UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: June 19, 2020

SUBJECT: Naled: Draft Human Health Risk Assessment for Registration Review

PC Code: 034401
Decision No.: 511665
Petition No.: NA
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D437731
Registration No.: Refer to Table 3.3
Regulatory Action: Registration Review
Case No.: 0092
CAS No.: 300-76-5
40 CFR: §180.215

FROM: Jessica Kidwell, Risk Assessor
Hannah Pope-Varsalona, PhD, Toxicologist
Thurston Morton, Dietary Exposure/Residue Chemist
Janet Camp, Dietary Exposure/Residue Chemist
Risk Assessment Branch 4 (RAB4) (7509P)

Matthew Crowley, Occupational/Residential Exposure Assessor
Chemistry and Exposure Branch (CEB)
Health Effects Division (HED, 7509P)

THROUGH: Shalu Shelat, Branch Chief
RAB4/HED (7509P)

and

Tom Moriarty, Risk Assessment Review Committee (RARC) Team 2
Danette Drew, RARC Co-chair

TO: Marianne Mannix, Team Lead
Lauren Bailey, Chemical Review Manager
Kelly Sherman, Branch Chief
Risk Management and Implementation Branch III (RMIB III)
Pesticide Re-Evaluation Division (7508P)

As part of Registration Review, PRD of the Office of Pesticide Programs (OPP) has requested that HED evaluate the hazard and exposure data and conduct dietary, occupational and residential exposure assessments, as needed, to estimate the risk to human health that will result from the currently registered uses of pesticides. This memorandum serves as HED's draft human health risk assessment of the dietary, occupational, and residential exposure; and aggregate risk from the registered uses of naled**.** The most recent quantitative human health risk assessment was the Reregistration Eligibility Decision (RED) for naled completed in 2006 upon completion of the Organophosphate (OP) Cumulative Risk Assessment along with a scoping document finalized in 2009 (King, M., 01/29/2009, D356244). The following risk assessment updates have been made:

- Since the RED, several toxicology studies were submitted, reviewed, and found to be acceptable by the agency. These include an immunotoxicity study, special acute dermal and inhalation toxicity studies with acetylcholinesterase (AChE) measurements, and triple pack dermal absorption data.
- Updated acute and steady state endpoints were established based on the new and existing data;
- An updated dietary exposure assessment was conducted using updated drinking water values along with updated USDA Pesticide Data Program (PDP) monitoring data and percent crop treated information;
- Exposure/risk assessments for non-occupational spray-drift, bystander exposure, and non-occupational exposure from wide area public pest control applications were completed reflecting recent updates to the naled risk assessment points of departure, HED's SOPs, and policy changes for body weight assumptions.
- An occupational exposure assessment for the registered uses was completed reflecting recent updates to the naled risk assessment points of departure, HED's SOPs, and policy changes for body weight assumptions.

In September 2020, EPA's Office of Pesticide Programs (OPP) plans to convene a Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) on activities using new approach methodologies (NAMs)[1] that have the potential to inform uncertainty factors for organophosphate (OP) compounds. This includes consideration of *in vitro* acetylcholinesterase data to develop data-derived extrapolation factors (DDEFs) and work by EPA's Office of Research and Development to develop a NAM for evaluating developmental neurotoxicity. As a result, the SAP recommendations may impact the human health risk assessment for naled. If so, the naled DRA will be updated accordingly.

A summary of the findings and an assessment of human risk resulting from the registered uses of naled are provided in this document.

[1] The term NAM has been adopted as a broadly descriptive reference to any non-animal technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment

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1.0 Executive Summary

The Health Effects Division (HED) has conducted a human health draft risk assessment (DRA) to evaluate all existing registrations of the active ingredient (ai) naled, an organophosphate (OP) pesticide. This assessment was conducted as part of Registration Review.

Use and Exposure Profile

Naled is used in wide area public pest control programs (e.g., mosquitocides) and to control other insects on agricultural crops, non-crop trees and ornamentals, in and around commercial settings (e.g., food handling establishments, loading docks), livestock feedlots/pastures/rangelands and in greenhouses. All products are restricted-use pesticides (RUP) precluding consumer use and there are no registrations for direct use in residential settings by professionals. The wide area mosquitocide application is intended to kill mosquitos in flight and not as a directed application to turf, therefore, the mosquitocide use is indirect and indicative of non-occupational bystander exposure. Naled degrades into dichlorvos (DDVP) within hours following application. DDVP, also an organophosphate, is itself separately registered as an active ingredient in other pesticide products. A separate risk assessment has been conducted for DDVP (Kidwell, J. *et al.*, 06/19/2020, D430516).

Naled products are formulated as liquid concentrates requiring dilution, applied broadcast via aerial or ground vehicles and handheld spray equipment. Greenhouse applications (i.e., roses and other ornamentals) are via vaporization on a hot plate. There are also special local need (SLN) registrations for use in/on bait traps strategically placed on trees or on wicks or blocks placed on trees or poles as traps to control insects. For most use patterns, product labels require engineering controls in the form of closed mixing/loading systems and applications in enclosed cab vehicles. Where engineering controls are not applicable, handlers are required to wear long pants, long-sleeved shirt, and personal protective equipment (PPE) including coveralls, chemical-resistant gloves, footwear, and headgear (for overhead exposure), and an organic vapor cartridge respirator. For applicable agricultural uses, the restricted entry interval (REI) is 48 hours, or, in the case of organophosphate pesticides specifically, 72 hours in arid conditions (i.e., less than 25 inches rainfall per year).

Humans may be exposed to naled in food and drinking water since naled may be applied directly to growing crops or from the public health use to control mosquitoes. Dietary exposure (food + drinking water) is anticipated and this document addresses dietary exposure for naled uses, in addition to a separate dietary assessment for potential DDVP exposure from naled uses. For occupational/non-occupational exposures, this preliminary risk assessment covers risks from uses of naled, which includes exposure to naled *per se* and exposure to DDVP resulting from degradation of naled; it does not cover exposure and risk as a result of uses of DDVP (which is covered in a separate DDVP risk assessment). Based on the use pattern for naled, dermal and inhalation exposures are anticipated for occupational handlers (mixer/loaders, applicators, etc.) and for workers who re-enter treated areas. As naled products are RUPs and there are no direct residential use site registrations, residential handler or direct post-application exposure assessments are not applicable. However, indirect non-occupational post-application dermal, inhalation, and/or incidental oral exposures are possible following wide area public pest control

uses and via spray drift from agricultural uses. Additionally, since naled and DDVP share a common mechanism of toxicity, when applicable, risks are presented in terms of their combined exposure from naled and DDVP from naled uses.

Hazard Characterization

The toxicology database for naled is complete. Several additional toxicity studies were conducted for refinement of the risk assessment. These include special acute route specific dermal and inhalation toxicity studies with acetylcholinesterase (AChE) measurements and a triple pack dermal absorption study to refine the dermal endpoint. Like other OPs, the initiating event in the adverse outcome pathway (AOP)/mode of action (MOA) for naled involves inhibition of the enzyme AChE via phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system. Inhibition of AChE is the most sensitive effect in all species, routes and life stages, and is being used in deriving points of departure (POD).

OPs exhibit a phenomenon known as steady-state AChEI which occurs after repeated dosing at the same dose level. The degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. At that point, the amount of AChEI at a given dose remains relatively consistent across durations. Naled has robust dose response data across multiple life stages, durations, and routes for both erythrocytes (RBC) and brain AChE inhibition (AChEI). Many of the studies on naled have been evaluated using benchmark dose (BMD) modeling techniques. In general, OPs reach steady-state within 2-3 weeks but this can vary among OPs; for naled, steady-state RBC AChEI is reached by seven days. The steady-state POD is protective of any exposure duration longer than 21 days for naled, including chronic exposure, since cholinesterase inhibition does not increase after reaching maximum inhibition.

Rat pups exhibited greater quantitative susceptibility to acute naled exposure for both RBC and brain AChEI compared to adults but were not uniquely susceptible to repeated exposure. Following repeat oral, dermal, and inhalation dose exposures, no differences were noted between compartment cholinesterase effects, life stages (including analysis of fetus and pregnant dam), or sexes in rat. As such, the adult rat is protective of all life stages following repeat exposure to naled. In addition, there is no clear evidence of increased susceptibility for non-AChE parameters in the developmental toxicity studies in rats and rabbits and the reproduction toxicity study in rats.

Acute PODs for naled were selected for dietary, dermal, and inhalation exposure scenarios based on BMD estimates of AChE inhibition in rats. Steady state PODs were selected for dietary, incidental oral, and inhalation exposure scenarios based on BMD estimates of AChE inhibition in rats, whereas the steady-state POD for dermal exposure scenarios was based on a No Observed Adverse Effect Level (NOAEL) in rats instead of a BMD. Steady-state risk estimates are presented for all repeat dose exposure scenarios because naled and DDVP toxicity exhibit a pattern consistent with steady-state AChE inhibition. For this reason, a steady-state point of departure (POD), instead of a chronic POD, was selected for repeated oral exposure to naled. The carcinogenic potential of naled is classified as “Group E: Evidence of Non-Carcinogenicity”. Quantification of cancer risk is not required.

The Food Quality Protection Act (FQPA) 10X Safety Factor (SF) has been retained for infants, children, youth, and women of childbearing age for all exposure scenarios due to uncertainty in the human dose-response relationship for neurodevelopmental effects (See Section 4.4). As a result, a total uncertainty factor of 1000X was applied for all exposure scenarios, except dietary exposures (acute and steady-state) for the adult population subgroup 50-99 years old where the FQPA SF of 10X does not apply and can be reduced to 1X (total uncertainty factor = 100X) and inhalation exposures where the interspecies uncertainty factor has been reduced to 3X, the intraspecies variation is 10X, and the FQPA SF is 10X (total uncertainty factor = 300X for acute and 300X for steady-state).

Dietary (Food and Water) Exposures and Risk

Highly refined acute and steady-state dietary (food and drinking water both from agricultural and mosquito control uses) exposure and risk assessments were conducted for naled using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 3.16. This software uses 2003-2008 food consumption data from the U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA). Field trial residues, processing studies, USDA PDP monitoring data, washing/rinsing/peeling studies, and percent crop treated were utilized in the acute and steady state assessments. The entire distribution of modeled water estimated drinking water concentrations were used in both the acute and steady state dietary exposure assessments.

Acute and steady state dietary (food and water) assessments for naled were run for food only from all registered uses and from mosquitocide uses alone, as well as for food and multiple water scenarios. These water scenarios included: citrus, peppers, cotton, and wide area mosquitocide use. Generally, HED is concerned when risk estimates exceed 100% of the population-adjusted dose (PAD). The acute risk estimates for naled (food and water) do not exceed HED's level of concern for all population subgroups. The acute risk estimate for the general U.S. population for food and water at the 99.9th level of exposure results in a maximum of 39% of the aPAD and the population subgroup with the highest acute dietary risk estimate for this scenario is all infants <1 year old, which uses 100% of the aPAD.

The steady state dietary risk estimates (food only) for naled do not exceed HED's level of concern for any population subgroups, including those comprised of infants and children. The steady state risk estimate (food and drinking water) for the general U.S. population results in a maximum of 200% of the ssPAD and the population subgroup with the highest steady-state dietary risk estimate for this scenario is All infants (<1 year old), which utilize 550% of the ssPAD at the 99.9th percentile of exposure. These risk estimates exceed HED's level of concern. A significant portion of the risk cup is occupied by drinking water.

The steady state dietary risk estimates for mosquitocide only uses (food and water) for naled do not exceed HED's level of concern for any population subgroups, including those comprised of infants and children.

In addition, DDVP is a residue of concern in both tolerances and risk assessment for the use of naled. Acute and steady state dietary exposure assessments were made for DDVP drinking water scenarios for naled agricultural uses. The DDVP acute and steady state drinking water scenarios do not exceed HED's level of concern at the 99.9th percentile of exposure. The worst-case acute drinking water only risk estimate was <1% of the aPAD for the infants (<1 years old) at the 99.9th percentile. While these acute and steady state DDVP drinking water only scenarios were not of concern, many DDVP dietary (food and water) scenarios do not pass at the 99.9th percentile. Since the DDVP dietary assessment used USDA Pesticide Data Program information and the source of the DDVP cannot be determined, the dietary exposures to DDVP from DDVP uses, naled uses, and trichlorfon will be addressed individually in the DDVP risk assessment. The results of the acute dietary exposure analysis for DDVP (from use of naled using naled percent crop treated) food and water does not exceed HED's level of concern (<100 % aPAD). However, the results of the steady state dietary exposure analysis for DDVP (from use of naled using naled percent crop treated) food and water does exceed HED's level of concern (>100 % ssPAD) for multiple population subgroups including children.

Residential Exposure and Risk

As naled products are both RUPs and not directly used in residential settings, neither residential handler/consumer applicator exposure nor residential post-application exposures are assessed. The wide area mosquitocide application is intended to kill mosquitos in flight and is not intended as a directed application to turf, therefore, the mosquitocide use is indirect and indicative of non-occupational bystander exposure.

Non-Occupational Spray Drift and Bystander Exposure

Spray Drift: Risks of concern (i.e., MOEs are < 1000) were identified for adults (dermal) and children (1<2 years old) (combined dermal + incidental oral) via spray drift following various agricultural applications (airblast, groundboom, and aerial equipment) at the field edge up to a buffer of 300 feet for naled, DDVP from naled, and combined naled and DDVP from naled. For both adults and children (1<2 years old), the distance downwind where risk estimates were not of concern varied widely depending on the application equipment, crop target, and spray type/nozzle configuration. Chemical-specific turf transferable residue (TTR) were used.

Bystander Exposure: Air monitoring data are available for naled and/or DDVP. None of the air concentrations resulted in acute inhalation risks of concern; however, inhalation exposure based on ambient air monitoring results in potential steady state risk estimates of concern for children 1 to <2 years old.

Wide Area Public Pest Control: Residential post-application dermal, inhalation, and/or incidental oral risk estimates of concern were identified following wide area public pest control applications.

Aggregate Exposure and Risk

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risk estimates from three major sources: food, drinking water and residential exposures. There are no non-dietary residential scenarios for naled that are applicable for aggregate risk assessment. Therefore, the aggregate assessment for naled is represented by the dietary assessment. Acute aggregate risk estimates are equivalent to the acute dietary risk estimates and are not of concern for all population subgroups. The only steady state dietary exposure scenario which had no dietary risks estimates of concern for all populations was the mosquito food and mosquito drinking water, therefore, steady state aggregate risks for this scenario were also not of concern. For the remaining steady state scenarios, the steady state dietary exposure analyses for naled included both food and drinking water scenarios which resulted, in most cases, in risk estimates of concern, therefore, steady state aggregate risk estimates were also of concern.

Occupational Exposure and Risk

Dermal and inhalation exposures are possible during occupational applications as well as to workers who re-enter treated areas. Many occupational handler scenarios such as those for large scale agricultural uses and wide area public pest control have risk estimates of concern (i.e., MOEs are < 1000), even with the use of engineering controls or maximum levels of PPE such as coveralls and half-face respirators. Handler scenarios without risk estimates of concern include small scale use patterns such as the bait trap uses and greenhouse hot plate vaporization treatments.

Naled is Toxicity Category I (severe irritation) for acute eye irritation and dermal irritation (corrosive). Under 40 CFR 156.208 (c)(2), active ingredients classified as Category I for dermal toxicity and eye irritation are assigned a 48-hour REI (and, for organophosphates, 72 hours in arid conditions). Except for activities related to harvesting cotton, post-application occupational dermal risk estimates are not of concern within the already-established REI of 2-3 days. Post-application occupational inhalation exposures based on air monitoring data also have risk estimates of concern.

Human Studies Review

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. Appendix C provides additional information on the review of human research used to complete the risk assessment. There is no regulatory barrier to continued reliance on these studies, and all applicable requirements of EPA's Rule for Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions

to Address Environmental Justice in Minority Populations and Low-Income Populations. [2]"

2.0 Risk Assessment Conclusions

Risks of concern were identified for a majority of steady state dietary assessments, non-occupational/ bystander/spray drift exposure scenarios, and occupational scenarios as presented below.

Dietary

- Dietary risks for naled are mainly driven by drinking water.

Non-Occupational/Bystander

- There are risk estimates of concern for many exposures scenarios resulting from contact with residues resulting from spray drift from agricultural uses. For example, for aerial applications, all risk estimates are of concern for contact with residues deposited at all downwind distances less than 300 feet from the application site for all crops and spray type/nozzle configurations. A few scenarios such as airblast applications to grapes and citrus do not have risk estimates of concern at relatively short distances from treated fields (e.g., 10 feet).

- Based on available air monitoring data representing indirect bystander exposure to ambient naled/DDVP air concentrations, acute inhalation risk estimates were not of concern, however steady-state risk estimates based on average exposures are potentially of concern.

- Dermal, inhalation, and/or incidental oral risk estimates of concern were identified following wide area public pest control applications.

Occupational

- Many handler exposure scenarios have risk estimates of concern even with the use of engineering controls or maximum levels of PPE such as coveralls and half-face respirators.

- Notably, current labels exempt aerial applications for wide area public pest control from the use of enclosed cockpits. Risk estimates for aerial applications are based on data of aerial applications in enclosed cockpits and are the only data available; data for open cockpit aerial applications would be needed to appropriately assess risk for such exposures. However, it is noted that aerial applications with enclosed cockpits for some use patterns have risk estimates of concern.

- With the exception of activities related to harvesting cotton, no occupational post-application dermal exposure scenarios have risk estimates of concern beyond the existing REI of 48 hours (or 72 hours, for organophosphate pesticides in arid conditions).

[2] https://www.epa.gov/laws-regulations/summary-executive-order-12898-federal-actions-address-environmental-justice

- Based on available air monitoring data at an application site during and up to 3 days after a naled application, post-application occupational inhalation risk estimates of concern were identified.

2.1 Data Deficiencies

Toxicology – None

Residue Chemistry – None

ORE – No data are required. Chemical-specific turf transferable residue (TTR) and dislodgeable foliar residue (DFR) data were used. For reference, the ORE assessment (Crowley, M., 06/18/2020, D437732) discusses what additional data could be used to reduce uncertainty in the risk assessment.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

Adequate residue analytical methods are available for the purposes of registration review. Two GC methods, Method I and A, are listed in the Pesticide Analytical Manual (PAM, Vol. II §180.215) for tolerance enforcement. Method I, a GC method using a thermionic detector (RM-3G), is applicable for the separate analysis of residues of naled and DDVP in/on crops and in animal commodities and milk. Method A, a microcoulometric GC method (RM-3C), is applicable for the combined residues of naled and DDVP in/on fruits and vegetables. The limits of detection are 0.01-0.02 ppm (milk and tissues) and 0.05 ppm, for Method I and Method A, respectively. Other GC methods (RM-3G-3 and the method of Boone) using thermionic detectors for separate determination of naled and DDVP are adequate for tolerance enforcement purposes. In addition, a GC method (RM 3G-4 revision of Method RM-3G-3) using nitrogen-phosphorous detection is adequate for enforcement of tolerances for residues in almonds, broccoli, oranges, and alfalfa. The limit of detection for both compounds is 0.01 ppm.

For residue data collection, adequate methods for analysis of naled and its metabolite DDVP either in combination or separately are available. Methods RM-3, RM-3A, and RM-3E are AChE inhibition methods, methods RM-3G and RM-3G-3 are GC methods using thermionic detection, and method RM-3C and the method of Boone are microcoulometric GC methods. Method RM-3 determines naled and DDVP in combination, method RM-3C determines naled and DDVP as DDVP, and methods RM-3A, RM-3E, RM-3G, and the method of Boone determine naled and DDVP separately.

2.2.2 Recommended and Established Tolerances

The tolerance expression for naled listed under 40 CFR §180.215(a)(1) should be updated to comply with HED's Interim Guidance on Tolerance Expressions (Knizner, S., 05/27/2009).

The tolerance expression should be revised to read: Tolerances are established for residues of the insecticide naled (1,2-dibromo-2,2-dichloroethyl dimethyl phosphate) and its metabolite 2,2-dichloroethenyl dimethyl phosphate (dichlorvos), including its metabolites and degradates, resulting from the application of the pesticide to growing crops or from direct application to livestock and poultry, in or on the following food commodities in the table below. Compliance with the tolerance levels specified below, is to be determined by measuring only the sum of naled and DDVP calculated as naled.

