor areas and poultry houses

Reclassification/Restriction:

- Domestic class pest strip product to be reclassified to Commercial class
- Commercial class fogging products to be reclassified to Restricted class
- For use by pest control operators only
- Provision of an information sheet to occupants for indoor pest strip and fogging products
- Treatment can only be repeated if the pest problem persists or reoccurs and only 7 days following the first fogging application.

Label improvement

- Add the following to the principal display panel of the label, if it's currently missing:

GROUP	1B	INSECTICIDE

- Replace Guarantee with Active ingredient
- Use instructions will be updated to include only acceptable use sites and pests

- Remove any instructions and/or references from the labels for all uses being cancelled, and update the directions and use instructions for any uses with the mitigation requirements identified in this document.

B. LABEL SPECIFIC AMENDMENTS

1. Technical Grade Product and Commercial Class End-use Products

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

TOXICOLOGY INFORMATION

"Dichlorvos 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."

2. Technical Grade Product

Add a new section, **ENVIRONMENTAL PRECAUTIONS**:

- TOXIC to aquatic organisms.

3. Commercial Class Fogging and Spray End-use Products

The following uses are cancelled and must be removed from the labels:

- greenhouse cucumbers, tomatoes and ornamentals
- fogging to dairies, piggeries and barns
- mushroom houses
- outdoor mosquito control
- outdoor residential living areas
- spray application to sheds, stables, barns, loafing sheds, pigpens, outdoor areas and poultry houses

Reclassification

All Commercial class products with fogging use are to be re-classified as RESTRICTED class products. The nature of restriction of these products is the requirement of sale to and use by a certified applicator only.

For all products with fogging use, add to the **principal display panel**:

"This product is only to be sold to and used by individuals holding an appropriate pesticide applicator certificate or license recognized by the provincial/territorial pesticide regulatory agency where the pesticide application occurs. Consult local pesticide regulatory authorities about use permits that may be required.

IT IS THE RESPONSIBILITY OF THE CERTIFIED/LICENSED APPLICATOR TO INFORM THE PERSON IN CHARGE OF THE FACILITY OR ESTABLISHMENT, WHERE APPLICATION WILL TAKE PLACE, OF ALL REQUIREMENTS PERTAINING TO HEALTH AND SAFETY OF WORKERS AND OTHER INDIVIDUALS (for example, personal protective equipment, re-entry conditions, ventilation requirements).

THE CERTIFIED/LICENSED APPLICATOR MUST COMPLETE THE INFORMATION SHEET FOR OCCUPANTS AND POST IT AT POINTS OF ENTRY AND PROVIDE DIRECTLY TO THE OCCUPANT OR THE PERSON IN CHARGE OF THE FACILITY OR ESTABLISHMENT, WHERE APPLICATION WILL TAKE PLACE."

Add a boxed **NATURE OF RESTRICTIONS** section containing the following:

"**NOTICE TO USER**: This pest control product is to be used only in accordance with the directions on the label. It is an offence under the Pest Control Products Act to use this product in a way that is inconsistent with the directions on the label.

NATURE OF RESTRICTIONS
This product is only to be sold to and used by individuals holding an appropriate pesticide applicator certificate or license recognized by the provincial/territorial pesticide regulatory agency where the pesticide application occurs. Consult local pesticide regulatory authorities about use permits which may be required.

FOR USE IN AUTOMATED FOGGING SYSTEMS ONLY. DO NOT apply using handheld equipment.

DO NOT apply when people or animals are present.
DO NOT enter or allow workers or other individuals to enter during the restricted-entry interval of 4 days. Entry into treated areas MUST only occur after the restricted-entry interval of 4 days has passed and after full ventilation.

Full ventilation is defined as:
- 10 air exchanges are completed; or
- 2 hours of ventilation using fans or other mechanical ventilating systems; or
- 4 hours of ventilation using vents, windows or other passive ventilation.