Table 2.2.2. Tolerance Summary for Naled (40 CFR §180.215)

Commodity/Correct Commodity Definition	Established Tolerance (ppm)	Recommended Tolerance (ppm)	Comments
Section (a)(1)			
Almond, hulls	0.5	0.5	
Almond	0.5	0.5	
Bean, dry, seed	0.5	0.5	
Bean, edible podded		0.5	Commodity definition correction
Bean, succulent shelled	--	0.5	Commodity definition correction
Bean, succulent	0.5	Remove	
Beet, sugar, roots	0.5	0.5	
Beet, sugar, leaves	--	0.5	Commodity definition correction.
Beet, sugar, tops	0.5	Remove	
Broccoli	1	1	
Brussels sprouts	1	1	
Cabbage	1	1	
Cauliflower	1	1	
Celery	3	3	
Collards	3	3	
Cotton, undelinted seed	0.5	0.5	
Cucumber	0.5	0.5	
Eggplant	0.5	0.5	
Grape	0.5	0.5	
Grapefruit	3	3	
Grass, forage, fodder and hay, group 17, forage	--	10	Commodity definition correction.
Grass, forage	10	Remove	
Hop, dried cones	0.5	0.5	
Kale	3	3	
Vegetable, foliage of legume, except soybean, subgroup 7A, forage	--	10	Commodity definition correction.
Legume, forage	10	Remove	
Lemon	3	3	
Melon subgroup 9A	--	0.5	Commodity definition correction.
Melon	0.5	Remove	
Orange	--	3	Commodity definition correction.
Orange, sweet	3	Remove	
Peach	0.5	0.5	
Pea, edible podded	--	0.5	Commodity definition correction.
Pea, succulent shelled	--	0.5	

Table 2.2.2. Tolerance Summary for Naled (40 CFR §180.215)			
Commodity/Correct Commodity Definition	**Established Tolerance (ppm)**	**Recommended Tolerance (ppm)**	**Comments**
Pea, succulent	0.5	Remove	
Pepper	0.5	0.5	
Pumpkin	0.5	0.5	
Safflower, seed	0.5	0.5	
Spinach	3	3	
Squash, summer	0.5	0.5	
Squash, winter	0.5	0.5	
Strawberry	1	1	
Swiss chard	3	3	
Tangerine	3	3	
Tomato	0.5	0.5	
Turnip greens	3	3	
Walnut	0.5	0.5	
Section (a)(2)			
All raw agricultural commodities, except those otherwise listed in this section, from use of the pesticide for area pest (mosquito and fly) control.	0.5	0.5	DDVP should be added to the tolerance expression, below.

The established 0.5-ppm tolerance from use of naled for wide area public pest control is adequate for naled and DDVP residues. The current tolerance listed under 40 CFR §180.215(a)(2) for wide area public pest control should be revised to include residues of DDVP as follows: A tolerance of 0.5 part per million is established for the pesticide naled and the metabolite DDVP (2,2-dichlorovinyl dimethyl phosphate), including other naled metabolites and degradates, expressed as naled equivalents, in or on all raw agricultural commodities, except those otherwise listed in this section, from use of the pesticide for area pest (mosquito and fly) control. Compliance with the tolerance levels specified below, is to be determined by measuring only naled and DDVP.

The established 10-ppm crop group tolerance for "legumes, forage" is outdated terminology, and the use on soybeans was cancelled, which is the third representative crop of the foliage of legume vegetables group. Therefore, this crop group tolerance should be revoked concomitant with the establishment of a tolerance for Crop subgroup 7A, foliage of legume vegetables (except soybeans) subgroup.

The terminology for the tolerance for orange, sweet should be revised to just orange. Further review of the orange field trial data, orange processing study, processing information for other commodities, and available reduction of residue studies (rinsing the citrus before processing), indicates that a tolerance for citrus oil is not needed (i.e., residues are not expected to exceed the 3 ppm RAC tolerance). The previous conclusion was based on the assumption that residue in oil would concentrate 13x which, given all the information available, seems very unlikely. Therefore, a tolerance does not need to be established for citrus oil.

2.2.3 International Harmonization

There are no Codex MRLs established or proposed for residues of naled. Therefore, there are no questions with respect to compatibility of U.S. tolerances with Codex MRLs. There are no known harmonization issues with Canada or Mexico tolerances/MRLs (see Appendix D).

2.3 Label Recommendations

2.3.1 Recommendations from Residue Reviews

None.

2.3.2 Recommendations from Residential Assessment

None.

2.3.3 Recommendations from Occupational Assessment

A summary of occupational risk estimates has been provided and shows that there are potential occupational handler risks of concern for registered uses of naled based on the use site and label-required PPE and REIs.

Notably, current naled product labels exempt aerial applications for wide area public pest control from the use of enclosed cockpits. Risk estimates for aerial applications are based on data for pilots in enclosed cockpits and are the only data available; some aerial application scenarios with enclosed cockpits had risk estimates of concern. Data for open cockpit aerial applications would be needed to accurately assess risk for such exposures.

Under 40 CFR 156.208 (c)(2), active ingredients classified as Category I for dermal toxicity and eye irritation are assigned a 48-hour REI (and, for organophosphates, 72 hours in arid conditions). The product label for EPA Reg. No. 5481-479 requires a 24-hour REI which is not consistent with 40 CFR guidance which would require a 48-hour REI for the hot plate vaporization use.

2.3.4 Recommendations from Non-Occupational Assessment

There are no label recommendations based on the non-occupational assessment (e.g., spray drift, wide area public pest control); however, HED notes that a summary of the risk estimates has been provided and shows that there are risk estimates of concern for registered uses of naled.

3.0 Introduction

3.1 Chemical Identity

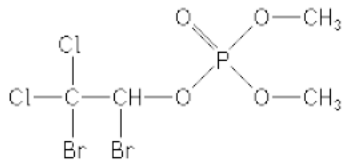
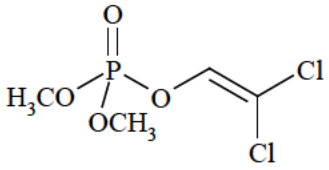
Table 3.1.1 Naled Nomenclature	
Chemical Structure	
Empirical Formula	$C_4H_7Br_2Cl_2O_4P$
Common name	Naled
IUPAC name	(RS)-1,2-dibromo-2,2-dichloroethyl dimethyl phosphate
CAS name	1,2-dibromo-2,2-dichloroethyl dimethyl phosphate
CAS registry number	300-76-5
End-use product/EP	Dibrom
Chemical class	Organophosphate, OP
Known impurities of concern	None

Table 3.1.2 DDVP Nomenclature	
Chemical Structure	
Empirical Formula	$C_4H_7Cl_2O_4P$
Common Name	Dichlorvos (ISO) or DDVP
IUPAC name	2,2-dichlorovinyl dimethyl phosphate
CAS Name	2,2-dichloroethenyl dimethyl phosphate
CAS Registry Number	62-73-7
End-use product/EP	Alco, Amvos
Chemical Class	Organophosphate, OP
Known Impurities of Concern	None

3.2 Physical/Chemical Characteristics

A detailed summary of the physical/chemical characteristics of naled and its metabolite, DDVP, is located in Appendix B.

Pure naled is a white solid with a melting point of 27ºC and is moderately volatile with a vapor pressure of 2 x 10^{-4} torr at 20°C. Naled is practically insoluble in water, has limited solubility in aliphatic solvents, and is highly soluble in oxygenated solvents such as ketones and alcohols. The octanol/water partition coefficent of naled (Log Kow of 1.4) suggests that accumulation in fatty tissues is unlikely to occur.

DDVP is a clear or slight yellow liquid at room temperature. It has a high solubility in water, aromatic hydrocarbons, chlorinated hydrocarbons, alcohols, ketones and esters, and essentially insoluble in kerosene and aliphatic hydrocarbons. DDVP has an octanol/water partition coefficient (Kow = 38.4; logKow = 1.58) which does not suggest that it will accumulate in fatty tissue. It has a high vapor pressure of 0.018 mmHg at 20 °C which suggests that residues in food and environmental surfaces will dissipate rapidly. Furthermore, it is not likely to persist long after forming in aerated soil or in the water column. DDVP is, however, more recalcitrant to metabolism in anaerobic environments.

3.3 Pesticide Use Pattern

All existing naled product registrations are liquid formulations and classified as restricted-use, requiring use only by or under the supervision of certified applicators. There are also SLN registrations covering some agricultural uses and bait trap uses. The bait traps use is an application of small amounts of product directly to tree limbs or poles or other inanimate objects in a localized area or to fiber blocks or wicks inside jars which are then placed in trees to attract and kill certain types of insects.

- Formulations: products are only liquid formulations requiring dilution.
- Use sites and targets:
    - Outdoor agricultural crops
        - Broadcast foliar applications (e.g., field crops, orchards/vineyards)
        - Dormant applications to peaches and almonds
    - Livestock feedlots/pastures/rangelands
    - Non-crop forest/shade trees, shrubs, and flowering plants
    - Greenhouse roses and ornamentals (hot plate/vaporization/gas application)
    - Indoor and outdoor commercial settings (e.g., food processing facilities, loading docks, refuse areas)
    - Wide area public pest control (e.g., over residential communities, woodlands, swamps), including ultra-low volume (ULV) applications
    - Bait traps (applied on trees or on wicks or blocks placed on trees or poles as traps)
- Applications are broadcast treatments.
    - Applications are generally made via aerial or ground vehicles and handheld sprayers.
    - The use in greenhouses uses a hot plate to vaporize the formulation for application as a gas.
    - As a bait (SLN registrations), applications are manual onto trees or on bait traps.
- Agricultural crop/commodity uses have retreatment intervals around 7-14 days, while other uses do not specify the retreatment or allow for more frequent treatments.
- Most uses require engineering controls in the form of closed mixing/loading systems and applications in enclosed vehicles. Where engineering controls are not applicable, handlers are required to wear long pants, long-sleeved shirt, coveralls, chemical-resistant gloves, footwear, and headgear (for overhead exposure), and a respirator (organic vapor cartridge).
- Flagging for aerial applications by workers is prohibited.
- For applicable agricultural uses, the REI is 48 hours, or for organophosphate pesticides

applied in arid conditions, 72 hours. The REI for the greenhouse hot plate vaporization treatment is 24 hours.

Table 3.3. Summary of Registered Use Directions for Naled

Application Type/Equip/etc.	Formulation [EPA Reg. No.]	Application Rate	PPE/Work Attire, REI, etc.
Greenhouse Roses/Ornamentals			
• Hot plate/pan vaporization	Liquid concentrate (RUP) EPA Reg. No. 5481-479 (Dibrom 8 Emulsive) 62% naled	0.06 lb ai/10,000 ft3	• Mixer/loader o Long-sleeve shirt, pants, shoes/socks o Coveralls o Chemical-resistant gloves/apron/footwear o Respirator • Automatic timer application, manual application prohibited • Re-entry ventilation requirements • 24 hour REI • Supplied air respirator or self-contained breathing apparatus (SCBA) for emergency entry • Handler PPE required for early re-entry
Agricultural Uses (alfalfa grown for seed, almonds, beans, broccoli, brussels sprouts, cabbage, cantaloupe, carrot grown for seed, cauliflower, celery, collards, cotton, eggplants, grapefruit, grapes, hops, kale, lemons, lima beans, melons, muskmelons, oranges, peaches, peas, peppers, safflower, strawberries, sugar beets, summer squash, swiss chard, tangerine, turnip tops, walnuts)			
• Aerial • Ground vehicles (boom, airblast, mist blower)	Liquid concentrate (RUP) EPA Reg. No. 5481-479 (Dibrom 8 Emulsive) 62% naled	0.9 – 2.1 lb ai/acre	• Engineering controls o Closed mixing/loading system o Enclosed cab vehicles • Non-engineering control o Long-sleeve shirt, pants, shoes/socks o Coveralls o Chemical-resistant gloves/apron/footwear/headgear o Respirator • Prohibitions o Human flagging o Chemigation o Backpack sprayers and handheld foggers • REI = 48 hours • For cotton: apply after boll opening up to 4 days before harvest (SLN CA-050011)
	SLN registrations: • CA-000006 • CO-990011 • OR-990032 • WA-990028 • CA-050011 • ID-010017 • TN-990007		
Indoor/Outdoor Commercial Settings (food processing plants, refuse areas, loading docks)			
• Handheld sprayers (e.g., manually pressurized handwand, mechanically pressurized handgun)	Liquid concentrate (RUP) EPA Reg. No. 5481-479 (Dibrom 8 Emulsive) 62% naled	0.04 lb ai/gallon solution	• Long-sleeve shirt, pants, shoes/socks • Coveralls • Chemical-resistant gloves/apron/footwear/headgear • Respirator
	Liquid concentrate (RUP) EPA Reg. No. 5481-482 (Fly Killer D)	0.024 lb ai/gallon solution	

Table 3.3. Summary of Registered Use Directions for Naled			
Application Type/Equip/etc.	**Formulation [EPA Reg. No.]**	**Application Rate**	**PPE/Work Attire, REI, etc.**
	36% naled		
Wide Area Public Pest Control (Residential Areas, Woodlands, Swamps)			
• Aerial • Ground vehicles	Liquid concentrate (RUP) EPA Reg. No. 5481-479 (Dibrom 8 Emulsive) 62% Naled Liquid concentrate (RUP) EPA Reg. No. 5481-480 (Dibrom Concentrate) 87.4% naled Liquid concentrate (RUP) EPA Reg. No. 5481-481 (Trumpet EC Insecticide) 78% naled	0.02 – 0.1 lb ai/acre	• Engineering controls o Closed mixing/loading system o Enclosed cab vehicles (except for aerial applicators) • Non-engineering control o Long-sleeve shirt, pants, shoes/socks o Coveralls o Chemical-resistant gloves/apron/footwear/headgear o Respirator
Forest/Shade Trees, Shrubs, Flowering Plants			
• Handheld sprayers (e.g., manually pressurized handwand, mechanically pressurized handgun) • Ground vehicles	Liquid concentrate (RUP) EPA Reg. No. 5481-479 (Dibrom 8 Emulsive) 62% naled	0.0094 lb ai/gallon solution 0.9 lb ai/acre	• Engineering controls o Closed mixing/loading system o Enclosed cab vehicles • Non-engineering control o Long-sleeve shirt, pants, shoes/socks o Coveralls o Chemical-resistant gloves/apron/footwear/headgear o Respirator • Prohibitions o Chemigation o Backpack sprayers and handheld foggers • REI = 48 hours
Livestock Pastures/Rangelands/Feedlots			
• Aerial and ground vehicles • Handheld sprayers	Liquid concentrate (RUP) EPA Reg. No. 5481-482 (Fly Killer D) 36% naled	0.06 – 0.1 lb ai/acre	• Engineering controls o Closed mixing/loading system o Enclosed cab vehicles • Non-engineering control o Long-sleeve shirt, pants, shoes/socks o Coveralls o Chemical-resistant gloves/apron/footwear/headgear o Respirator

Table 3.3. Summary of Registered Use Directions for Naled			
Application Type/Equip/etc.	**Formulation [EPA Reg. No.]**	**Application Rate**	**PPE/Work Attire, REI, etc.**
Bait Traps (Application to wicks, fiber blocks placed in trees/poles/etc. or applications directly to tree limbs/poles or other inanimate objects)			
• Handheld sprayer • Brush • Dropper/syringe	Liquid concentrate (RUP) SLN: HI-000005 (EPA Reg. No. 5481-480 (Dibrom Concentrate)	0.017 lb ai/bait trap 600 traps/square mile 10.1 lb ai/square mile	• Engineering controls o Closed mixing/loading system • Non-engineering control o Long-sleeve shirt, pants, shoes/socks o Coveralls o Chemical-resistant gloves/apron/footwear/headgear o Respirator
	Liquid concentrate (RUP) SLN: CA-090011 (EPA Reg. No. 5481-479 (Dibrom 8 Emulsive)	0.00325 lb ai/trap	• Engineering controls o Ventilated fume hoods, glove boxes, etc. • Non-engineering control o Long-sleeve shirt, pants, shoes/socks o Coveralls o Chemical-resistant gloves/apron/footwear/headgear o Respirator

3.4 Anticipated Exposure Pathways

Humans may be exposed to naled in food and drinking water since naled may be applied directly to growing crops or from the public pest control of mosquitoes and other insects. Applications may also result in naled reaching surface and ground water sources of drinking water. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. There is a potential for post-application exposure for workers re-entering treated areas. As naled products are RUPs and there are no direct residential use site registrations, residential handler or direct post-application exposure assessments are not applicable. However, indirect non-occupational post-application dermal, inhalation, and/or incidental oral exposures are possible following wide area public pest control uses and via spray drift.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group.

Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Spray drift can also potentially result in post-application exposure and it was considered in this analysis. Further considerations are also currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to other types of possible bystander exposures and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

Naled is a member of the organophosphate (OP) class of pesticides. Like other OPs, the molecular initiating event in the adverse outcome pathway (AOP)/mode of action (MOA) for naled involves inhibition of the enzyme acetylcholinesterase (AChE) via phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system (see Figure 1). For naled, AChE inhibition is the most sensitive known endpoint in the naled toxicology database in multiple species, durations, life stages, and routes. AChE inhibition is the focus of this hazard characterization; the availability of reliable AChE inhibition dose response data is one of the key determinants in evaluating the toxicology database. DDVP, another OP, is the major breakdown product of naled in animals and the environment and is considered more potent than naled. A separate risk assessment has been conducted for DDVP (Kidwell, J. *et al*, 06/19/2020, D430516) and the hazard characterization for DDVP can be found in that assessment. However, this assessment includes co-exposures to naled and DDVP for some scenarios, and therefore, the DDVP endpoint table is included in Section 4.6.4.

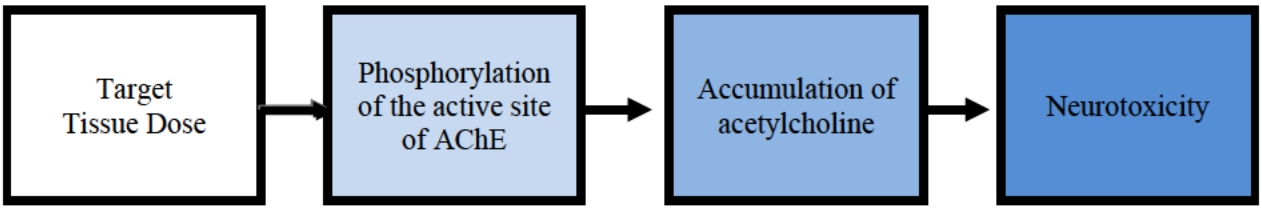


Figure 1. Adverse outcome pathway for OPs

4.1 Toxicology Studies Available for Analysis

The toxicology database for naled is complete for the purposes of this draft risk assessment. An immunotoxicity study was previously recommended to be required in the 2009 Human Health Assessment Scoping Document (King, M., 01/29/2009, D356244). This study has been submitted (MRID 48777301) and found to be acceptable/guideline by the agency. Special acute route specific studies with AChE measurements have also been submitted since the 2009 Human Health Assessment Scoping Document for dermal and inhalation routes (MRID 50795201, 50823901, respectively). In addition, rationale for calculating a refined dermal equivalent dose (RDD) using triple pack dermal absorption data (MRID 45099301 and 45099302) has been incorporated into the current assessment. The naled toxicology database includes the following toxicity studies:

- Subchronic oral in rat
- Acute dermal in rat (special AChE study)
- Subchronic dermal in rat (two studies)
- Acute inhalation in rat (special AChE study)
- Subchronic inhalation in rat
- Developmental in rat and rabbit
- Two-generation reproduction in rat
- Chronic oral in rat (two-year carcinogenicity), dog (one-year), and mouse (two-year carcinogenicity)
- Acute and subchronic neurotoxicity in rat
- Acute and subchronic delayed neurotoxicity in hen
- Developmental neurotoxicity (DNT) in rat and preliminary DNT in rats (includes AChE)
- Comparative cholinesterase assay in rat (CCA) (acute, repeat-dose, and time course)
- Immunotoxicity in rat
- Mutagenicity battery
- Metabolism (DDVP metabolism studies)
- *In vivo* (rat) and *in vitro* (rat and human) dermal penetration studies

More detail concerning the characterization and quantification of the toxic effects of naled is provided in Appendix A. Naled toxicity data requirements are found in Appendix A.1. A toxicity profile table can be found in Appendix A.2, followed by the "Summary of OPP's ChE Policy and Use of BMD Modeling" described in Appendix A.4. Additionally, tables of the BMD results are also provided in Appendix A.4.

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

Some OPs require metabolic activation to the oxon metabolite; however, for naled, the parent compound is responsible for AChE inhibition activity. Generally, absorption and distribution are rapid with extensive metabolism and no accumulation in the tissues for OPs. A naled metabolism study in rat requirement was waived since the database for naled is essentially complete and no cancer or developmental concerns are indicated (Khasawinah, A., 05/29/2001, TXR 0014575). Furthermore, the existing animal studies demonstrate that naled is rapidly absorbed, distributed and excreted. Additionally, and based on the quick metabolism to the more potent DDVP, relevant metabolism data are available for DDVP and are detailed below.

For DDVP, rat metabolism data indicate nearly 88-94% was absorbed through the gastrointestinal tract and, within 24 hours, nearly 43-57% was eliminated in expired air and excreta. After seven days, the total excreted/air expired recovery was approximately 60-77%; and, of the original dose, 11-17% was recovered in urine/cage washes, 4-7% in feces, and 41-58% as expired $^{14}CO_2$. The relative amounts of radioactivity retained in carcass, liver, and other tissues combined were 13-26%, 3-5%, and 1-2%, respectively. During the seven days post-dosing period, males expired slightly less $^{14}CO_2$ than females (41-45% vs. 52-54%, respectively). The excretion patterns were similar after i.v. or oral administration and little, if any, other differences relating to sex or dose were found in the excretion or distribution of [^{14}C] DDVP. Of the five radiolabeled compounds that were detected in urine, two were identified as hippuric acid

(HA) (4.2-10.5 %) and urea (19.6-51.1%). Urea and HA also seemed to be present in feces at lower concentrations than in urine. Three other urinary compounds were not identified but were assumed to be de-halogenated metabolites. Other metabolites, representing nearly 8 to 19% of total urinary radioactivity, were considered to be glucuronide conjugates (not identified). The overall metabolic profile suggests the involvement of the one-carbon pool biosynthetic pathway, as evidenced by the presence of a relatively large amount of radioactivity in the form of expired $^{14}CO_2$ and the presence of de-halogenated metabolites, urea, and HA.

4.2.1 Dermal Absorption

"Triple pack" dermal absorption studies are available for naled, which includes rat *in vivo* and rat and human *in vitro* studies (MRID 45099301, 45099302, respectively). In the rat *in vivo* study, dermal absorption at the lowest dose tested following 10 hours and 24 hours of exposure were estimated at 21 and 23% (calculated as the sum of excreta, intestinal tract contents, residual carcass, and that collected exhaled air traps). After normalization of recovery to 100%, absorption following 24 hours was estimated at 27%, respectively. In the *in vitro* studies, rat skin was found to be more permeable than human skin. At the lowest dose, the potentially absorbed dose after 24 hours was 70.06% and 27.44% (calculated as sum of receptor fluid and epidermis) for rat and human skin, respectively. After normalization of recovery to 100%, the potentially absorbed dose after 24 hours was 81.34% and 30.57% for rat and human skin, respectively. The resulting rat to human skin ratio is 2.66. Using the "triple pack" approach, if *in vitro* data obtained using animal skin is shown to be a good predictor of animal *in vivo* dermal absorption for a chemical, then the identical technique performed *in vitro* with human skin may be useful in extrapolating human dermal absorption. The PODs derived from both the single-dose dermal toxicity rat study and the two co-critical repeat dose dermal toxicity rat studies have been adjusted to account for greater rat skin permeability (2.7 to 3.6-fold) compared to human skin (calculations are provided in Section 4.6.1).

4.3 Toxicological Effects

Naled is a halogenated OP with a neurotoxic MOA/AOP. Inhibition of AChE is the most sensitive effect in all species, routes and life stages, and is being used in deriving points of departure (POD). Naled has robust dose response data across multiple life stages, durations, and routes for both erythrocytes (RBC) and brain AChEI. Many of the studies on naled have been evaluated using benchmark dose (BMD) modeling techniques. OPP does not have a defined benchmark response (BMR) for OPs, however, the 10% level represents a 10% reduction in AChE activity (i.e., inhibition) compared to background (i.e., controls). A comprehensive description on BMD modeling can be found in Appendix A.4.

Following acute oral exposures, RBC AChEI was slightly more sensitive than brain AChEI in the adult rat, and males were slightly more sensitive than females. The acute CCA showed that on average, a 10% inhibition of AChE occurred in pups at doses 4x lower than adults for brain and 2x lower than adults for RBC. However, following repeat oral, dermal, and inhalation dose exposures, no differences were noted between compartment cholinesterase effects, life stages (including analysis of fetus and pregnant dam), or sexes in rat.

Table 4.3.1 shows the available RBC AChEI rat data from repeat dose studies to inform patterns across multiple life stages and to better characterize life stage sensitivity. Rat fetuses were not more sensitive compared to either the adult rats or PND 18 rat pups. Furthermore, the PND 18 pups and adults (including pregnant females) were similar in the level of RBC and brain ChE inhibition. As such, the adult rat is protective of all life stages following repeat exposure to naled.

Table 4.3.1 Life stage Comparison of Naled Brain and RBC AChEI Results for Sensitive Subpopulations in Rats (All oral gavage administration)

MRID, Study	Life stage	Dose at effect (mg/kg/day)	Mean % AChE inhibition for different compartments and genders
46153101; Developmental Neurotoxicity (DNT) Range-Finding	Fetus (GD 22)	3 mg/kg/day (LDT)	9% brain males
			4% brain females
			11% RBC males
			12% RBC females
46153104; Repeat Dose CCA	PND 18	BMD_{10} = 1.5 mg/kg/day	10% brain males
		0.4 mg/kg/day (LDT)	3% brain females
		10 mg/kg/day^	46% RBC males
		0.4 mg/kg/day (LDT)	22% RBC females
46153101; Developmental Neurotoxicity (DNT) Range-Finding	Pregnant female	10 mg/kg/day^	37% brain females
		3 mg/kg day (LDT)	27% RBC females
	Post-partum female	3 mg/kg day (LDT)	16% brain females
		3 mg/kg day (LDT)	25% RBC females
46153104; Repeat Dose CCA	Adult	3 mg/kg/day (MDT)	12% brain males
		BMD_{10} = 2.2 mg/kg/day	10% RBC males
00141784 Carcinogenicity	Adult	BMD_{10} = 0.8 mg/kg/day	10% brain males
		BMD_{10} = 0.7 mg/kg/day	10% brain females
		0.2 mg/kg/day^	2% RBC males
		0.2 mg/kg/day^	4% RBC females

GD = Gestation Day
PND = Postnatal Day
MDT = Mid-dose tested
LDT = lowest dose tested
^Values represent doses at which AChEI was closest to 10%

Naled did not demonstrate frank indications of OP-induced delayed neuropathy (OPIDN) in the hen, but a degenerative neuronal effect (axonal degeneration in the spinal cord was increased and brain AChE activity decreased 50% at 42 mg/kg) was manifested in the spinal cord. All treated hens showed clinical signs of neurotoxicity (subdued, unsteady) but none demonstrated locomotor ataxia characteristic of delayed neurotoxicity. Neurotoxicity is supported throughout the toxicity database for naled and delineated moreover in the acute and subchronic neurotoxicity studies in rats via effects on functional observational battery (FOB), including convulsion, tremors, increased secretions, exophthalmos, respiratory changes, reduced muscle strength, and slowed response to stimuli. Motor activity was also reduced. These effects were identified at doses 24x those causing 10% AChEI following oral acute (single dose) exposure to naled in adult rats. Observed effects in the oral subchronic (90-day) neurotoxicity study included sporadic occurrences of tremors (forelimb, hindlimb and/or whole body) at doses 12.5x higher than those causing 10% AChEI in the adult rat following subchronic (repeat dose) exposure to naled.

There is no clear evidence of increased susceptibility for non-AChE parameters in the developmental toxicity studies in rats and rabbits and the reproduction toxicity study in rats. Maternal toxicity was noted in the developmental rat study (tremors, hypoactivity, discharge from mouth and eyes, dyspnea, and weight loss) at the high dose (50x greater than the dose eliciting AChEI via the oral route). Marginal effects on resorptions at this same dose were observed but not considered significant enough to confirm adversity. The developmental rabbit study did not identify any maternal or developmental toxicity. The two-generation reproductive toxicity study in rats observed decreased body weights in the maternal animals and reduced pup survival at the highest dose tested (22x greater than the dose eliciting 10% AChEI via the oral route of exposure for these populations) that was consistent with decreased pup weights during lactation. There is also no evidence of increased susceptibility for rat pups compared to adults following exposure to naled in repeat dose CCA studies. In the developmental neurotoxicity (DNT) study, decreased motor activity in offspring was observed in the absence of non-cholinesterase effects in maternal animals. However, a range-finding study was submitted with the DNT study that included AChE measurements and indicated that AChEI was significant for all life stages at the lowest dose tested (3 mg/kg/day; 4x higher than the 10% AChEI doses used in the studies selected for endpoints for these subpopulations), which was approximately the same as the dose eliciting offspring effects (2 mg/kg/day). AChEI was observed at all dose levels in the range-finding study with the greatest AChEI observed in maternal animals (maternal AChEI: brain 16%; RBC 25-27%; fetus AChEI: brain [only] 9%; pup AChEI: brain 10%, RBC 11%).

A 90-day inhalation toxicity study is available for naled. The chemical was intended to be released as an aerosol in full-body chambers but most of the exposure was in the vapor phase according to the investigator, due to the volatility of naled. The AChE data underwent BMD analyses and resulted in a BMD_{10} = 0.3 mg/m^3 based on RBC AChE inhibition in adult males and females. Clinical effects were observed such as salivation, nasal discharge, and abnormal respiration at the same concentrations as the BMD_{10}. The nasal passage, trachea, and lung histopathology did not reveal any treatment-related adverse effects. A three-week range finding study preceded the 90-day inhalation study and reported microscopic squamous metaplastic lesions in the nasal epithelium at all concentrations tested. The low concentration in the range-finding study was 13x higher than the BMD_{10} resulting from the 90-day inhalation study.

The acute oral, dermal (rabbit), inhalation (rat) toxicity of naled is Toxicity Category II. Naled is Toxicity Category I (severe irritation) for acute eye irritation and dermal irritation (corrosive). Naled was weakly positive for the skin sensitization study in guinea pig.

4.3.1 Critical Durations of Exposure

One of the key elements in risk assessment is the appropriate integration of the temporal relationship between the exposure and hazard. One advantage of an AOP understanding is that human health risk assessments can be refined and focused on the most relevant durations of exposure. For this risk assessment, HED used an analysis of the temporal pattern of AChE inhibition from acute, single dose and repeated dose studies in laboratory animals for naled. This analysis provides the basis for determining which exposure durations are appropriate for assessing human health risk. Table 4.3.1.1 provides a summary of the results from experimental

toxicology studies in which AChEI of both adult male and female rat RBC (brain not shown as there were no remarkable differences compared to RBC in adults) were selected to highlight the effect of duration and to identify a critical duration pattern.

Table 4.3.1.1 Temporal Comparison of Naled RBC AChEI Results in Adult Rats

Study (MRID)	Dosing Duration	RBC Dose* (mg/kg/day)		Route of Administration
		Male^	Female^	
Acute CCA (46153107)	1 day (single dose)	BMD_{10} = 8.3	BMD_{10} = 10.0	Oral (gavage)
Repeat Dose CCA (46153104)	7 days	BMD_{10} = NF 8% inhibition at LDT = 0.4	BMD_{10} = NF 3% inhibition at LDT = 0.4	Oral (gavage)
Oral Toxicity (46153108)	90 days	26% inhibition at MDT = 2	7% inhibition at LDT = 0.4	Oral (gavage)
Carcinogenicity (00141784)	25/26 weeks Or 2 years	BMD_{10} = NF 2% inhibition at LDT = 0.2	BMD_{10} = NF 3% inhibition at LDT = 0.2	Oral (gavage)

CCA = Comparative cholinesterase assay
LDT = lowest dose tested; MDT = mid-dose tested
N/A = not applicable
NF = no adequate fit (BMD modeling)
*Dose at 10% AChE inhibition or at lowest inhibition measured in study
^Values represent those closes to 10% AChEI

BMD results from both sexes in the rat were not always available due to BMD modeling issues noted in the table and discussed in more detail in Appendix A.3. In such cases, a dose was selected from the study that approximates 10% AChE inhibition, or as close as possible to 10% AChE inhibition, to provide the best possible comparison to the available BMD_{10} values.

OPs exhibit a phenomenon known as steady-state AChE inhibition. After repeated dosing at the same dose level, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. At that point, the amount of AChEI at a given dose remains relatively consistent across durations. In general, OPs reach steady-state within 2-3 weeks (by 21 days), although this can vary among OPs.

As demonstrated in Table 4.3.1.1, steady-state RBC AChEI is reached by seven days for naled. From the available data, brain AChEI data did not correspond to the same steady-state finding as that of RBC. However, since there was no compartment sensitivity identified, it will be assumed for purposes of risk assessment, that both compartments reach steady-state by seven days. Additionally, there are no clear differences in either male or female rat RBC or brain AChE levels following a single dose and repeated doses up to two years. Although there are data at a shorter time period than 21 days, exposure assessments of 21 days and longer will be conducted for all routes of exposure (i.e., oral, dermal and inhalation) for all single chemical OP assessments. Although the durations of the toxicity and exposure assessments may differ, an exact match is not necessary and would suggest a level of precision that the toxicity data do not support. Given this, the 21-day and longer exposure assessment is scientifically supportable and

also provides consistency with the OP cumulative risk assessment (OP CRA; 2002, 2006) and across the single chemical risk assessment for the OPs. The steady-state point of departure is protective of any repeated exposures for naled, including chronic exposure, since AChEI does not increase after reaching maximum inhibition or steady-state.

4.4 Literature Review

4.4.1 Literature Review for Naled Regarding Endpoint Sensitivity

As part of registration review for naled, a broad survey of the literature was conducted to identify studies that report toxicity following exposure to naled via exposure routes relevant to human health pesticide risk assessment not accounted for in the agency's naled toxicology database. The search strategy employed terms restricted to the name of the chemical plus any common synonyms, and common mammalian models to capture as broad a list of publications as possible for the chemical of interest. The search strategy returned 39 studies from the literature. During the title/abstract and/or full text screening of these studies, none of the studies were deemed to contain potentially relevant information (either quantitative or qualitative) for the naled human health risk assessment. Appendix A.5 has detailed information regarding the literature review.

4.4.2 Literature Review for OPs Regarding Neurodevelopment Effects

For the OPs, historically, and presently the agency uses AChE inhibition activity as the POD for human health risk assessment. This science policy is based on decades of scientific research which shows that AChE activity inhibition is the initial event in the pathway to acute cholinergic neurotoxicity from OPs. The use of AChE activity inhibition data for deriving PODs was supported by the FIFRA SAP (2008, 2012) for chlorpyrifos as the most robust source of dose-response data for extrapolating risk and is the source of data for PODs for naled. A detailed review of the epidemiological studies used in this review can be found either in the 2014 chlorpyrifos revised draft human health risk assessment (Drew, D. *et al*., 12/29/2014, D424485) or in the 2015 literature review for other organophosphates (Lowit, A., 09/15/2015, D331251).

Newer lines of research on OPs in the areas of potential AOPs, *in vivo* animal studies, and notably epidemiological studies in mothers and children, have raised some uncertainty about the agency's risk assessment approach with regard to the potential for neurodevelopmental effects in fetuses and children. Many of these studies have been the subject of review by the agency over the last several years as part of efforts to develop a risk assessment for chlorpyrifos (Drew, D., *et al*., 12/29/2014, D424485). Initially, the agency focused on studies from three US cohorts: 1) the Mothers and Newborn Study of North Manhattan and South Bronx, studied by the Columbia Children's Center for Environmental Health (CCCEH) at Columbia University; 2) the Mt. Sinai Inner-City Toxicants, Child Growth and Development Study, or the "Mt. Sinai Child Growth and Development Study;" and 3) the Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS), conducted by researchers at University of California Berkeley. The agency has evaluated these studies and sought external peer review (FIFRA SAP reviews in 2008 and 2012; federal panel, 2013[3]) and concluded they are of high quality. In the three US

[3] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0170

epidemiology cohorts, mother-infant pairs were recruited for the purpose of studying the potential health effects of environmental exposures during pregnancy on subsequent child development. Each of these cohorts evaluated the association between prenatal chlorpyrifos and/or OP exposure with adverse neurodevelopmental outcomes in children through age seven years. For the 2014 chlorpyrifos revised human health risk assessment (Drew, D., *et al.*, 12/29/2014, D424485), EPA included epidemiologic research results from these three US prospective birth cohort studies but primarily focused on the results of CCCEH since this cohort has published studies on the association between cord blood levels of chlorpyrifos and neurodevelopmental outcomes. The agency retained the FQPA 10x Safety Factor (SF) in the 2014 chlorpyrifos revised risk assessment, in large part, based on the findings of these studies.

In the 2015 updated literature review (Lowit, A., 09/15/2015, D331251), the agency conducted a systematic review expanding the scope of the 2012/2014 review focused on US cohort studies with particular emphasis on chlorpyrifos. The expanded 2015 review includes consideration of the epidemiological data on any OP pesticide, study designs beyond prospective cohort studies, and non-U.S. based studies. The updated literature review identified seven studies which were relevant (Bouchard *et al.*, 2010; Fortenberry *et al.*, 2014; Furlong *et al.*, 2014; Guodong *et al.*, 2012; Oulhote and Bouchard, 2013; Zhang *et al.*, 2014; Shelton *et al.*, 2014). These seven studies have been evaluated in context with studies from the 2012/2014 review (Drew, D., *et al.*, 12/29/2014, D424485). A brief summary of the update review is provided below.

Many of the studies assessed by the updated review used concentrations of urinary dialkyl phosphate metabolites (DAPs) as the urinary biomarker of OP exposure. Total DAPs is a non-specific measure of OP exposure and is the sum of six separate molecules: three dimethyl alkylphosphate (DMAP) molecules of DMP, DMTP, DMDTP, and three diethyl alkylphosphate (DEAP) molecules of DEP, DETP, and DEDTP. Each metabolite is a breakdown product from multiple OPs (Table 4.4.1; CDC, 2008)[4], therefore DAP is a non-specific measure of overall OP exposure. Specifically, DMP, DMTP, and DMDTP are associated with 18, 13, and 5 OPs, whereas DEP, DETP, and DEDTP are associated with 10, 10, and 4 OPs, respectively. Thus, using urinary DAPs alone as an exposure measure, it is not possible to separate the exposure and associated effects for single, specific OPs.

Table 4.4.2. CDC Table of organophosphate pesticides and their dialkyl phosphate metabolites (CDC 2008[2]).

Pesticide	DMP	DMTP	DMDTP	DEP	DETP	DEDTP
Azinphos methyl	X	X	X			
Chlorethoxyphos				X	X	
Chlorpyrifos				X	X	
Chlorpyrifos methyl	X	X				
Coumaphos				X	X	
Dichlorvos (DDVP)	X					
Diazinon				X	X	
Dicrotophos	X					
Dimethoate	X	X	X			

[4] http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/l26opd_c_met_organophosphorus_pesticides.pdf

Table 4.4.2. CDC Table of organophosphate pesticides and their dialkyl phosphate metabolites (CDC 2008[2]).

Pesticide	DMP	DMTP	DMDTP	DEP	DETP	DEDTP
Disulfoton				X	X	X
Ethion				X	X	X
Fenitrothion	X	X				
Fenthion	X	X				
Isazaphos-methyl	X	X				
Malathion	X	X	X			
Methidathion	X	X	X			
Methyl parathion	X	X				
Naled	X					
Oxydemeton-methyl	X	X				
Parathion				X	X	
Phorate				X	X	X
Phosmet	X	X	X			
Pirimiphos-methyl	X	X				
Sulfotepp				X	X	
Temephos	X	X				
Terbufos				X	X	X
Tetrachlorvinphos	X					
Trichlorfon	**X**					

DMP = dimethylphosphate; DEP = diethylphosphate; DMTP = dimethylthiophosphate; DMDTP = dimethyldithiophosphate; DETP = diethylthiophosphate; DEDTP = diethyldithiophosphate.

For studies which measured urinary 3,5,6-trichloro-2-pyridinol (TCPy) (e.g., Fortenberry *et al*., 2014; Eskenazi *et al*., 2007; Whyatt *et al*., 2009), this metabolite can be derived from chlorpyrifos, chlorpyrifos-methyl, and the herbicide triclopyr. TCPy is also the primary environmental degradate of chlorpyrifos, chlorpyrifos-methyl, and triclopyr; thus exposure can be found directly on food treated with these pesticides. CCCEH studies have largely used chlorpyrifos measured in cord blood as the specific biomarker (e.g., Lovasi *et al*., 2010; Whyatt *et al*., 2004; Rauh *et al*., 2011). The CHARGE study (Shelton *et al*., 2015) did not measure biomarkers but instead used geospatial analysis to focus on the residential proximity to OP exposure using data from the California Department of Pesticide Regulation, with five OPs accounting for a total of 73% of the pesticide applied near residential settings (chlorpyrifos, acephate, diazinon, bensulide, and dimethoate).

Similarly, DAPs can be found directly on food following OP applications (Zhang *et al et al*., 2008; Chen *et al*., 2012). Specifically, studies have shown that DAPs may form as environmental degradates from abiotic hydrolysis, photolysis, and plant metabolism (Zhang *et al*., 2008; Chen *et al*., 2012; Racke *et al*., 1994). Furthermore, since these DAPs are excreted more rapidly and extensively than the parent OPs (Zhang *et al*., 2008; Forsberg *et al*., 2008), direct exposure to DAPs may lead to an overestimate of OP exposure when using urinary DAPs as a biomarker of OP exposure. The agency recognizes that this is a source of uncertainty when using DAPs for assessing OP exposure and will continue to monitor this issue in future assessments.