Due to inhalation risk concerns, entry before 4 days is not permitted, including for non-hand labour tasks or short tasks such as opening a vent.

Under exceptional circumstances, only certified pesticide applicators may enter treated areas before the 4-day restricted-entry interval has passed for short-term tasks not involving hand

labour. The certified applicator must wear chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks and chemical-resistant footwear and either a NIOSH-approved full face supplied-air respirator (SAR) with organic-vapour-filter OR a NIOSH-approved self-contained breathing apparatus (SCBA) with a full facepiece. Time spent in the treated area cannot exceed 1 hour in a 24 hour period up until the end of the 4-day restricted-entry interval and following full ventilation.

It is the responsibility of the certified/licensed applicator to inform the person in charge of the facility or establishment, where application will take place, of all requirements pertaining to health and safety of workers and other individuals (for example, personal protective equipment, re-entry conditions, ventilation requirements).

The certified/licensed applicator must complete the information sheet for occupants and post it at points of entry and provide directly to the occupants or the persons in charge of the facility or establishment, where application will take place. The information sheet must be provided with this label."

The information sheet must contain the following information:

- name and registration number of the product applied
- date and time of application
- restricted-entry interval and re-entry precautions
- symptoms of overexposure and poisoning
- contact information for pest control company and registrant company

Under **PRECAUTIONS**, for all fogging product labels, add the following:

"Wear chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks, and chemical-resistant footwear during mixing, loading, clean-up and repair. In addition, a respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister for pesticides, MUST be worn."

Under a new or existing heading, **ENVIRONMENTAL PRECAUTIONS**, add:

- TOXIC to aquatic organisms.

Under **STORAGE**, add:

- Store this product away from food or feed.

Under "**DIRECTIONS FOR USE**", for all products with fogging use, add the following:

- **DO NOT** apply when people or animals are present.
- **DO NOT** apply using handheld equipment.
- For use with automatic fogging/ULV application equipment only.
- **DO NOT** contaminate food/feed. Cover or remove all food/feed. Cover all food/feed processing surfaces, equipment and utensils or thoroughly wash following treatment. "
- All ventilation to or from the room or building being treated must be shut off and covered. The area being treated must be as airtight as possible to prevent airflow exchange between treated and untreated areas.

4. **Commercial Class Pest Strip (for Insect Pheromone Traps) End-use Product**

Add:

- Wear chemical-resistant gloves when opening insect traps and for disposal of the pest strip.
- For outdoor use only.
- Not for use in residential areas. Residential areas are defined as any use site where bystanders including children could be present during or after application. This includes around homes, schools, public buildings or any other areas where the general public including children could be present.

Under a new or existing heading, **ENVIRONMENTAL PRECAUTIONS**, add:

- TOXIC to aquatic organisms.

Under **STORAGE**, add:

- Store this product away from food or feed.

Ensure the following disposal statement is updated to:

- Do not reuse empty packaging. Wrap and dispose of empty package and used strips in garbage.

5. **Domestic Class Pest Strip End-use Product**

The product is also to be re-classified from a Domestic class product to a COMMERCIAL class product, with addition of the following statement:

- For Use by Pest Control Operators only.
- The pest control operator must post and provide an information sheet to all occupants of buildings where the product is to be used. The following statement must be added to the label under

  NOTICE TO USER:
  Prior to product use, the pest control operator must complete the Information Sheet for Occupants and provide directly to the occupant and post it at points of entry. The information sheet must be provided with this label.

The information sheet must contain the following information:

- name and registration number of the product applied
- date and time of application
- restricted-entry interval and re-entry precautions
- symptoms of overexposure and poisoning
- contact information for pest control company and registrant company

Under **DIRECTIONS FOR USE**, add:

- The entire building, including all indoor sites adjacent to the area being treated must remain unoccupied for at least 4 months following application.