With respect to neurological effects near birth, the CHAMACOS and Mt. Sinai cohorts measured neurological effects at birth, and observed a putative association with total DEAP, total DMAP, and total DAP exposure (Engel *et al*., 2007; Young *et al*., 2005). Similarly, a Chinese study (Zhang *et al*., 2014) reported statistically significant associations for total DEAPs, total DMAPs, and total DAPs from prenatal OP pesticide exposure and neonatal neurodevelopment assessed three days after birth. However, another cross-sectional Chinese study, Guodong *et al.* (2012), observed no association with urinary DAPs and a developmental quotient score for 23-25 month old children.

The three US cohorts (CCCEH, Mt. Sinai, CHAMACOS) each reported evidence of impaired mental and psychomotor development, albeit not consistent by age at time of testing (ranging from 6 months to 36 months across the three cohorts). Attentional problems and ADHD were reported by three prospective cohorts [Rauh *et al*., 2006; Eskenazi *et al*., 2007; Marks *et al*., 2010; and Fortenberry *et al*. 2014] with additional support from a case control study [Bouchard *et al*. 2010]. The exposure metric varied among these studies. Specifically, Fortenberry *et al*. (2014) found suggestive evidence of an association with TCPy and ADHD in boys, whereas statistically significant associations were observed by Rauh *et al*. (2006) with chlorpyrifos exposure and ADHD. Eskenazi *et al*. (2007) reported associations with total DMAPs and total DAPs and ADHD; Marks *et al*. (2010) reported associations with total DEAP, DMAP, and total DAP exposure and ADHD. In a national cross-sectional study of Canadian children, using 2007-2009 data for children age 6-11 years (Oulhote and Bouchard, 2013), there were no overall statistically significant associations observed between child urinary DEAP, DMAP, or total DAP metabolite levels and parentally reported behavioral problems. In contrast, Bouchard *et al*. (2010), looking at U.S. children age 8-15 years in the 2000-2004 NHANES, observed a positive association between attention and behavior problems and total DAPs and DMAPs, but not DEAPs. As part of their analysis, Oulhote and Bouchard (2013) noted that their outcome assessment for behavioral problems may not have been as sensitive as Bouchard *et al*. (2010), which may in part account for the difference in the observed results from these studies.

In addition, the three US cohorts and the CHARGE study have reported suggestive or positive associations between OP exposure and autism spectrum disorders (Rauh *et al*., 2006; Shelton *et al*., 2014; Eskenazi *et al*., 2007; Furlong *et al*., 2014). Specifically, Furlong *et al*. (2014) documented suggestive evidence of an association between total DEAP exposure and reciprocal social responsiveness among African Americans and boys. Eskenazi *et al*. (2007) reported a statistically significant association between pervasive developmental disorder (PDD) and total DAP exposure, whereas Eskenazi *et al*. (2010) reported non-significant, but suggestive, increased odds of PDD of 2.0 (0.8 to 5.1; p=0.14). Rauh *et al*. (2006) documented a significant association between PDD and specifically chlorpyrifos exposure. Both PDD and reciprocal social responsiveness are related to the autism spectrum disorder. Using a different exposure assessment method (geospatial analysis and residential proximity to total OP exposure), Shelton *et al*. (2014) also showed statistically significant associations between total OP exposure and ASD. While these studies vary in the magnitude of the overall strength of association, they have consistently observed a positive association between OP exposure and ASD. Finally, CCCEH, Mt. Sinai, CHAMACOS have reported an inverse relation between the respective prenatal measures of chlorpyrifos and intelligence measures at age seven years (Rauh *et al*., 2011; Engel *et al*., 2011; Bouchard *et al*., 2011).

Across the epidemiology database of studies, the maternal urine, cord blood, and other (meconium) measures provide evidence that exposure did occur to the fetus during gestation but the actual level of such exposure during the critical window(s) of susceptibility is not known. While significant uncertainties remain about the actual exposure levels experienced by mothers and infant participants in the children's health cohorts, it is unlikely that these exposures resulted in AChE inhibition. As part of the CHAMACOS study, Eskenazi *et al*. (2004) measured AChE activity and showed that no differences in AChE activity were observed. The biomarker data (chlorpyrifos) from the Columbia University studies are supported by the agency's dose reconstruction analysis using the PBPK-PD model (Drew, D. *et al*., 12/29/2014, D424485). Following the recommendation of the FIFRA SAP (2012), the agency conducted a dose reconstruction analysis of residential uses available prior to 2000 for pregnant women and young children inside the home. The PBPK-PD model results indicate for the highest exposure considered (i.e., indoor broadcast use of a 1% chlorpyrifos formulation) <1% RBC AChE inhibition was produced in pregnant women. While uncertainty exists as to actual OP exposure at (unknown) critical windows of exposure, EPA believes it is unlikely individuals in the epidemiology studies experienced RBC AChE inhibition.

A review of the scientific literature on potential modes of action/adverse outcome pathways (MOA/AOP)[5] leading to effects on the developing brain was conducted for the 2012 FIFRA SAP meeting (USEPA, 2012) and updated for the December 2014 chlorpyrifos revised risk assessment (Drew, D. *et al*., 12/29/2014, D424485). In short, multiple biologically plausible hypotheses and pathways are being pursued by researchers that include targets other than AChE inhibition, including cholinergic and non-cholinergic systems, signaling pathways, proteins, and others. However, no one pathway has sufficient data to be considered more credible than the others. The fact that there are, however, sparse AOP data to support the *in vitro* to *in vivo* extrapolation, or the extrapolation from biological perturbation to adverse consequence significantly limits their quantitative use in risk assessment. The SAP concurred with the agency in 2008 and 2012 about the lack of definable key events in a MOA/AOP leading to developmental neurobehavioral effects. However, since the 2014 literature review, there are no substantive changes in the ability to define and quantitate steps in an MOA/AOP leading from exposure to effects on the developing brain. Published and submitted guideline DNT laboratory animal studies have been reviewed for OPs as part of the 2012/2014 review (Drew *et al*., 12/29/2014, D424485) and the updated 2015 review (Lowit, A., 09/15/2015, D331251). Neurobehavioral alterations in laboratory animals were often reported, albeit at AChE inhibiting doses, but there was generally a lack of consistency in terms of pattern, timing, or dose-response for these effects, and a number of studies were of lower quality. However, this information does provide evidence of long-lasting neurodevelopmental disorders in rats and mice following gestational exposure.

At this time, a MOA(s)/AOP(s) has/have not been established for neurodevelopmental outcomes. This growing body of literature does demonstrate, however, that OPs are biologically active on a number of processes that affect the developing brain. Moreover, there is a large body of *in vivo* laboratory studies which show long-term behavioral effects from early life exposure, albeit at doses which cause AChE inhibition. EPA considers the results of the toxicological studies

[5] Mode of action (MOA) and adverse outcome pathways (AOPs) describe a set of measurable key events that make up the biological processes leading to an adverse outcome and the causal linkages between such events.

relevant to the human population, as qualitatively supported by the results of epidemiology studies. The agency acknowledges the lack of established MOA/AOP pathway and uncertainties associated with the lack of ability to make strong causal linkages and unknown window(s) of susceptibility. These uncertainties do not undermine or reduce the confidence in the findings of the epidemiology studies. The epidemiology studies reviewed in the 2012/2014 and 2015 literature reviews represent different investigators, locations, points in time, exposure assessment procedures, and outcome measurements. Despite all these differences in study design, with the exception of two negative studies in the 2015 literature review (Guodong *et al*., 2012; Oulhote and Bouchard, 2013), authors have identified associations with neurodevelopmental outcomes associated with OP exposure across four cohorts and twelve study citations. Specifically, there is evidence of delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children who were exposed to OPs during gestation. Investigators reported strong measures of statistical association across several of these evaluations (odds ratios: 2-4 fold increases in some instances), observed evidence of exposures-response trends in some instances, *e.g.*, intelligence measures.

As section 408(b)(2)(C) of the FFDCA instructs EPA, in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects, an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children." Section 408 (b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children." Given the totality of the evidence, there is sufficient uncertainty in the human dose-response relationship for neurodevelopmental effects which prevents the agency from reducing or removing the statutory 10x FQPA Safety Factor. For the naled DRA, a value of 10x has been applied. Similarly, a database uncertainty factor of 10x will be retained for occupational risk assessments. The agency will continue to evaluate the epidemiology studies and pursue approaches for quantitative or semi-quantitative comparisons between doses which elicit AChEI and those which are associated with neurodevelopmental outcomes prior to a revised human health risk assessment.

4.5 Safety Factor for Infants and Children (FQPA Safety Factor)[6]

As noted above, the lack of an established neurodevelopmental MOA/AOP makes quantitative use of the epidemiology studies in risk assessment challenging, particularly with respect to determining dose-response, critical duration of exposure, and window(s) of susceptibility. However, exposure levels in the range measured in the epidemiology studies are likely low enough that they are unlikely to result in AChEI. Epidemiology studies consistently identified associations with neurodevelopmental outcomes associated with OP exposure such as delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children. Therefore, there is a need to protect children from exposures that may cause these effects; this need prevents the agency from reducing or removing the statutory FQPA Safety Factor. **Thus, the FQPA 10X Safety**

[6] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

Factor will be retained for naled for the population subgroups that include infants, children, youth, and women of childbearing age for all exposure scenarios.

4.5.1 Completeness of the Toxicology Database

The toxicology database for naled is considered complete. The available studies to inform on the FQPA SF evaluation include two developmental studies (rat and rabbit), the two-generation reproduction study (rat), the developmental neurotoxicity study (rat), the single and repeat dose CCA studies (rat), and the acute and subchronic neurotoxicity studies.

4.5.2 Evidence of Neurotoxicity

As discussed in Section 4.4, there is uncertainty in the human dose-response relationship for neurodevelopmental effects and this warrants retention of the FQPA Safety Factor for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.

Naled is an OP with a neurotoxic MOA/AOP; AChE inhibition is the most sensitive quantitative effect in all species, routes, and life stages and is being used to derive PODs for risk assessment. The PODs selected for risk assessment are based on 10% AChEI for all exposure scenarios. Therefore, the risk assessment with the FQPA SF is protective of potential neurotoxicity for every life stage and route of exposure.

4.5.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

Rat pups exhibited greater susceptibility to single dose oral exposure to naled for both RBC and brain AChEI compared to adults but were not uniquely susceptible to repeat dose exposure. As a result, acute dietary endpoints are based on AChEI in pups. Overall, increased sensitivity was not evident in developing or young animals compared to adults following repeat exposure to naled. There is no evidence of increased susceptibility following *in utero* exposure to naled in rats and rabbits as well as pre/post-natal exposure in developmental, two-generation reproduction, and gestational CCA studies in rats. While the DNT study identified non-cholinesterase effects in the offspring at doses lower than that of the maternal, significant AChE decreases (measured in the DNT range-finding study) were identified at approximately the same dose eliciting offspring effects, with the greatest changes observed in maternal animals. In spite of the apparent sensitivity observed in the DNT, there are clearly established NOAEL/LOAEL values for the observed effects, the offspring effects occurred at a dose that would cause significant AChEI in maternal animals, and the steady-state PODs selected are protective of all repeat-dose effects identified in the developing or young rat.

4.5.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties with regard to the exposure databases. The acute and steady-state dietary assessments are highly refined (incorporated field trial residues, processing studies, USDA PDP monitoring data, and anticipated residues). Although data were used to refine the acute and steady-state dietary exposure assessments, the assessments are not expected to

underestimate dietary (food and water) exposures. The non-occupational post-application exposure assessments are based upon the 2012 Standard Operating Procedures (SOPs) for Residential Exposure Assessment. The 2012 Residential SOPs are based upon conservative assumptions and are not expected to underestimate risks from naled exposure.

4.6 Toxicity Endpoint and Point of Departure Selections

4.6.1 Dose Response Assessment

Tables 4.6.4.1-3 summarize the naled toxicity endpoints and PODs selected from an evaluation of the naled database. PODs have been updated since the previous risk assessment and this endpoint selection was based on a weight of the evidence evaluation using the following considerations:

- *Relative sensitivity of the brain and RBC compartments*: The data available on naled exposure are derived from the rat. Following acute oral exposures, RBC AChEI was slightly more sensitive than brain AChEI in the adult rat. However, following repeat oral, dermal, and inhalation dose exposures, no differences were noted between compartment AChE effects. OPP has relied on both RBC and brain AChE measurements for steady-state scenarios depending on which compartment resulted in the lowest and most reliable data for each individual exposure scenario.
- *Potentially susceptible populations (fetuses, juveniles, pregnancy, or sex*): The available AChE data across multiple life stages (adult, pregnant adult, fetus, and juvenile rat) indicate that males were slightly more sensitive than females after acute exposure (but not after repeat exposure). The acute oral CCA showed that on average, a 10% inhibition of AChE occurred in pups at doses 4x lower than adults for brain and 2x lower than adults for RBC. However, following repeat oral, dermal, and inhalation dose exposures, no differences were noted between life stages in rat. The rat fetus was not more sensitive than pup and adult rats (including pregnant dams) after repeat dosing. Pup and adult rats share similar sensitivity to RBC/brain AChE depression following repeated naled exposure (Table 4.3.1).
- *Route of exposure:* It is preferred to match, to the degree possible, the route of exposure in the toxicity study with that of the exposure scenario(s) of interest. Acute and repeat dose studies were available for oral, dermal, and inhalation route-specific assessments following single dose and steady-state exposure to naled.
- *Duration of exposure:* It is preferred to match, to the degree possible, the duration of a toxicity study with that of the exposure duration of interest. There are single-day and repeat dose oral, dermal, and inhalation studies available.
- *Consistency across studies:* In cases where multiple datasets are available for a single duration, it is important to evaluate the extent to which data are consistent (or not) across studies. Considering the presence of sensitive populations that different labs reproduced in studies conducted across several years, the naled database demonstrated consistent AChEI and effects within the rat species.

Descriptions of the primary toxicity studies used for selecting toxicity endpoints and points of departure for various exposure scenarios are presented in Appendix 2 of this document.

Summary tables of BMD analyses can be found in Appendix A.4, and the technical details of the analysis can be found in the BMD memorandums (Liccione, J., 09/19/2019, TXR 0057943; Bever, R, 08/23/2016, TXR 0057475; Lowit, A., 06/09/2006, TXR 0054223).

Consistent with risk assessments for other AChE-inhibiting compounds, OPP has used a benchmark response (BMR) level of 10% and has thus calculated BMD_{10} and $BMDL_{10}$ (see Appendix A.4 for summary of OPP's ChE policy). The BMD_{10} is the estimated dose where AChE is inhibited by 10% compared to background. The $BMDL_{10}$ is the lower confidence bound on the BMD_{10}. As a matter of science policy, the agency uses the BMDL, not the BMD, for use as the POD (USEPA, 2012). Data were analyzed from rats in an acute comparative cholinesterase assay (CCA; MRIDs 46153105 and 46153107), repeated dose CCA (MRID 46153104), 90-day oral toxicity study (MRID 46153108), 2-year chronic toxicity/carcinogenicity study (MRID 00141784), 28-day dermal toxicity studies (MRIDs 00160750 and 45222001), and an inhalation toxicity study (MRID 00265680). All data from these studies were considered; however, some data were not amenable to BMD analysis. Analyses was completed using USEPA BMD Software, version 2.4 and USEPA BMD Software, version 2.6 for the single dose dermal and inhalation studies; an exponential model or Hill model was used to fit these data. Summary tables of BMD analyses can be found in Appendix A.4, and the technical details of the analyses can be found in the BMD memoranda (Bever, R., 08/23/2016, TXR 0057475).

Tables 4.6.4.5-7 summarize DDVP toxicity endpoints and PODs selected. Detailed information on DDVP endpoint selection can be found in the DDVP risk assessment (Kidwell, J. *et al*, 06/19/2020, D430516).

Acute Dietary Endpoint

A POD for the acute dietary exposure scenario was derived from the rat oral AChE study (MRID 46153105). A $BMDL_{10}$ of 3.2 mg/kg was selected based on RBC AChE inhibition in female PND 22 rats. The corresponding BMD_{10} is 4.2 mg/kg. Data from female pups are appropriate for acute POD derivation, since they demonstrated the most sensitivity to acute naled exposure in the database. This time point also provided data for the most robust BMD modeling and therefore BMD_{10} estimate. The POD is considered the most protective of all subpopulations (infants and children, females 13+, and adults).

An uncertainty factor of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA safety/database uncertainty factor due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)) is applied to the $BMDL_{10}$ to obtain an aPAD of 0.0032 mg/kg for exposure scenarios with infants, children, youth, and women of childbearing age. The only population subgroup for which the FQPA SF is not retained is adults 50-99 years old; therefore, the aPAD for this population subgroup is 0.032 mg/kg/day.

Steady-State Dietary Endpoint

A POD for the steady-state dietary (all populations) exposure scenario was derived from the dose response observed in the rat carcinogenicity study (MRID 00141784). A $BMDL_{10}$ of 0.6

mg/kg/day was selected based on brain AChEI in adults (both sexes) since it demonstrated the most sensitivity to repeat dose exposure and the most robust BMD modeling. The corresponding BMD_{10} was 0.8 mg/kg/day. Brain AChEI was selected over RBC AChEI as the endpoint for the POD, since the data on RBC AChEI reported weak dose-response and high variability. The POD is considered the most protective of all subpopulations (infants and children, females 13+, and adults).

An uncertainty factor of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA safety/database uncertainty factor due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)) is applied to the $BMDL_{10}$ to obtain a steady-state PAD (ssPAD) of 0.0006 mg/kg/day for all exposure scenarios, except adults 50-99 years old. Excluding the FQPA SF for adults 50-99 years old, the ssPAD is 0.006 mg/kg/day.

Acute Incidental Oral Endpoint

A POD for the acute incidental oral exposure scenario was derived from the rat oral AChE study (MRID 46153105). A $BMDL_{10}$ of 3.2 mg/kg was selected based on RBC AChE inhibition in female PND 22 rats. The corresponding BMD_{10} is 4.2 mg/kg. Data from female pups are appropriate for acute incidental oral POD derivation, since they demonstrated the most sensitivity to acute naled exposure in the database. This time point also provided data for the most robust BMD modeling and therefore BMD_{10} estimate. The POD is considered the most protective of all subpopulations (infants and children, females 13+, and adults). An uncertainty factor of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA safety/database uncertainty factor due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)) is applied to the $BMDL_{10}$ resulting in a Level of Concern (LOC) of 1000.

Steady-State Incidental Oral Endpoint

A POD of 0.6 mg/kg/day was selected from the rat carcinogenicity study (MRID 00141784), based on the same rationale provided above for the steady-state dietary exposures. A total uncertainty factor of 1000X is appropriate for incidental oral exposures (10X for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA SF due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)) resulting in a LOC of 1000.

Acute Dermal Endpoint

Due to the use pattern for naled, an acute dermal endpoint is necessary for exposure assessment. A POD of 14.2 mg/kg was selected from the Single-Dose Dermal Toxicity Study in Rats (MRID 50795201). A $BMDL_{10}$ of 14.2 mg/kg was selected and associated with RBC AChE inhibition in adult females. The corresponding BMD_{10} was 28.8 mg/kg. Data from the adults was appropriate for acute POD derivation since effects were observed after a single exposure and the endpoint is considered protective of all populations (infants and children, females 13-49 yr old, and adults) due to lack of increased susceptibility in fetus and offspring.

A refined dermal equivalent dose (RDD) may be derived using the "triple pack" dermal absorption data. The RDD was calculated by the following formula:

Refined Dermal Equivalent Dose (RDD) (mg/kg/day) =

$$\textbf{Dermal POD (mg/kg/day)} \times \frac{\textbf{Animal } \textit{\textbf{In Vitro}} \textbf{ Absorption (\%)}}{\textbf{Human } \textit{\textbf{In Vitro}} \textbf{ Absorption (\%)}}$$

Using the equation above, the POD derived from the Single-Dose Dermal Toxicity Study in Rats can be refined to account for higher skin permeability in rat skin compared to human skin. As described in Section 4.2.1, the animal to human *in vitro* ratio is 2.66. Therefore, the RDD to use as the acute dermal POD is 37.8 mg/kg. The calculations are shown in the table below.

Table 4.6.1.1 Calculations of Acute Refined Dermal Equivalent Dose Using "Triple Pack" Dermal Absorption Data

Study	Rat Dermal POD	Animal *in vitro* / Human *in vitro*	RDD = POD x Animal *In Vitro* / Human *In Vitro*
Single-Dose Dermal Toxicity (MRID 50795201)	14.2 mg/kg	2.66	14.2 x 2.66 = 37.8 mg/kg

An uncertainty factor of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10x for FQPA safety/database uncertainty factor due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)) resulting in a LOC of 1000.

Steady-State Dermal Endpoint

The steady-state dermal POD of 10 mg/kg/day was selected from two subchronic dermal studies in rat (MRID 00160750, 45222001). Although the data from both rat dermal studies were modeled for BMDs, the results were not reliable as the ground truthing of inhibition at the known dose levels failed, there was excessive variation, and AChE data often lacked a dose-response. Therefore, the NOAEL of 10 mg/kg/day was relied upon as the POD based upon the lowest dose eliciting brain and RBC AChEI in both sexes (20 mg/kg/day in the adult rat).

Using the same equation above for the acute RDD, the POD derived from the 28-day dermal rat toxicity study can be refined to account for higher skin permeability in rat compared to human skin using the animal to human in vitro ratio of 2.66. Therefore, the RDD to use as the steady-state dermal POD is 26.6 mg/kg/day. The calculations are shown in the table below.

Table 4.6.1.2 Calculation of Steady-State Refined Dermal Equivalent Dose Using "Triple Pack" Dermal Absorption Data

Study	Rat Dermal POD	Animal *in vitro* / Human *in vitro*	RDD = POD x Animal *In Vitro* / Human *In Vitro*
28-day Dermal Toxicity	10 mg/kg/day	2.66	10 x 2.66 = 26.6 mg/kg/day

A total uncertainty factor of 1000X is appropriate for dermal exposures (10X for interspecies extrapolation, 10X for intraspecies variation, and a 10X FQPA SF for residential assessments or a database uncertainty factor in occupational assessments due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)), resulting in a LOC of 1000.

Acute Inhalation Endpoint

A POD of 9.9 mg/m^3 was selected from the Single Dose Inhalation Toxicity Study in rat (MRID 50823901). A $BMDL_{10}$ of 9.9 mg/m^3 was selected and was associated with RBC AChEI in adult females. The corresponding BMD_{10} was 15.2 mg/m^3. Data from adults are appropriate for acute POD derivation, since effects were observed after a single exposure. The endpoint is considered protective of all populations (infants and children, females 13-49, and adults) since there was lack of increased susceptibility in fetus and offspring in the oral CCAs. Though there are no inhalation CCAs available in the database, it is unlikely that the absorption patterns differ from that of oral given all of the evidence observed in both the naled and DDVP databases.

Human Equivalent Concentrations (HECs)/Human Equivalent Doses (HEDs) were calculated using the $BMDL_{10}$ and the Regional Deposited Dose Ratio (RDDR) and are presented in Section 4.6.4 (Tables 4.6.4.3). The RDDR accounts for the particle diameter [mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD)] and estimates the different dose fractions deposited along the respiratory tract. The RDDR also accounts for interspecies differences in ventilation and respiratory tract surface areas. Additional details can be found in Appendix A.3. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 3X due to the calculation of HECs (which account for pharmacokinetic, not pharmacodynamic, interspecies differences). Therefore, the LOC for inhalation exposures is 300 (3X interspecies extrapolation, 10X intraspecies variation, and 10X for FQPA safety/database uncertainty factor (UF_{DB}) due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)).

Steady-State Inhalation Endpoint

A route-specific 90-day inhalation study in rats (MRID 00265680) was used to assess the toxicity of naled following inhalation exposure. A POD of 0.2 mg/m^3 was selected based on RBC AChE inhibition in adults (both sexes). The corresponding BMD_{10} was 0.3 mg/m^3. Data from adults are appropriate for steady-state POD derivation, since effects were observed after a single exposure and the endpoint is considered protective of all populations (infants and children, females 13-49, and adults) due to lack of increased susceptibility in fetus and offspring in the oral CCAs. Although there are no inhalation CCAs available in the database, it is unlikely that the absorption patterns differ from that of oral given all of the evidence observed in both the naled and DDVP databases.

HECs and HEDs were calculated using the $BMDL_{10}$ and the RDDR and are presented in Section 4.6.4 (Tables 4.6.4.4). Additional details can be found in Appendix A.3. The standard interspecies extrapolation uncertainty factor can be reduced from 10x to 3x due to the calculation of HECs (which account for pharmacokinetic, not pharmacodynamic, interspecies differences). Therefore, the LOC for inhalation exposures is 300 (3X interspecies extrapolation, 10X intraspecies variation, and 10X for FQPA safety/database uncertainty factor (UF_{DB}) due to

uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)).

4.6.2 Recommendation for Combining Routes of Exposures for Risk Assessment

When there are potential occupational and residential/non-occupational exposures to a pesticide, the risk assessment must address exposures from three major sources (oral, dermal, and inhalation) and determine whether the individual exposures can be combined if they have the same toxicological effects. PODs for the dietary, incidental oral, dermal, and inhalation routes are all derived from brain and RBC AChE inhibition. All acute scenarios rely on RBC AChEI and, therefore, can be combined. Following repeat oral, dermal, and inhalation dose exposures, no differences were noted between compartment AChE effects and both compartments were relied upon for exposure PODs. Therefore, since neither RBC nor brain AChEI were considered more sensitive for steady-state exposure to naled, all steady-state scenarios can be combined.

4.6.3 Cancer Classification and Risk Assessment Recommendation

The carcinogenic potential of naled has been classified as Group E "Evidence of non-carcinogenicity for humans" (Ghali, G., 08/31/1994, TXR 0011199) under the Guidelines for Cancer Risk Assessment (April 10, 1986). This classification is used for agents that show no evidence for carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies. Naled was negative in an *in vivo* coat color mutation study in mice. In the *S. typhimurium* reverse mutation assay naled was mutagenic with metabolic activation at the highest dose tested (2 µM) and toxic in the absence of metabolic activation. However, naled was negative for DNA damage *in vitro*, negative for cytogenetic effects *in vivo*, and negative for clastogenic effects *in vivo*. Therefore, there is no concern for mutagenicity due to exposure to naled.

4.6.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.6.4.1. Summary of Toxicological Doses and Endpoints and Points of Departure for Naled in Dietary and Non-Occupational Human Health Risk Assessments

Exposure Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations Except Adults 50-99 Years)	$BMDL_{10}$ = 3.2 mg/kg	UF_A = 10X UF_H = 10X FQPA SF = 10X* Total = 1000	Acute RfD = 0.032 mg/kg aPAD = 0.0032 mg/kg	Rat acute oral cholinesterase study (CCA) (MRID 46153105) BMD_{10} = 4.2 mg/kg for RBC ChE depression (PND 22 female) (Bever, R., 08/23/2016, TXR 0057475)

Table 4.6.4.1. Summary of Toxicological Doses and Endpoints and Points of Departure for Naled in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (Adults 50-99 Years)	$BMDL_{10}$ = 3.2 mg/kg	UF_A = 10X UF_H = 10X FQPA SF = 1X Total = 100	Acute RfD = 0.032 mg/kg aPAD = 0.032 mg/kg	Rat acute oral cholinesterase study (CCA) (MRID 46153105) BMD_{10} = 4.2 mg/kg for RBC ChE depression (PND 22 female) (Bever, R., 08/23/2016, TXR 0057475)
Steady-State Dietary (All Populations Except Adults 50-99 Years)	$BMDL_{10}$ = 0.6 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 10X* Total = 1000	ssRfD = 0.006 mg/kg/day ssPAD = 0.0006 mg/kg/day	Rat Carcinogenicity Study (MRID 00141784) BMD_{10} = 0.8 mg/kg/day for brain ChE depression (adult male and female). (Bever, R., 08/23/2016, TXR 0057475)
Steady-State Dietary (Adults 50-99 Years)	$BMDL_{10}$ = 0.6 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X Total = 100	ssRfD = 0.006 mg/kg/day ssPAD = 0.006 mg/kg/day	Rat Carcinogenicity Study (MRID 00141784) BMD_{10} = 0.8 mg/kg/day for brain ChE depression (adult male and female) (Bever, R., 08/23/2016, TXR 0057475)
Acute Incidental Oral	$BMDL_{10}$ = 3.2 mg/kg	UF_A = 10X UF_H = 10X FQPA SF = 10X* Total = 1000	Residential LOC = 1000	Rat acute oral cholinesterase study (MRID 46153105) BMD_{10} = 4.2 mg/kg for RBC AChE depression (PND 22 female) (Bever, R., 08/23/2016, TXR 0057475)
Steady-State Incidental Oral	$BMDL_{10}$ = 0.6 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 10X* Total = 1000	Residential LOC MOE = 1000	Rat Carcinogenicity Study (MRID 00141784) BMD_{10} = 0.8 mg/kg/day for brain ChE depression (adult male and female) (Bever, R., 08/23/2016, TXR 0057475)
Acute Dermal	$BMDL_{10}$ = 14.2 mg/kg RDD = 37.8 mg/kg (see Section 4.6.1 for calculation)	UF_A = 10X UF_H = 10X FQPA SF = 10X* Total = 1000	Residential LOC MOE = 1000	Single-Dose Dermal Toxicity Study in Rats (MRID 50795201) BMD_{10} = 28.8 mg/kg for RBC ChE depression (adult female). (Liccione, J., 09/19/2019, TXR 0057943)
Steady State Dermal	Dermal study NOAEL = 10 mg/kg/day RDD = 26.6 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 10X* Total = 1000	Residential LOC MOE = 1000	Co-critical Rat 28-day Dermal Studies (MRIDs 00160750, 45222001) LOAEL = 20 mg/kg/day for RBC and brain ChE depression (adult male and female)

Table 4.6.4.1. Summary of Toxicological Doses and Endpoints and Points of Departure for Naled in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
	(see Section 4.6.1 for calculation)			
Acute Inhalation	$BMDL_{10}$ = 9.9 mg/m^3 For HEC and HED see table 4.6.4.3a	UF_A = 3X UF_H = 10X FQPA SF = 10X* Total = 300	Residential LOC MOE = 300	Single Dose Inhalation Toxicity Study in Rat (MRID 50823901) BMD_{10} = 15.2 mg/m^3 for RBC ChE depression (adult female). (Liccione, J., 09/19/2019, TXR 0057943)
Steady-State Inhalation	$BMDL_{10}$ = 0.2 mg/m^3 For HEC and HED see table 4.6.4.3b	UF_A = 3X UF_H = 10X FQPA SF = 10X* Total = 300	Residential LOC MOE = 300	Rat 90-day inhalation study (MRID 00265680) BMD_{10} = 0.3 mg/m^3 based on RBC ChE inhibition (adult males and females) (Bever, R., 08/23/2016, TXR 0057475)
Cancer (Oral, Dermal, Inhalation)	Group E: Evidence of non-carcinogenicity			

Explanation of Abbreviations:
Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. Post-natal day = (PND). UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern. RBC = red blood cell. $BMDL_{10}$ = benchmark dose lower limit for 10% response. PAD = population adjusted dose. (a = acute, ss = steady-state or maximal AChE inhibition which occurs around 2-3 weeks for OPs, 7 days for naled, and is a specific exposure assessment conducted for OPs instead of the traditional short, intermediate, or chronic assessments. The SS assessment is protective of longer durations of exposure, including chronic). HEC = human equivalent concentration. HED: human equivalent dose. DAF = dermal absorption factor.
*The 10x FQPA SF is retained for infants, children, youth, and women of childbearing age for all exposure scenarios due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4). This includes all exposure scenarios, except the dietary exposure scenarios for the population subgroup adults 50-99 years old for which the FQPA SF has been reduced to 1x.

Table 4.6.4.2. Summary of Toxicological Doses and Endpoints for Naled for Use in Occupational Human Health Risk Assessments				
Exposure Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dermal	$BMDL_{10}$ = 14.2 mg/kg RDD = 37.8 mg/kg (see Section 4.6.1 for calculation)	UF_A = 10X UF_H = 10X UF_{DB} = 10X* Total = 1000	Occupational LOC MOE = 1000	Single-Dose Dermal Toxicity Study in Rats (MRID 50795201) BMD_{10} = 28.8 mg/kg for RBC ChE depression (adult female). (Liccione, J., 09/19/2019, TXR 0057943)

Table 4.6.4.2. Summary of Toxicological Doses and Endpoints for Naled for Use in Occupational Human Health Risk Assessments

Exposure Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Steady State Dermal	Dermal study NOAEL = 10 mg/kg/day RDD = 26.6 mg/kg/day (see Section 4.6.1 for calculation)	UF_A = 10X UF_H = 10X UF_{DB} = 10X* Total = 1000	Occupational LOC MOE = 1000	Co-critical Rat 28-day Dermal Studies (MRIDs 00160750, 45222001) LOAEL = 20 mg/kg/day for RBC and brain ChE depression (adult male and female)
Acute Inhalation	$BMDL_{10}$ = 9.9 mg/m^3 For HEC and HED see table 4.6.4.3a	UF_A = 3X UF_H = 10X UF_{DB} = 10X* Total = 300	Occupational LOC MOE = 300	Single Dose Inhalation Toxicity Study in Rat (MRID 50823901) BMD_{10} = 15.2 mg/m^3 for RBC ChE depression (adult female). (Liccione, J., 09/19/2019, TXR 0057943)
Inhalation Steady-State (All Populations)	$BMDL_{10}$ = 0.2 mg/m^3 For HEC and HED see table 4.6.4.3b	UF_A = 3X UF_H = 10X UF_{DB} = 10X* Total = 300	Occupational LOC MOE = 300	Rat 90-day inhalation study (MRID 00265680) BMD_{10} = 0.3 mg/m^3 based on RBC ChE inhibition (adult males and females) (Bever, R., 08/23/2016, TXR 0057475)
Cancer (Oral, Dermal, Inhalation)	Group E: Evidence of non-carcinogenicity			

Explanation of Abbreviations:
Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. Post-natal day = (PND). UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies).). UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). . MOE = margin of exposure. LOC = level of concern. RBC = red blood cell. $BMDL_{10}$ = benchmark dose lower limit for 10% response. PAD = population adjusted dose. (a = acute, ss = steady-state or maximal AChE inhibition which occurs around 2-3 weeks for OPs, 7 days for naled, and is a specific exposure assessment conducted for OPs instead of the traditional short, intermediate, or chronic assessments. The SS assessment is protective of longer durations of exposure, including chronic). HEC = human equivalent concentration. HED: human equivalent dose. DAF = dermal absorption factor.
*The 10X UF_{DB} is retained for women of childbearing age for all exposure scenarios due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4).

Table 4.6.4.3. Human Equivalent concentrations (HECs) and Human Equivalent Doses (HEDs) Based on Acute Inhalation Study MRID 50823901 and RDDR Methodology

Population	Scenario	Tox duration adjustment		HEC		HED (mg/kg-day)
		Daily	Weekly	mg/L	mg/m^3	
Occupational	Handler	1	1	0.026	25.799	2.441
Residential	Handler	NA	NA	0.026	25.799	0.610
	Outdoor post-application	NA	NA	0.026	25.799	0.702
	Indoor Post-application	NA	1	0.026	25.799	0.610
	Bystander	1	1	0.026	25.799	NA

*Calculations for HECs and HEDs can be found in Appendix A.3

Table 4.6.4.4. Human Equivalent concentrations (HECs) and Human Equivalent Doses (HEDs) Based on Repeat Inhalation Study MRID 00265680 and RDDR Methodology

Population	Scenario	Tox duration adjustment		HEC		HED (mg/kg-day)
		Daily	Weekly	mg/L	mg/m^3	
Occupational	Handler	0.75	1	0.001	0.626	0.059
Residential	Handler	NA	NA	0.001	0.835	0.020
	Outdoor post-application	NA	NA	0.001	0.835	0.023

Table 4.6.4.4. Human Equivalent concentrations (HECs) and Human Equivalent Doses (HEDs) Based on Repeat Inhalation Study MRID 00265680 and RDDR Methodology

Population	Scenario	Tox duration adjustment		HEC		HED (mg/kg-day)
		Daily	Weekly	mg/L	mg/m^3	
	Indoor Post-application	NA	0.71	0.001	0.597	0.014
	Bystander	0.25	0.71	0.000	0.149	NA

*Calculations for HECs and HEDs can be found in Appendix A.3

Table 4.6.4.5. Summary of Toxicological Doses and Endpoints and Points of Departure for DDVP in Dietary and Non-Occupational Human Health Risk Assessments

Exposure Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations Except Adults 50-99 Years)	Oral study $BMDL_{10}$ = 0.83 mg/kg	UF_A = 10X UF_H = 10X FQPA SF = 10X* Total = 1000	Acute RfD = 0.0083 mg/kg/day aPAD = 0.00083 mg/kg/day	Rat acute oral cholinesterase (CCA) studies (MRIDs 45805703, 45842301) BMD_{10} = 1.5 mg/kg for RBC ChE depression (PND 8). (Lowit, A., 06/09/2006, TXR 0054223)
Acute Dietary (Adults 50-99 Years)	Oral study $BMDL_{10}$ = 0.83 mg/kg	UF_A = 10X UF_H = 10X FQPA SF = 1X Total = 100	Acute RfD = 0.0083 mg/kg aPAD = 0.0083 mg/kg	Rat acute oral cholinesterase (CCA) studies (MRIDs 45805703, 45842301) BMD_{10} = 1.5 mg/kg for RBC ChE depression (PND 8). (Lowit, A., 06/09/2006, TXR 0054223)
Steady-State Dietary (All Populations Except Adults 50-99 Years)	Oral study $BMDL_{10}$ = 0.06 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 10X* Total = 1000	ssRfD = 0.0006 mg/kg/day ssPAD = 0.00006 mg/kg/day	Rat Repeat Dose Comparative ChEI (CCA) Study (MRID 46153304) BMD_{10} = 0.09 mg/kg/day for RBC AChE depression (adult female). (Bever, R., 06/08/2016, TXR 0057449)

Table 4.6.4.5. Summary of Toxicological Doses and Endpoints and Points of Departure for DDVP in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Steady-State Dietary (Adults 50-99 Years)	Oral study $BMDL_{10}$ = 0.06 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X Total = 100	ssRfD = 0.0006 mg/kg/day ssPAD = 0.0006 mg/kg/day	Rat Repeat Dose Comparative ChEI (CCA) Study (MRID 46153304) BMD_{10} = 0.09 mg/kg/day for RBC ChE depression (adult female). (Bever, R., 06/08/2016, TXR 0057449)
Acute Incidental Oral	Oral study $BMDL_{10}$ = 0.83 mg/kg	UF_A = 10X UF_H = 10X FQPA SF = 10X* Total = 1000	Residential LOC MOE = 1000	Rat acute oral cholinesterase studies (MRIDs 45805703, 45842301) BMD_{10} = 1.5 mg/kg for RBC AChE depression (PND 8). (Lowit, A., 06/09/2006, TXR 0054223)
Steady-State Incidental Oral	Oral study $BMDL_{10}$ = 0.06 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 10X* Total = 1000	Non-Occupational LOC MOE = 1000	Rat Repeat Dose Comparative ChEI (CCA) Study (MRID 46153304) BMD_{10} = 0.09 mg/kg/day for RBC ChE depression (adult female). (Bever, R., 06/08/2016, TXR 0057449)
Acute Dermal (All Populations)	$BMDL_{10}$ = 17.9 mg/kg	UF_A = 10X UF_H = 10X FQPA SF = 10X* Total = 1000	Non-Occupational LOC MOE = 1000	*In Vivo* Single-Dose Dermal Toxicity Study in Rats (MRID 50824001) BMD_{10} = 32.8 mg/kg for RBC ChE depression (adult female) (Liccione, J., 09/19/2019, TXR 0057943)
Steady-State Dermal (All Populations)	$BMDL_{10}$ = 4.2 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 10X* Total = 1000	Non-Occupational LOC MOE = 1000	28-Day Dermal Toxicity Study in Rats (MRID 50832001) BMD_{10} = 8.0 mg/kg/day for RBC ChE depression (adult female) (Liccione, J., 09/19/2019, TXR 0057943)
Acute Inhalation (All Populations)	$BMDL_{10}$ = 3.7 mg/m^3 See Table 4.6.4.3a for HEC and HED.	UF_A = 3X UF_H = 10X FQPA SF = 10X* Total = 300	Non-Occupational LOC MOE = 300	Single Dose Inhalation Toxicity Study in Rat (MRID 50828501) BMD_{10} = 10.3 mg/m^3 for RBC ChE depression (adult female). (Liccione, J., 09/19/2019, TXR 0057943)
Steady-State Inhalation (All Populations)	LOAEL= 0.04 mg/m^3	UF_A = 3X UF_H = 10X FQPA SF = 100X*/# Total = 3000	Non-Occupational LOC MOE = 3000	Rat carcinogenicity inhalation study (MRID 00057695, 00632569) No NOAEL was established; LOAEL = 0.04 mg/m^3 based on RBC ChE inhibition in female rats.

Table 4.6.4.5. Summary of Toxicological Doses and Endpoints and Points of Departure for DDVP in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
	See Table 4.6.4.3b for HEC and HED.			
Cancer (oral, dermal, inhalation)	"Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential" under the 1999 Draft Cancer Guidelines and no quantitative assessment of cancer risk is required.			