Under **USES**, add:

- "For use only in unoccupied structures that are continuously unoccupied for at least 4 months immediately following placement of the pest strip, such as cottages, cabins and trailers. Not for use in occupied homes."

Under **PRECAUTIONS**, add:

- **DO NOT** apply when people or animals are present.

Ensure the following is present:

- Do not reuse empty packaging. Wrap and dispose of empty package and used strips in garbage.

Appendix VI References considered following publication of PRVD2017-16

A. Information Considered in the Updated Toxicology Assessment

List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
2844666	2012, Dichlorvos (DDVP): 4 week oral (Gavage) Immunotoxicity Study in the Female Sprague-Dawley Rat, DACO: 4.8(B)
2844667	2018, Chronic Point-of-Departure for Dichlorvos, DACO: 4.5
2844668	2008, Chemical-Specific Adjustment Factors for DDVP, DACO: 4.5
2875288	2018, Inhibition Kinetics of DDVP on Human and Rat Erythrocyte Acetylcholinesterase, DACO: 4.5
2875289	2018, Interactions of Inhibitory Forms of Organophosphorus (OP) Pesticides, Metabolites, and Isomers with Rat and Human Acetylcholinesterase (AChE): Computational Molecular Modeling, DACO: 4.8.
2930502	1990, A 52-Week Chronic Toxicity Study on DDVP in Dogs, DACO: 4.4.5
3003814	2019, Comments on PMRA Risk Assessment on Naled, DACO: 12.7.4, Document M, Document N
3003818	2019, Dichlorvos (DDVP): Toxicity Study by Dermal Administration to Sprague Dawley Rats for 4 Weeks, DACO: 4.3.5

C. Information Considered in the Dietary Assessment

No additional studies or information relating to dietary assessment were submitted during the PRVD comment period.

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

Task Force Studies/Information

PMRA Document Number	Reference
2572745	2015, Agricultural Handler Exposure Scenario Monograph: Open Pour Mixing and Loading of Liquid Formulations, DACO: 5.3,5.4
2115788	2008, Data Submitted by the Agricultural Rentry Task Force (ARTF) to Support Revision of Agricultural Transfer Coefficients, DACO: 5.6

Additional Information Considered

Published Information

Reference
Boman, A.; Estlander, T.; Wahlburg J.E.; Maibach, H.I. 2005. Protective Gloves for Occupational Use Second edition. CRC Press LLC.
Brouwer, R.; Brouwer, D.H.; Tigssen, S.; van Hemmen, J.J. 1992. Pesticides in the Cultivation of Carnations in Greenhouses: Part II- Relationship Between Foliar Residues and Exposures. Am. Ind. Assoc. J. 53(9): 582-587.
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Garrigou, A.; Baldi, I.; Le Frious, P.; Anselm, R., Vallier M. 2011. Ergonomics contribution to chemical risks prevention: An ergotoxicological investigation of the effectiveness of coverall against plant pest risk in viticulture. 42: 321-330.
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Keifer, M.C., 2000. Effectiveness of Interventions in Reducing Pesticide Overexposure and Poisonings. American Journal of Preventive Medicine. 18 (4S); 80-89.
Rawson, B.V.; Cocker, J.; Evans, P.G.; Wheeler, J.P.; Akrill, P.M. 2005. Internal contamination of Gloves: routes and Consequences. Am. Occup. Hyg. 49 (6): 535-541.
Rech, C.; Bissell, S.; Margotich, S. 1989. Worker Exposure to Chlorothalonil Residues during the harvest of fresh market pole tomatoes. Report HS-1456. California Department of Food and Agriculture. June 19, 1989.
Schneider, F; Hernandez, B.; Benson, C. 2002. Pesticide Exposure of Workers in Greenhouses. Health and Safety Report HS-1835. California Environmental Protection Agency. Nov.19, 2002.
Pest Management Regulatory Agency, 2014. PRO2014-02. Updated Agricultural Transfer Coefficients for Assessing Occupational Postapplication Exposure to Pesticides.