Explanation of Abbreviations: Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. Post-natal day = (PND). UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). DAF = dermal absorption factor. MOE = margin of exposure. LOC = level of concern. RBC = red blood cell. $BMDL_{10}$= benchmark dose lower limit for 10% response. PAD = population adjusted dose. (a = acute, ss = steady-state or maximal AChE inhibition which occurs around 7 days for DDVP and is a specific exposure assessment conducted for OPs instead of the traditional short, intermediate, or chronic assessments. The SS assessment is protective of longer durations of exposure, including chronic). HEC = human equivalent concentration. HED = human equivalent dose. AED = animal equivalent dose.
*The 10x FQPA SF is retained for infants, children, youth, and women of childbearing age for all exposure scenarios due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4). This includes all exposure scenarios, except the dietary exposure scenarios for the population subgroup adults 50-99 years old for which the FQPA SF has been reduced to 1x.
#The UF_L is applied together with the FQPA SF

Table 4.6.4.6. Summary of Toxicological Doses and Endpoints for DDVP for Use in Occupational Human Health Risk Assessments				
Exposure Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dermal (All Populations)	$BMDL_{10}$ = 17.9 mg/kg	UF_A = 10X UF_H = 10X UF_{DB} = 10X* Total = 1000	Occupational LOC MOE = 1000	Single-Dose Dermal Toxicity Study in Rats (MRID 50824001) BMD_{10} = 32.8 mg/kg for RBC ChE depression (adult female) (Liccione, J., 09/19/2019, TXR 0057943)
Steady-State Dermal (All Populations)	$BMDL_{10}$ = 4.2 mg/kg/day	UF_A = 10X UF_H = 10X UF_{DB} = 10X* Total = 1000	Occupational LOC MOE = 1000	28-Day Dermal Toxicity Study in Rats (MRID 50832001) BMD_{10} = 8.0 mg/kg for RBC ChE depression (adult female) (Liccione, J., 09/19/2019, TXR 0057943)
Acute Inhalation (All Populations)	$BMDL_{10}$ = 3.7 mg/m^3 See Table 4.6.4.3a for HEC and HED.	UF_A = 3X UF_H = 10X UF_{DB} = 10X* Total = 300	Occupational LOC MOE = 300	Single Dose Inhalation Toxicity Study in Rat (MRID 50828501) BMD_{10} = 10.3 mg/m^3 for RBC ChE depression (adult female). (Liccione, J., 09/19/2019, TXR 0057943)

Table 4.6.4.6. Summary of Toxicological Doses and Endpoints for DDVP for Use in Occupational Human Health Risk Assessments				
Exposure Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Inhalation Steady-State (All Populations)	LOAEL= 0.04 mg/m^3 See Table 4.6.4.3b for HEC and HED.	UF_A = 3X UF_H = 10X UF_L = 10X UF_{DB} = 10X* Total = 3000	Occupational LOC MOE = 3000	Rat carcinogenicity inhalation study (MRID 00057695, 00632569) No NOAEL; LOAEL = 0.04 mg/m^3 based on RBC ChE inhibition in female rats.
Cancer (oral, dermal, inhalation)	"Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential" under the 1999 Draft Cancer Guidelines and no quantitative assessment of cancer risk is required.			

Explanation of Abbreviations: Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). UF_L = use of a LOAEL to extrapolate NOAEL. DAF = dermal absorption factor. MOE = margin of exposure. LOC = level of concern. RBC = red blood cell. $BMDL_{10}$= benchmark dose lower limit for 10% response. PAD = population adjusted dose. (a = acute, ss = steady-state or maximal AChE inhibition which occurs around 7 days for DDVP and is a specific exposure assessment conducted for OPs instead of the traditional short, intermediate, or chronic assessments. The SS assessment is protective of longer durations of exposure, including chronic). HEC = human equivalent concentration. HED = human equivalent dose. AED = animal equivalent dose.
*The 10x UF_{DB} is retained women of childbearing age for all exposure scenarios due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4).

Table 4.6.4.7a. Human Equivalent Concentration (HEC) and Human Equivalent Dose (HED)* Based on the Acute Inhalation Study MRID 50828501 and the RGDR Methodology - DDVP						
Population	**Scenario**	**Toxicity duration adjustment**		**HEC****		**HED** (mg/kg-day)**
		Daily	**Weekly**	**mg/L**	**mg/m^3**	
Occupational	Handler	1	1	0.004	3.700	0.349
Residential	Indoor Post-application	1	1	0.004	3.700	0.09
	Bystander	1	1	0.004	3.700	1.048

**Anticipated exposure and single-dose inhalation study were both 2 h. Therefore, no duration adjustment was made.
*Calculations for HECs and HEDs can be found in Appendix A.5 of the DDVP DRA.

Table 4.6.4.7b. Human Equivalent Concentration (HEC) and Human Equivalent Dose (HED)* Based on the Repeat Dose Inhalation Study MRIDs 00057695, 00632569 and the RGDR Methodology - DDVP

Population	Scenario	Toxicity duration adjustment		HEC		HED (mg/kg-day)
		Daily	Weekly	mg/L	mg/m^3	
Occupational	Handler	1	1	0.00004	0.040	0.004
Residential	Indoor Post-application	1	1	0.00004	0.040	0.008
		1	1	0.00004	0.040	0.009
	Bystander	0.958	1	0.00004	0.038	0.011

*Calculations for HECs and HEDs can be found in the DDVP DRA.

4.7 Endocrine Disruptor Screening Program

As required by FIFRA and FFDCA, the EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic, and chronic durations and assess carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, the agency evaluates acute tests and chronic studies that assess growth, developmental, and reproductive effects in different taxonomic groups. As part of its reregistration decision for naled, the agency reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), naled is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).
The agency has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP, where the agency will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the agency must screen all pesticide chemicals. Between October 2009 and February 2010, the agency issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients[7]. A second list of chemicals identified for EDSP screening was published on June 14, 2013[8] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors. Naled is not on List 1 or List 2. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website[9].

5.0 Dietary Exposure and Risk Assessment

5.1 Residues of Concern Summary and Rationale

Tolerances are established for residues of naled (1,2-dibromo-2,2-dichloroethyl dimethyl phosphate) and its conversion product DDVP (2,2-dichlorovinyl dimethyl phosphate), calculated as naled equivalents in/on raw agricultural commodities. Tolerances range from 0.5 ppm in almonds and other RACs to 10 ppm in grass and legume forage. Adequate enforcement methods are available for the determination of the regulated compounds in/on plant commodities. There are no naled tolerances for livestock commodities.

The qualitative nature of the residue in plants is adequately understood. Naled is generally considered to be non-systemic based on studies with a variety of plants including cucumbers, cotton and Swiss chard. Metabolism studies with oranges and tomato processed fractions have also been conducted to investigate the nature and magnitude of organic brominated components of the residue derived from naled per se or from its bromine-containing impurities. These studies indicated that the only residues of organic bromine compounds are parent naled, and metabolite bromodichloroacetaldehyde (BDCA), both of which are rapidly debrominated by sulfhydryl compounds or by hydrolysis.

The residues of concern in plants, livestock commodities, and drinking water for risk assessment are parent naled and DDVP. The residues of concern in plants and livestock commodities for tolerance enforcement are also naled (parent) and DDVP.

Table 5.1.4 Compounds Included in the Risk Assessment and Tolerance Expression.

Matrix		Residues included in Risk Assessment*	Residues included in Tolerance Expression
Plant	Primary Crop	Naled, DDVP	Naled and DDVP
Livestock	Ruminant	Naled, DDVP	Naled and DDVP
	Poultry	Naled, DDVP	Naled and DDVP
Drinking Water		Naled, DDVP	NA

*A separate risk assessment is being conducted for DDVP.

[7] See https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2004-0109-0080 for the final first list of chemicals

[8] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.

[9] http://www.epa.gov/endo/

5.2 Food Residue Profile

Livestock tolerances were removed from 40 CFR 180 based on section 180.6(a)(3), i.e., no expectation of finite residues in these commodities (Herndon, G., 03/25/2002, D281439).

The requirements for magnitude of the residue in plants are fulfilled. Adequate field trial data depicting the residues of naled and DDVP following treatments according to the maximum registered use patterns have been submitted for these commodities. Available processing study data has shown that residues do not concentrate in processed commodities (citrus oil, etc.). The requirements for magnitude of the residue in wide area and general outdoor treatments for area pest (mosquito and fly) control are also fulfilled. Confined rotational crop studies have concluded no rotational crop tolerances or plant-back intervals for naled are needed.

USDA Pesticide Data Program (PDP) data for naled are only available for a limited number of commodities from 2008 to 2014 (2-5 commodities per year). There were a total of 11,380 samples analyzed for naled, and only one strawberry sample had detectable residues. HED is confident that this assessment reflects a conservative risk assessment. In some cases, the PDP data were not used due to the high limit of detection (LOD - 0.02 ppm). In some cases, HED used field trial data and was then able to apply rinsing factors that are not used with PDP data, since the samples are rinsed prior to analysis.

Adequate residue chemistry data are available for the draft risk assessment and finite residues of naled are not expected for most treated crops.

5.3 Water Residue Profile

Drinking water residues were provided by the Environmental Fate and Effects Division (EFED) for the dietary risk assessment for naled (Negrón-Encarnación, I. & Wente, S., 06/17/2020, D433560). The estimated drinking water concentrations (EDWCs) for naled residues in surface water were generated using the Pesticide Water Calculator (PWC version 1.52). Since EDWCs from surface water modeling are much higher than those estimated from this screening level approach for groundwater, no further groundwater estimates were derived.

For the acute and steady state assessments, the entire 30-year distribution of estimated daily concentrations was incorporated into the DEEM-FCID probabilistic analyses for the scenarios specified in Table 5.3.1. For steady state, the daily time series was recalculated using the 21-day forward rolling averages. In the 21-day rolling average distributions, the first data point is the average of days 1-21, the second data point is the average of days 2-22, the third data point is the average of days 3-23, etc.

Naled has a public health (mosquito control) use with a rate of 0.10 pounds per acre (0.12 kilograms per hectare). The modeling for this use was conducted using the Florida turf PRZM scenario. This scenario was chosen because naled is commonly used in Florida to control mosquito populations.

Table 5.3.1 Recommended EDWCs for Naled (ppb) Agricultural Uses							
Use	**PWC Scenario**	**Application Date**	**Annual Rate lbs a.i./A, App type**	**1-in-10 year EDWC, µg/L**			**30-year Ave**
				1-day	**21-days**	**365-days**	
NALED							
Citrus	FLcitrusSTD[1]	76 DSE*	1.9x5, ground	**140**	**9.6**	**0.68**	**0.29**
			0.9x5, ground (Florida spec.)	67	4.6	0.32	0.14
	CAcitrus_WirrigSTD	20 DSE	1.9x5, ground	34	2.7	0.18	0.069
Cotton	TXcottonOP	62 DSE	0.9x5, aerial	**82**	**6.7**	**0.41**	**0.15**
Pepper	FLpeppersSTD[2]	48 DSE	1.9x3, aerial	**109**	**8.6**	**0.49**	**0.22**
		48 DSE	0.9x3, aerial (Florida spec.)	52	4.1	0.24	0.11
	CAfruit_WirrigSTD	27 DSE	1.9x3, aerial	13	1.4	0.084	0.043

***DSE (days since emergence**

[1] Most of the citrus production in the USA occurs in Florida and California while 5 % is grown in Texas and Arizona (2019 USDA Citrus Summary).

[2] Bell Peppers are mainly produced in Florida and California but also in Georgia, Michigan, New Jersey, New York, North Carolina, Ohio and Pennsylvania (2018 USDA Vegetables Summary). Chilli peppers (*i.e.* all peppers excluding bell peppers) are mainly produced in California and New Mexico but also in Arizona and Texas. The FL pepper scenario may be representative of some of these states.

Table 5.3.2. Recommended EDWCs for Naled (ppb) Mosquitocide Uses									
Use	**App. Rate**	**Number of Apps.**	**PRZM Scenario**	**Chemical**	**Drift Assumption**	**Peak**	**21-Day**	**Chronic**	**Cancer**
Mosquito Control	0.1	50	FL Citrus	Naled	100%	3.1	1.1	0.46	0.46

5.4 Dietary Risk Assessment

Acute and steady-state dietary [food and drinking water both from agricultural and mosquito control uses] exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 3.16. This software uses 2003-2008 food consumption data from the U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA). The analyses include the following updates to the previous risk

assessment: (1) new toxicological endpoints; and (2) new drinking water estimates provided by the Environmental Fate and Effects Division (EFED).

DDVP, a registered organophosphate insecticide, is a metabolite of naled. A preliminary risk assessment for DDVP, which encompassed exposure to DDVP from registered uses as well as DDVP derived from naled and trichlorfon use, was completed as a separate action, and addresses dietary exposure concerns for this metabolite from all sources (Camp, J. & Morton, T., 06/17/2020, D435619). A summary of the results of the acute and steady state dietary exposures and risks for DDVP from the use of naled are also presented in Section 5.4.3.

5.4.1 Description of Residue Data Used in Dietary Assessment

Probabilistic assessments were performed for the acute and steady-state analyses. Foods were classified as blended, partially blended, or non-blended based on Dietary Exposure Science Advisory Committee (DE SAC) guidance. The acute and steady-state analysis assumed a distribution of residues based on field trial residue data and limited monitoring data from the USDA Pesticide Data Program (PDP) (for orange juice, strawberries, and grape juice) for non-blended and partially blended commodities. For blended commodities, the mean field trial values were used as a point estimate. When field trial data were used, a value of ½ limit of quantification (LOQ) was used for samples that contained less than LOQ residues. Residue distribution files (RDFs) were also created for the commodities for which PDP data were used in accordance with guidance provided in HED SOP 99.6. [Note: Much more data are available in the dietary memo to evaluate DDVP exposures from all sources (Camp, J. & Morton, T. 06/17/2020, D435619)].

Anticipated residues (ARs) for the acute and steady-state analysis are based on a probabilistic analysis using field trial data, and using rinsing, cooking, or other reduction factors. For the purpose of incorporating the full range of residue data in the probabilistic assessment, RDFs were prepared from the available field trial data, or from the USDA PDP data for grape juice, orange juice, and fresh strawberries. The RDFs for these commodities were based on the maximum percent crop treated estimates or were based on 100% crop treated, if percent crop treated information was not available.

Details concerning data translation, commodity blending classifications, processing information, the treatment of mosquito control data, etc., can be found in the dietary exposure memo prepared in support of this draft risk assessment (Camp, J. & Morton, T., 06/17/2020, D435620). Data reflecting residue decline are available. These data include common practices such as rinsing, peeling, and cooking that could reduce dietary exposure to naled. These data were used in the dietary risk assessments. A reduction factor of 0.1X (average of the celery/collard/snap bean studies) was applied to all cooked forms of naled, except for a few commodities, where commodity-specific factors were available, e.g., the 0.17 cooking factor was used for celery. Rinsing factors were not applied to PDP data, since these data already reflect rinsing before analysis.

5.4.2 Percent Crop Treated Used in Dietary Assessment

The following maximum percent crop treated estimates (BEAD, 09/20/2019) were used in the acute and steady state dietary risk assessments for the following crops that are currently registered for naled: cabbage: <2.5%; cotton: <2.5%; cucumbers: 5%; grapefruit: <2.5%; grape: <2.5%; lemons: <2.5; orange: 5%; peppers: <2.5%; plums/prunes: <2.5%; safflower: 75%; strawberries: 45%; sugar beets: <2.5%; and walnuts: 5%. 100% percent crop treated estimates were assumed if percent crop treated data were not available.

In the acute and steady-state assessments, the mosquito adulticide percent crop treated estimate of 1% was used to modify the adulticide residue values. Residues from the adulticide use were included for all commodities with the exception of livestock commodities and fish.

5.4.3 Acute and Steady State Dietary Risk Assessment

Acute and steady state dietary (food and drinking water) assessments for naled were run for food only from all registered uses and from mosquitocide uses alone, as well as for food and multiple drinking water scenarios. These water scenarios included: citrus, peppers, cotton, and wide area mosquito use. See Tables 5.4.5.1-5.4.5.6 for naled summary results.

The acute risk estimates for naled (food and water) do not exceed HED's level of concern for all population subgroups. Generally, HED is concerned when risk estimates exceed 100% of the population-adjusted dose (aPAD). The acute risk estimate for the general U.S. population for food and water at the 99.9th level of exposure results in a maximum of 39% of the aPAD and the population subgroup with the highest acute dietary risk estimate for this scenario is all infants <1 year old, which uses 100% of the aPAD.

The steady state risk dietary risk estimates (food only) for naled do not exceed HED's level of concern for any population subgroups, including those comprised of infants and children. Generally, HED is concerned when risk estimates exceed 100% of the population-adjusted dose (aPAD).

The steady state risk estimates (food and drinking water) for the general U.S. population results in in exposure estimates up to 200% of the ssPAD and the population subgroup with the highest steady-state dietary risk estimate for this scenario is all infants (<1 year old), which utilize 550% of the ssPAD at the 99.9th percentile of exposure. A significant portion of the risk cup is occupied by drinking water.

The steady state dietary risk estimates for mosquito food and mosquito water for naled do not exceed HED's level of concern for any population subgroups, including those comprised of infants and children.

In addition, DDVP is a residue of concern in both the tolerance and risk assessment for the use of naled. Acute and steady state evaluations were made for DDVP drinking water scenarios for naled agricultural uses. The DDVP acute and steady state drinking water scenarios do not exceed HED's level of concern at the 99.9th percentile of exposure. The worst-case acute and steady

state drinking water only risk estimates were <1% of the PAD for the infants (<1 years old) at the 99.9th percentile. Since the DDVP dietary assessment used USDA Pesticide Data Program information and the source of the DDVP cannot be determined, the dietary exposures to DDVP from all sources (naled, DDVP and trichlorfon) will be addressed in a separate risk assessment. However, the summary results of the acute dietary exposure analysis for DDVP (from use of naled using naled percent crop treated) food and water does not exceed HED's level of concern (<100 % aPAD). The results of the steady state dietary exposure analysis for DDVP (from use of naled using naled percent crop treated) food and water does exceed HED's level of concern (>100 % ssPAD) for multiple population subgroups including children. See Tables 5.4.5.7-5.4.5.9 for DDVP summary results.

5.4.4 Cancer Dietary Risk Assessment

An assessment for cancer was not performed because naled is classified as "Group E: Evidence of non-carcinogenicity for humans".

5.4.5 Summary Tables

Table 5.4.5.1. Summary of Dietary (Food Only) Exposure and Risk for All Registered Uses of Naled.

Population Subgroup	Acute Dietary (99.9 Percentile)		Steady State Dietary (99.9 Percentile)	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% ssPAD*
General U.S. Population	0.000279	8.7	0.000233	39
All Infants (<1 year old)	0.000519	16	0.000362	60
Children 1-2 years old	**0.000686**	**21**	**0.000479**	**80**
Children 3-5 years old	0.000576	18	0.000346	58
Children 6-12 years old	0.000298	9.3	0.000204	34
Youth 13-19 years old	0.000172	5.4	0.000113	19
Adults 20-49 years old	0.000199	6.2	0.000187	31
Adults 50+ years old	0.000290	<1	0.000242	4.0
Females 13-49 years old	0.000201	6.3	0.000157	26

**The values for the highest exposed population for each type of risk assessment is bolded*

Table 5.4.5.2. Summary of Dietary (Food Only) Exposure and Risk for Mosquito Use of Naled.

Population Subgroup	Acute Dietary (99.9 Percentile)		Steady State Dietary (99.9 Percentile)	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% ssPAD*
General U.S. Population	0.000032	1.0	0.000026	4.4
All Infants (<1 year old)	0.000072	2.2	0.000055	9.2
Children 1-2 years old	**0.000132**	**4.1**	**0.000104**	**17**
Children 3-5 years old	0.000091	2.9	0.000073	12
Children 6-12 years old	0.000049	1.5	0.000039	6.5
Youth 13-19 years old	0.000025	<1	0.000020	3.3

Table 5.4.5.2. Summary of Dietary (Food Only) Exposure and Risk for Mosquito Use of Naled.				
Population Subgroup	**Acute Dietary (99.9 Percentile)**		**Steady State Dietary (99.9 Percentile)**	
	Dietary Exposure (mg/kg/day)	**% aPAD***	**Dietary Exposure (mg/kg/day)**	**% ssPAD***
Adults 20-49 years old	0.000022	<1	0.000017	2.8
Adults 50+ years old	0.000023	<1	0.000017	<1
Females 13-49 years old	0.000022	<1	0.000017	2.9

**The values for the highest exposed population for each type of risk assessment is bolded*

Table 5.4.5.3. Summary of Dietary (Food and Citrus Water) Exposure and Risk for Naled.				
Population Subgroup	**Acute Dietary (99.9 Percentile)**		**Steady State Dietary (99.9 Percentile)**	
	Dietary Exposure (mg/kg/day)	**% aPAD***	**Dietary Exposure (mg/kg/day)**	**% ssPAD***
General U.S. Population	0.001241	39	0.001220	200
All Infants (<1 year old)	**0.003224**	**100**	**0.003306**	**550**
Children 1-2 years old	0.001794	56	0.001684	280
Children 3-5 years old	0.001472	46	0.001507	250
Children 6-12 years old	0.001172	37	0.001076	180
Youth 13-19 years old	0.000916	29	0.000873	150
Adults 20-49 years old	0.001228	38	0.001220	200
Adults 50+ years old	0.001196	3.7	0.001212	20
Females 13-49 years old	0.001238	39	0.001212	200

**The values for the highest exposed population for each type of risk assessment is bolded*

Table 5.4.5.4. Summary of Dietary (Food and Peppers Water) Exposure and Risk for Naled.				
Population Subgroup	**Acute Dietary (99.9 Percentile)**		**Steady State Dietary (99.9 Percentile)**	
	Dietary Exposure (mg/kg/day)	**% aPAD***	**Dietary Exposure (mg/kg/day)**	**% ssPAD***
General U.S. Population	0.001028	32	0.000977	160
All Infants (<1 year old)	**0.002751**	**86**	**0.002659**	**440**
Children 1-2 years old	0.001441	45	0.001416	240
Children 3-5 years old	0.001245	39	0.001235	210
Children 6-12 years old	0.000962	30	0.000932	160
Youth 13-19 years old	0.000703	22	0.000706	120
Adults 20-49 years old	0.000985	31	0.000981	160
Adults 50+ years old	0.001028	3.2	0.000962	16
Females 13-49 years old	0.000961	30	0.000964	160

**The values for the highest exposed population for each type of risk assessment is bolded*

Table 5.4.5.5. Summary of Dietary (Food and Cotton Water) Exposure and Risk for Naled.				
Population Subgroup	**Acute Dietary (99.9 Percentile)**		**Steady State Dietary (99.9 Percentile)**	
	Dietary Exposure (mg/kg/day)	**% aPAD***	**Dietary Exposure (mg/kg/day)**	**% ssPAD***
General U.S. Population	0.000635	20	0.000539	90
All Infants (<1 year old)	**0.001570**	**49**	**0.001405**	**230**
Children 1-2 years old	0.001024	32	0.000742	120
Children 3-5 years old	0.000775	24	0.000644	110
Children 6-12 years old	0.000563	18	0.000543	91
Youth 13-19 years old	0.000371	12	0.000361	60
Adults 20-49 years old	0.000582	18	0.000503	84
Adults 50+ years old	0.000656	2.1	0.000543	9.1
Females 13-49 years old	0.000528	17	0.000491	82

**The values for the highest exposed population for each type of risk assessment is bolded*

Table 5.4.5.6. Summary of Dietary (Mosquito Food and Water) Exposure and Risk for Naled.				
Population Subgroup	**Acute Dietary (99.9 Percentile)**		**Steady State Dietary (99.9 Percentile)**	
	Dietary Exposure (mg/kg/day)	**% aPAD***	**Dietary Exposure (mg/kg/day)**	**% ssPAD***
General U.S. Population	0.000276	8.6	0.000129	21
All Infants (<1 year old)	**0.000696**	**22**	**0.000256**	**43**
Children 1-2 years old	0.000421	13	0.000211	35
Children 3-5 years old	0.000323	10	0.000137	23
Children 6-12 years old	0.000252	7.9	0.000111	18
Youth 13-19 years old	0.000230	7.2	0.000096	16
Adults 20-49 years old	0.000238	7.4	0.000091	15
Adults 50+ years old	0.000214	<1	0.000082	1.4
Females 13-49 years old	0.000240	7.5	0.000087	15

**The values for the highest exposed population for each type of risk assessment is bolded*

Summary of DDVP Exposure from the Use of Naled

Table 5.4.5.7. Summary of DDVP Dietary (Food Only) Exposure and Risk From All Registered Uses of Naled.				
Population Subgroup	**Acute Dietary (99.9 Percentile)**		**Steady State Dietary (99.9 Percentile)**	
	Dietary Exposure (mg/kg/day)	**% aPAD***	**Dietary Exposure (mg/kg/day)**	**% ssPAD***
General U.S. Population	0.00071	8.6	0.000055	92
All Infants (<1 year old)	0.000115	14	0.000084	140
Children 1-2 years old	**0.000171**	**21**	**0.000121**	**200**
Children 3-5 years old	0.000126	15	0.000093	160
Children 6-12 years old	0.000081	9.7	0.000059	98
Youth 13-19 years old	0.000045	5.4	0.000034	56
Adults 20-49 years old	0.000038	4.6	0.000027	45
Adults 50+ years old	0.000041	<1	0.000032	5.3

Table 5.4.5.7. Summary of DDVP Dietary (Food Only) Exposure and Risk From All Registered Uses of Naled.				
Population Subgroup	**Acute Dietary (99.9 Percentile)**		**Steady State Dietary (99.9 Percentile)**	
	Dietary Exposure (mg/kg/day)	**% aPAD***	**Dietary Exposure (mg/kg/day)**	**% ssPAD***
Females 13-49 years old	0.000039	4.7	0.000029	49

**The values for the highest exposed population for each type of risk assessment is bolded*

Table 5.4.5.8 Summary of DDVP Dietary (Food and Citrus Water) Exposure and Risk From Naled.				
Population Subgroup	**Acute Dietary (99.9 Percentile)**		**Steady State Dietary (99.9 Percentile)**	
	Dietary Exposure (mg/kg/day)	**% aPAD***	**Dietary Exposure (mg/kg/day)**	**% ssPAD***
General U.S. Population	0.000072	8.6	0.000056	93
All Infants (<1 year old)	0.000113	14	0.000085	140
Children 1-2 years old	**0.000170**	**21**	**0.000122**	**200**
Children 3-5 years old	0.000126	15	0.000094	160
Children 6-12 years old	0.000081	9.7	0.000059	98
Youth 13-19 years old	0.000045	5.4	0.000034	56
Adults 20-49 years old	0.000038	4.6	0.000027	45
Adults 50+ years old	0.000041	4.9	0.000032	5.3
Females 13-49 years old	0.000039	4.7	0.000029	49

**The values for the highest exposed population for each type of risk assessment is bolded*

Table 5.4.5.9 Summary of DDVP Dietary (Food and Peppers Water) Exposure and Risk From Naled.				
Population Subgroup	**Acute Dietary (99.9 Percentile)**		**Steady State Dietary (99.9 Percentile)**	
	Dietary Exposure (mg/kg/day)	**% aPAD***	**Dietary Exposure (mg/kg/day)**	**% ssPAD***
General U.S. Population	0.000071	8.6	0.000056	93
All Infants (<1 year old)	0.000113	14	0.000084	140
Children 1-2 years old	**0.000170**	**20**	**0.000122**	**200**
Children 3-5 years old	0.000126	15	0.000094	160
Children 6-12 years old	0.000081	9.7	0.000059	98
Youth 13-19 years old	0.000045	5.5	0.000034	56
Adults 20-49 years old	0.000038	4.6	0.000027	45
Adults 50+ years old	0.000041	<1	0.000032	5.3
Females 13-49 years old	0.000039	4.7	0.000029	49

**The values for the highest exposed population for each type of risk assessment is bolded*

Table 5.4.5.10 Summary of DDVP Dietary (Mosquito Food and Water) Exposure and Risk From Naled.				
Population Subgroup	Acute Dietary (99.9 Percentile)		Steady State Dietary (99.9 Percentile)	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% ssPAD*
General U.S. Population	0.000071	8.6	0.000056	93
All Infants (<1 year old)	0.000113	14	0.000085	140
Children 1-2 years old	**0.000170**	**20**	**0.000122**	**200**
Children 3-5 years old	0.000126	15	0.000094	160
Children 6-12 years old	0.000081	9.7	0.000059	98
Youth 13-19 years old	0.000045	5.5	0.000034	56
Adults 20-49 years old	0.000038	4.6	0.000027	44
Adults 50+ years old	0.000041	<1	0.000032	5.3
Females 13-49 years old	0.000039	4.7	0.000030	49

**The values for the highest exposed population for each type of risk assessment is bolded*

6.0 Residential Exposure/Risk Characterization

Naled is a restricted use pesticide, therefore products are only available for sale to, and use by, certified applicators or under the supervision of a certified applicator. Furthermore, there are no uses for direct application to residential settings. Therefore, neither residential handler/consumer applicator exposure nor residential post-application exposures are assessed. Consequently, there are no residential use scenarios to be recommended for aggregate exposure.

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. There are no non-dietary residential scenarios for naled that are applicable for aggregate risk assessment as explained in Section 6.0. Therefore, only food and water is included in the acute and steady state aggregate dietary assessments for naled.

7.1 Acute Aggregate Risk

Acute aggregate risk of exposure to naled is composed of exposure to residues in food and drinking water alone. The acute dietary exposure analysis for naled included both food and drinking water; therefore, acute aggregate risk estimates are equivalent to the acute dietary risk estimates, as discussed in detail in Section 5.4.3. Acute dietary aggregate risks are not of concern for all population subgroups.

7.2 Steady State Aggregate Risk

Steady state aggregate risk of exposure to naled is composed of exposure to residues in food and drinking water alone. The steady state dietary exposure analyses for naled included both food and

drinking water scenarios which resulted, in most cases, in risk estimates of concern. Steady state aggregate risk estimates are equivalent to the steady state dietary risk estimates, as discussed in detail in Section 5.4.3. The only steady state dietary exposure scenario which had no dietary risk estimates of concern for all populations was the mosquito food and mosquito water, therefore, steady state aggregate risks for this scenario were also not of concern.

8.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (*e.g.*, children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling onto 50 feet wide lawns coupled with methods employed for residential risk assessments for turf products.

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.[10] Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

In order to evaluate the drift potential and associated risks, an approach based on drift modeling coupled with techniques used to evaluate residential uses of pesticides was utilized. Essentially, a residential turf assessment based on exposure to deposited residues has been completed to address drift from the agricultural applications of naled. In the spray drift scenario, the deposited residue value was determined based on the amount of spray drift that may occur at varying distances from the edge of the treated field using the AgDrift (v2.1.1) model and the *Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift Policy*. Once the deposited residue values were determined, the remainder of the spray drift assessment was based on the algorithms and input values specified in the recently revised (2012) *Standard Operating Procedures for Residential Risk Assessment (SOPs)*. Additionally, the TTR data described below in Section 9 were also utilized, with each study location's dataset being assigned to particular crops based on the variations in naled application rates and where the crops are predominantly grown:

Naled Application Rate	Example Crop(s)/Group	TTR Study Used
2.1 lb ai/acre	Safflower	California
1.9 lb ai/acre	Citrus, Peppers, Cole crops	Florida
1.4 lb ai/acre	Row crops (e.g. cotton, beans)	Mississippi

[10] This approach is consistent with the requirements of the EPA's Worker Protection Standard.

Naled Application Rate	Example Crop(s)/Group	TTR Study Used
0.9 lb ai/acre	Grapes, Berries, Melons	California

A screening approach was developed based on the use of the AgDrift model in situations where specific label guidance that defines application parameters is not available.[11] AgDrift is appropriate for use only when applications are made by aircraft, airblast orchard sprayers, and groundboom sprayers. When AgDrift was developed, a series of screening values (i.e., the Tier 1 option) were incorporated into the model and represent each equipment type and use under varied conditions. The screening options specifically recommended in this methodology were selected because they are plausible and represent a reasonable upper bound level of drift for common application methods in agriculture. These screening options are consistent with how spray drift is considered in a number of ecological risk assessments and in the process used to develop drinking water concentrations used for risk assessment. In all cases, each scenario is to be evaluated unless it is not plausible based on the anticipated use pattern (e.g., herbicides are not typically applied to tree canopies) or specific label prohibitions (e.g., aerial applications are not allowed). Section 8.1 provides the screening level drift related risk estimates.

In many cases, risks are of concern when the screening level estimates for spray drift are used as the basis for the analysis. In order to account for this issue and to provide additional risk management options, additional spray drift deposition fractions were also considered. These drift estimates represent plausible options for pesticide labels.

8.1 Combined Risk Estimates from Lawn Deposition Adjacent to Applications

The spray drift risk estimates are based on an estimated deposited residue concentration as a result of the screening level agricultural application scenarios. Naled is used on a variety of agricultural crops and can be applied via airblast, groundboom, and aerial equipment. The recommended drift scenario screening level options are listed below:

- **Groundboom applications** are based on the AgDrift option for high boom height and using very fine to fine spray type using the 90th percentile results.
- **Orchard airblast applications** are based on the AgDrift option for Sparse (Young/Dormant) tree canopies.
- **Aerial applications** are based on the use of AgDrift Tier 1 aerial option for a fine to medium spray type and a series of other parameters which will be described in more detail below (e.g., wind vector assumed to be 10 mph in a downwind direction for entire application/drift event).

In addition to the screening level spray drift scenarios described above, additional results are provided which represent viable drift reduction technologies (DRTs) that represent potential risk management options. In particular, different spray qualities have been considered as well as the

[11] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment#AgDrift

impact of other application conditions (e.g., boom height, use of a helicopter instead of fixed wing aircraft, "normal" crop canopy conditions versus "sparse").

Exposures were considered for 50 feet wide lawns where the nearest side of the property was directly adjoining the treated field (at field edge) and at varied distances up to 300 feet downwind of a treated field (300 feet is the maximum distance available in the AgDrift model). As previously described, naled degrades to DDVP and they share a common mechanism of toxicity (i.e., AChE inhibition), thus risk estimates are presented which represent exposures to combined residues of both naled and DDVP, accounting for both the differential in toxicological PODs (see Section 4.0 above) and differential in magnitude and proportions of the deposited residue. As described in more detail in Section 9 below, proportions of residue consisting of naled and DDVP are determined based on the TTR data conducted in 2017.

For adults, dermal risk estimates are characterized in comparison to a LOC of 1000. For children (1< 2 years old) dermal and incidental oral risk estimates were combined because they share a common toxicity endpoint for each route of exposure (i.e., AChE inhibition) and are characterized in comparison to a LOC of 1000. Combined risk estimates follow the formula below. Consistent with spray drift exposure methodologies, risks in this section are characterized in the context of steady state toxicity for naled/DDVP.

$$\textbf{Combined MOE}_{Adult/Child} = \frac{1}{\frac{1}{\left(\frac{Naled\ PoD_{Route\ A}}{Naled\ Dose_{Route\ A}}\right)} + \frac{1}{\left(\frac{DDVP\ PoD_{Route\ A}}{DDVP\ Dose_{Route\ A}}\right)} + \frac{1}{\left(\frac{Naled\ PoD_{Route\ B}}{Naled\ Dose_{Route\ B}}\right)} + \frac{1}{\left(\frac{DDVP\ PoD_{Route\ B}}{DDVP\ Dose_{Route\ B}}\right)} + etc.}$$

For adults and children (1<2), the distance downwind where risk estimates are not of concern varies widely depending on the application equipment, crop target, and spray type/nozzle configuration. This demonstrates the impact of various application conditions that drift less and reduce risk including nozzle types with coarser sprays, lowering boom height for groundboom sprayers, or applications to normal/typical crop canopies with airblast sprayers.

Table 8.1. Summary of Spray Drift Buffers by Agricultural Crop for Naled.

Crop	App. rate (lb ai/A)	Adult Buffer Summary (Dermal)			Children 1 < 2 years Buffer Summary (Dermal + Incidental Oral)		
		Buffers Necessary to reach MOE ≥ LOC (Feet)			Buffers Necessary to reach MOE ≥ LOC (Feet)		
		Aerial	Groundboom	Airblast	Aerial	Groundboom	Airblast
Safflower	2.1	> 300 feet	• 200 ft (Low Boom, Fine to Medium/Coarse) • > 300 ft (High Boom Very fine to Fine)	Not applicable	> 300 ft	> 300 ft	Not applicable
Citrus, Peppers, Cole crops	1.9		• 50 ft (Low Boom, Fine to Medium/Coarse) • > 300 ft (High Boom Very fine to Fine)	• 0 ft (Normal) • 100 ft (Sparse)		• 200 ft (Low Boom, Fine to Medium/Coarse) • > 300 ft (High Boom Very fine to Fine)	• 10 ft (Normal) • 250 ft (Dense)

Table 8.1. Summary of Spray Drift Buffers by Agricultural Crop for Naled.							
Crop	App. rate (lb ai/A)	Adult Buffer Summary (Dermal)			Children 1 < 2 years Buffer Summary (Dermal + Incidental Oral)		
		Buffers Necessary to reach MOE ≥ LOC (Feet)			Buffers Necessary to reach MOE ≥ LOC (Feet)		
		Aerial	Groundboom	Airblast	Aerial	Groundboom	Airblast
Row crops (e.g. cotton, beans)	1.4		• 50 ft (Low Boom, Fine to Medium/Coarse) • 300 ft (High Boom Very fine to Fine)	Not applicable		• 200 ft (Low Boom, Fine to Medium/Coarse) • >300 ft (High Boom Very fine to Fine)	Not applicable
Grapes, Berries, Melons	0.9		• 75 ft (Low Boom, Fine to Medium/Coarse) • > 300 ft (High Boom Very fine to Fine)	• 0 ft (Normal) • 125 ft (Sparse)		> 300 ft	• 25 ft (Normal) • 300 ft (Dense)

9.0 Non-Occupational Bystander Post-Application Exposure and Risk Estimates

9.1 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010[12]. The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis[13]. During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for naled.

In addition to the volatilization screening tool, the Agency has developed a preliminary bystander volatilization inhalation exposure assessment for naled utilizing currently available inhalation toxicity and air monitoring data. Air monitoring for naled and/or DDVP are available from the California Department of Pesticide Regulation (CDPR) and the California Air Resources Board (CARB). Standard ambient air monitoring results for naled/DDVP are available from Lompoc, CA in May-August, 2000, and in Tulare, CA in May/June 1991 and application site air monitoring is available from Tulare, CA in June 1995.

Ambient air monitoring typically is focused on characterizing the airborne pesticide levels within a localized airshed or community structure of some definition (e.g., city, township, or municipality). This type of monitoring effort also can be focused on capturing chronic background levels or other temporal characteristics of interest such as focusing on seasonal

[12] http://www regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037
[13] http://www regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219

pesticide use patterns. Typically, samples are generally taken for 24 consecutive hours and collected at the same site over an extended period of time (e.g., several weeks or months). In contrast to application site air monitoring, information on the precise timing and location of pesticide applications are rarely collected in ambient air monitoring studies. However, this does not mean that an application did not occur near an ambient sampler during the monitoring period.

Application site air monitoring (i.e., also known as field volatility) refers to the collection of air samples around the edges of a treated field during and after a pesticide application. Samples are generally collected for short intervals (e.g., < 8 hours), for at least the first day or two after application with subsequent samples increasing in duration. In this type of study, it is typically known when an application occurred, the equipment used for the application, and the application rate. Application site monitoring data represents an exposure to vapors at or near the field edge resulting from an application.

A summary of the available CDPR and CARB studies is provided below.

- Lompoc, CA 2000 Ambient Air Monitoring (CDPR)
  http://www.cdpr.ca.gov/docs/specproj/lompoc/exec_sum_march2003.pdf
  - Ambient air monitoring of 22 pesticides and five oxygen analog breakdown products (including naled) simultaneously during the peak use period for most of the pesticides, between May 31 and August 3, 2000.
  - CDPR collected 24-hour samples, four consecutive days per week at each of four monitoring locations.
  - Four sampling sites were located within the city limits of Lompoc, one each in the northwest, central-west, southwest, and near the center of Lompoc. These sites plus an additional site on the northeast side of Lompoc were used.
  - Samplers at all locations were on rooftops to ensure the security of the samples.
  - CDPR maintains a database of all agricultural pesticide applications in California, including date applied, amount applied, and application location.
  - Of the 31 pesticides or breakdown products monitored, DPR detected 27 of them in one or more of the 451 samples collected and analyzed.
  - All results for naled were characterized as "trace" detections, with results as follows based on the limit of quantitation (LOQ)
    - Highest one-day air concentration for naled = 2.9 ng/m^3
    - Highest 14-day air concentration for naled = 2.2 ng/m^3
    - Highest 10-week air concentration for naled = 1.08 ng/m^3

- Tulare County, CA 1991 Ambient Air Monitoring (CDPR)
  https://www.arb.ca.gov/research/apr/past/a032-094a.pdf
  - Ambient air monitoring was conducted in May and June of 1991.
  - Samples for ambient air monitoring are collected over 24-hour periods, four samples per week for four to eight weeks.
  - Five monitoring sites (schools, field stations).
  - Monitoring was intended to coincide with expected naled applications to orange groves.
  - Monitored naled and DDVP

  - 80 total samples for each (16 at each site), approximately 75% < LOQ
    - 11 of 80 naled samples > LOQ (0.04 ug/m3)
    - 14 of 80 DDVP samples > LOQ (0.02 ug/m3)
  - The monitoring site that served as an urban background site located away from any expected applications (Visalia, CA) had detections of both naled and DDVP.

- Tulare County, CA 1995 Application Site Air Monitoring (CARB) http://www.cdpr.ca.gov/docs/emon/pubs/tac/tacpdfs/nalapsi.pdf
  - Air monitoring was conducted at a 20-acre orange grove before, during, and 72 hours after an application of naled from June 5-9, 1995.
  - Naled was applied at a rate of 1 pint product per acre (equivalent to 0.94 lb naled/acre)
  - Five samplers were set up around the perimeter of the application site
  - Analysis of samplers conducted for both naled and DDVP
  - LOQ = 0.03 ug/sample for both naled and DDVP
  - The breakdown of samples was as follows:
    - During application: 5, 4-hour samples
    - Immediately post-application: 5, 2 hour samples
    - 2 hours post-application: 5, 3-hour samples
    - 5 hours post-application: 5, 3-hour samples
    - 8 hours post-application: 5, 11.5-hour samples
    - 24 hours post-application: 5, 24-hour samples
    - 48 hours post-application: 5, 24 hour samples

Given that neither Tulare (1991) nor Lompoc (2000) were known to reflect air concentrations as a direct result of an application of naled, no consideration was given as to the necessity to adjust the air concentration results to consider contemporary application parameters such as application rates. And, in the case of Tulare (1995), whose air concentrations were a direct result of an application of naled, no adjustments were made based on the application rate as the rate in the study (0.94 lb ai/acre) was considered sufficiently representative of the range of contemporary agricultural application rates of naled (0.6 to 2.1 lb ai/acre).

The bystander volatilization inhalation exposure assessment for naled compares the maximum naled and DDVP air concentrations detected in each of the monitoring studies to the acute HEC for residential bystanders. This comparison was done to represent a potential resident who lives next to a treated field and may be exposed to the peak concentration of naled or DDVP resulting from naled applications volatilizing from a treated field. In addition, various average air concentrations from each study were compared to the steady-state HECs for residential bystanders, for characterization of potential steady state toxicity.

Combined risks are presented since naled and DDVP share a common toxicological endpoint (AChE inhibition). Acute inhalation risk estimates are presented as MOEs since the LOCs are the same (e.g., see Section 8.1) whereas the LOCs for each chemical are different for steady-state toxicity and the aggregated risk index (ARI) approach was used. The target ARI is 1; therefore, ARIs of less than 1 indicate risk estimates of concern. The aggregate risk index (ARI) was calculated as follows:

$$ARI = \frac{1}{\frac{Naled\ LOC_{Inhalation}}{\left(\frac{Naled\ PoD_{Inhalation}}{Naled\ Dose_{Inhalation}}\right)} + \frac{DDVP\ LOC_{Inhalation}}{\left(\frac{DDVP\ PoD_{Inhalation}}{DDVP\ Dose_{Inhalation}}\right)}}$$

Table 9.1-1 provides risk estimates representing both adults and children based on the air concentrations from the ambient air monitoring studies. None of the air concentrations resulted in acute risks of concern; however, some average air concentrations resulted in steady-state risk estimates of concern (ARI < 1); the 3000-fold uncertainty factors for DDVP inhalation toxicity are a significant factor in these risk estimates.

These include results from the Tulare (1995) samples taken up to 72 hours around the perimeter of a treated field – sampling beyond 72 hours might have shown reduced levels and be more appropriate for a steady-state exposure estimate. For example, in that same study, "background" samples taken prior to application did not yield any detectable residues and steady-state risk estimates based on ½ LOQ were not of concern. Similarly, results from Lompoc (2000) where all samples were non-detects, did not result in steady-state risk estimates of concern. However, results from Tulare (1991) resulted in steady-state risk estimates of concern, despite non-detections comprising approximately 75% of all samples. Unless otherwise noted, risk estimates for concentrations < LOQ were based on assuming air concentrations at ½ LOQ.

Table 9.1-1 Summary of Air Monitoring Results for Non-Occupational Ambient/Bystander Risk Assessment

Monitoring Type	Location/Year	Sampling Time/Result Presentation	Chemical	Concentration (ng/m3)		Risk Characterization: Acute MOE[1] (LOC_{Naled}=300) (LOC_{DDVP}=300)	Risk Characterization: Acute Combined MOE[2] (LOC = 300)	Risk Characterization: Steady State MOE[1] (LOC_{Naled}=300) (LOC_{DDVP}=3000)	Risk Characterization: Steady State ARI[2] (LOC = 1)
Ambient	Lompoc, CA 2000 (24-hour samples at 4 sites for 8 weeks)	1-day maximum	Naled only	All values characterized as "trace" detections (risk estimates based on the full LOQ)	2.9	9,000,000	-- (no DDVP measured)	NA	-- (no DDVP measured)
		14-day average			2.2	-- (not applicable for acute risk estimation)		68,000	
		10-week			1.08			138,000	
Ambient	Tulare, CA 1991 (24-hour samples at 5 sites for 4 weeks)	Maximum (across all sites and days)	Naled	77		335,000	53,000	-- (not applicable for steady state risk estimation)	
			DDVP	59		63,000			
		Average of all samples[3]	Naled	25 (based on 69 of 80 samples < LOQ)		-- (not applicable for acute risk estimation)		5900	0.9
			DDVP	13 (based on 66 of 80 samples < LOQ)				2800	
Application	Tulare, CA 1995	Maximum (across all samplers and days)	Naled	6300 (4-hour sample, during application)		4100	2000	-- (not applicable for steady state risk estimation)	
			DDVP	994 (24-hour sample, 1-day post-application)		3700			
		24-hour time-weighted average, 48-72 hours after application	Naled	136		-- (not applicable for acute risk estimation)		1100	0.11
			DDVP	111				340	
		Pre-application samples (11-hour samples) – all non-detects[4]	Naled	1.5		-- (not applicable for acute risk estimation)		99,000	8
			DDVP	1.5				25,000	

1. Acute or Steady-state MOE = Acute or Steady-state HEC (ng/m3) / Study air concentration (ng/m^3). See Section 4.0 for HECs.

2. Combined MOE = $1/((1/MOE_{Naled}) + (1/MOE_{DDVP}))$; ARI = $1/[(LOC_{Naled}/MOE_{Naled})+(LOC_{DDVP}/MOE_{DDVP})]$
3. Report only presents averages for samples > LOQ (0.04 ug/m^3 for naled and 0.02 ug/m^3 for DDVP). Results shown in table account for 11 and 14 of 80 samples < LOQ for naled and DDVP respectively. For samples < LOQ (40 ng/m^3 for naled, 20 ng/m^3 for DDVP), ½ LOQ was assumed. Example calculation for naled: average of (11) samples > LOQ from report = 59 ng/m^3. Average presented in this table, accounting for samples < LOQ: [(59 ug/m^3 * 11) + (20 ng/m^3 * 69)] / 80 = 25 ng/m^3.
4. Values based on ½ the LOQ. The LOQ for both naled and DDVP was 0.03 ug/sample. Each pre-application sample collected a volume of 10 m^3 of air. Thus, 0.03 ug/sample ÷ 10 m^3/sample = 0.003 ug/m^3. ½ LOQ = 0.003 ug/m^3 / 2 = 0.0015 ug/m^3 or 1.5 ng/m^3.

Some of the limitations and considerations that should be considered in the interpretation of these results include:

- Most of the data utilized in this preliminary assessment are 24-hour air samples. When these data are used, an assumption is made that an individual is exposed to the same air concentration for 24-hours every day. However, this is not always the case as real world time-activity data indicate that many parts of the population move from site to site on a daily basis (e.g., go to work and back).

- This assessment is only representative of outdoor concentrations (i.e., the exposure and risk estimates assume an individual is outdoors all the time). It does not take into account potential effects of air conditioning systems and similar air filtration systems which could potentially reduce air concentrations of naled/DDVP indoors. The Agency believes that indoor concentrations will be at worst equivalent to outdoor concentrations and may potentially be lower.

- All data used for this analysis were conducted in California. Therefore, the results based on the limited available air monitoring data were used to represent the rest of the country due to a lack of adequate information for any other region. It is unclear what potential impacts this extrapolation might have on the risk assessment. Factors such as meteorology and cultural practices may impact the overall amounts of naled/DDVP that volatilize from a treated field as well as the rate at which it volatilizes.

9.2 Wide Area Public Pest Control Post-Application Exposure and Risk Estimates

Naled can be used as an aerial and ground-based ultra-low volume (ULV) mosquito adulticide and other wide area public pest control applications made in residential areas or other areas frequented by the general public. Two products, Dibrom® Concentrate (EPA Registration No. 5481-480; 87.4% naled) and Trumpet® EC (EPA Registration No. 5481-481; 78% naled), are currently registered for wide area public pest control aerial and ground-based ULV treatments with application rates ranging from 0.05 to 0.1 lb ai/A for aerial applications and 0.02 to 0.1 lb ai/A for ground applications. In a February 2017 meeting with the Agency, the American Mosquito Control Association (AMCA) indicated that ground applications of naled, though registered and permitted on product labels, are very rare due to corrosivity to the application equipment and surrounding vehicles.

As a result of these uses, there is the potential for post-application dermal (adults and children) and incidental oral exposures (children) as a result of contact with settled residues on lawns/turfgrass and potential for inhalation exposures to unsettled airborne aerosols for both adults and children. Note: Naled mosquitocide applications are distributed into the air in a manner so that the active ingredient remains aloft for a contact kill. These applications are not intended for direct application onto turf as is typical for residential post-application assessment of high contact activities on treated turf with use of the 2012 Residential SOPs. Instead, post-application exposures are assumed to occur to an adult or child bystander who is exposed indirectly from airborne naled, or from the settling of naled onto residential turf following the

mosquitocide application. These assessments are conducted using the methodologies and inputs of the 2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment: Lawns/Turf SOP coupled with:

1) empirical data relating to residue deposition (the fraction of the application rate expected to deposit on the ground) following ground-based application;
2) a Well Mixed Box (WMB) Model approach (based on the Residential SOPs for outdoor yard foggers and space sprays) for determination of the airborne concentration of a.i. following ground-based applications;
3) the AgDISP model (v8.2.6) for estimation of airborne concentrations and residue deposition following aerial applications; and,
4) chemical-specific turf transferable residue (TTR) data, measuring both naled and DDVP in three locations in the U.S. (California, Mississippi, and Florida) following experimental applications of a naled mosquitocide.

The representative lifestages selected for this assessment – adults and children 1<2 years old – are based on an analysis provided in the 2012 Residential SOPs. While not the only lifestages potentially exposed for these post-application scenarios, the lifestages that are included in the quantitative assessment are health protective for the exposures and risk estimates for all who are potentially exposed.

9.2.1 Post-Application Exposure Data and Assumptions

Exposure Duration: According to the Dibrom® Concentrate and Trumpet® EC labels, aerial and ground applications are allowed every 7 days at the maximum application rate. Based on this use pattern and anticipated airborne residue and surface deposition profile, post-application inhalation exposures following aerial and ground-based ULV applications are expected to only be acute in nature. In order to be efficacious the product must remain in the air following treatment; however, it is expected that within several hours of treatment, airborne residues will have drifted, dispersed, and/or settled out. Thus, inhalation exposures and risks estimated for aerial and ground applications are representative of airborne concentrations of naled and DDVP immediately following treatment. Additionally, based on the extremely rapid dissipation of both naled and DDVP following deposition on turf (see descriptions of TTR data below), and the unlikely situation that individuals will be exposed to new mosquitocide applications every day, dermal and incidental oral exposures are also considered to be acute in nature.

Application Rate: The maximum labeled application rate for aerial and ground applications of the Dibrom® Concentrate and Trumpet® EC products, 0.10 lb ai/A, serves as the primary input for the risk assessment. However, risk estimates are also shown for lower rates (e.g., 0.075 lb ai/A and 0.05 lb ai/A) also used by mosquito control operations. Though once per week applications are considered typical, two applications on successive nights in high pest pressure situations were considered as well.

Modeling Residues in Air and Surface Deposition – Ground-based ULV: In the study conducted by Moore *et al.,* [*Downwind Drift and Deposition of Malathion on Human Targets From Ground Ultra-Low Volume Mosquito Sprays*: J.C. Moore, J.C. Dukes, J.R. Clark, J. Malone, C.F.

Hallmon, and P.G. Hester; Journal of the American Mosquito Control Association; Vol. 9, No. 2 (June, 1993)] both human exposure and deposition was quantified over 5 separate application events. A 91 percent formulation of malathion was applied in April and May of 1989 in the early evening (a time of day for relative atmospheric stability). A Leco HD ULV cold aerosol generator (Lowndes Engineering Company, Valdosta Georgia) was used to make each application. The application parameters included a fluid flow rate of 4.3 fluid ounces per minute, a vehicle ground speed of 10 mph, and a nominal application rate of 0.05 lb ai/acre (i.e., equates to a deposition rate of 0.51 $\mu g/cm^2$). Deposition was monitored at three locations downwind from the treatment area (i.e., 15.2 m, 30.4 m, and 91.2 m). For the events considered in the deposition calculations, "average amounts of malathion deposited on ground level at 15.2, 30.4, and 91.2 m were not significantly different." The percentage of the application rate reported to have deposited ranged from 1 to 14 percent. The mean deposition value for all measurements was 4.3 percent (n=35, CV=98).

In the study conducted by Tietze *et al.,* [*Mass Recovery of Malathion in Simulated Open Field Mosquito Adulticide Tests*: N.S. Tietze, P.G. Hester, and K.R. Shaffer; Archives of Environmental Contamination and Toxicology; 26: 473-477 (1994)] only deposition was quantified over 6 separate application events (i.e., one event was not included in deposition calculations "due to negative air stability"). The application parameters were similar to that used by Moore *et al*. A 95 percent formulation of malathion was applied from May to August of 1993. A Leco 1600 ULV cold aerosol generator (Lowndes Engineering Company, Valdosta Georgia) was also used to make each application. The application parameters included a fluid flow rate of 4.3 fluid ounces per minute, a vehicle ground speed of 10 mph, and a nominal application rate of 0.057 lb ai/acre (i.e., equates to a deposition rate of 0.58 $\mu g/cm^2$). Deposition was monitored at four locations downwind from the treatment area (i.e., 5 m, 25 m, 100 m and 500 m). For the events considered in the deposition calculations, "malathion mass deposited differed significantly between the 500 m site and the three closer sites (df = 3; F-value = 3.42; $P<0.05$)." The percentage of the application rate reported to have deposited (not including 500 m samples which were much less) ranged up to 5.8 percent. The mean deposition value for all measurements was 3.8 percent.

Additionally, in an analysis from 2013 (Peck, C., 03/28/2013, D407817), the Environmental Fate and Effects Division (EFED) reviewed eight published studies on ground ULV application in which deposition was measured. The studies varied in collection media (i.e., grass clippings and coupons), distance from application or spray head (ranging from 8 meters to 500 meters), and chemical measured (i.e., fenthion, malathion, naled, and permethrin). The analysis included the Moore *et al.,* and Tietze *et al*., studies discussed above. After considering the available data, HED has determined that an off-target deposition rate of 8.7 percent of the application rate may be used by HED to evaluate ground-based ULV applications (i.e., 8.7 percent of the target application rate deposits on turf). This value is the 90 percent upper confidence limit on the mean and is slightly higher than the mean values from all the data points observed in the studies (mean = 7.1%, n= 94). The adjusted application rate was then used to define TTR levels by scaling the available TTR data as appropriate.

In order to calculate airborne concentrations from ULV truck fogger applications, HED used the 2012 Residential SOPs for Outdoor Fogging/Misting Systems, with minimal modification to the

WMB model. The WMB model allows for the estimation of air concentrations in the breathing zones of adults and children for use in calculating the post-application inhalation exposure to individuals residing in areas being treated by ground application of naled. The methodology more accurately accounts for dilution in outdoor air using the WMB model.

Modeling Residues in Air and Surface Deposition – Aerial ULV: Surface deposition and air concentrations from aerial ULV applications were modeled using the AgDISP model (v8.2.6) which is currently recommended for assessment of mosquito adulticide and other wide area public pest control applications. AgDISP predicts the motion of spray material released from aircraft, and determines the amount of application volume that remained aloft and the amount of the resulting droplets deposited on the surfaces in the treatment area, as well as downwind from the treatment area. Deposition and air concentrations are dependent on model application parameters that are defined by the product label including minimum height of release, maximum wind speed, droplet size needed for efficacy, and the number of nozzles on the application equipment. The model also allows for the estimation of air concentrations in the breathing zones of adults and children for use in calculating the post-application inhalation risks to individuals residing in areas being treated by aerial application of naled.

In 2016, repeated aerial ULV applications of naled were used to prevent the transmission of the Zika virus into Southern FL (specifically, Miami-Dade County) resulting in an overall reduction of mosquito populations. The Centers for Disease Control and Prevention (CDC) have the lead on these mosquito control efforts with support from EPA. Under CDC guidance, aerial ULV applications of naled have been used in Southern FL as a part of an integrated mosquito control program in this area which also includes: source reduction; structural barriers; larval mosquitocide control; and community education efforts[14]. HED communicated with CDC relating to the assessment of post-application exposures resulting from these aerial applications via teleconference on 09/20/2016. On this teleconference, CDC described the manner in which FL mosquito control districts have been using naled for Zika transmission prevention. Aerial ULV applications were applied using the Dibrom® Concentrate at the maximum registered application rate, 0.10 lbs ai/A. These applications were conducted 7 days apart under the following conditions: a 300-foot release height; a wind speed of 10 mph; and a 50th percentile volume median diameter (VMD) less than 40 microns (Dv 0.5 < 40 µm). Ground applications of naled were not being conducted as these are not typical for these treatment areas. HED later followed up with the CDC to determine the 90th percentile droplet size, or the Dv 0.9, since this parameter was not outlined in the Dibrom® Concentrate label for a Dv < 40 µm. Per a November 9, 2016 email communication with Janet McAllister of CDC via Susan Jennings of EPA, the Dv 0.9 droplet size was characterized as less than 77 µm. HED has used the above parameters in conjunction with the AgDISP model to estimate post-application risks reflective of the exposures anticipated from naled aerial applications in Southern FL.

On February 23, 2017, HED met with the representatives from the AMCA to discuss naled usage for mosquito control. AMCA described the application equipment used, application parameters, frequency and timing of applications, and, more generally, the need for naled as a critical tool for mosquito control. AMCA indicated that, of the aerial and ground ULV public health application types allowed by naled labeling, the aerial ULV is the principal equipment used. Ground ULV

[14] https://www.cdc.gov/zika/vector/aerial-spraying.html

applications were not supported by any of the mosquito control districts present, despite being a labeled application type, since ground applications of naled can corrode the equipment used and cause harm if residues settle on nearby vehicles following application. Application rates for aerial ULV application ranged between 0.050 lb ai/A and 0.075 lb ai/A, with the majority of AMCA participants indicating that the 0.075 lb ai/A rate was more typically used to ensure efficacy. A Dv < 40 µm droplet size was supported, consistent with the information shared from CDC, although the larger Dv < 60 µm droplet size was needed on occasion dependent upon environmental conditions. AMCA indicated that all aerial ULV applications of naled occurred either at dawn or at dusk when mosquito activity is at its highest. Further, AMCA stressed the importance of maintaining applications on successive days, as is currently allowed by the label, since the entire mosquito population is not expected to be out on a single night and successive day applications ensure maximum kill and resistance control. Although successive applications could occur in a single location, AMCA representatives made clear the need to limit the number of applications to control cost over the course of the mosquito breeding season. Table 9.2.1-1 below presents the range of application parameters indicated by AMCA as reflective of naled usage in their representative mosquito districts.

Table 9.2.1-1. AMCA Application Parameters

App. Rate (lb ai/A)	0.050 lb ai/A, Lee Co. FL; 0.075 lb ai/A, all others
Release Height (feet)	100 – 300
Wind Speed (mph)	4 -10
Droplet size (µm) – DV < 0.5	40
Droplet size (µm) – DV < 0.9	77
Retreatment Interval	1X and 2X per week

The outputs of the AgDISP model (v8.2.6) were used in conjunction with the 2012 Residential SOPs to assess post-application exposures following mosquito adulticide and other wide area public pest control applications. As described previously, in 2016 the EPA communicated with CDC to define the conditions under which naled aerial ULV applications in Southern FL were being conducted: the maximum application rate of 0.1 lbs ai/A; a 300-foot release height; a wind speed of 10 mph; and VMD parameters of Dv 0.5 < 40 µm and Dv 0.9 < 77 µm. Using these parameters with the AgDISP model resulted in the following outputs: the aerial fraction of the application rate applied (0.10 lb ai/A) is 0.31 (i.e., 31% of the application rate is deposited on turf); and the airborne concentration at the breathing height of adults and children of naled 1 hour following aerial application is 0.00747 mg/m^3.

Figures 9.2.1-1 and 9.2.1-2 below present the estimated aerial naled residue fraction deposited on turf, and aerial airborne concentration for the 1 hour following application, respectively, based on parameters described in the Dibrom® Concentrate and Trumpet® EC product labels. Because the resulting fraction of deposition and air concentration are determined by the application parameters, HED has also provided analyses of a range of application parameters allowable by registered labelling.

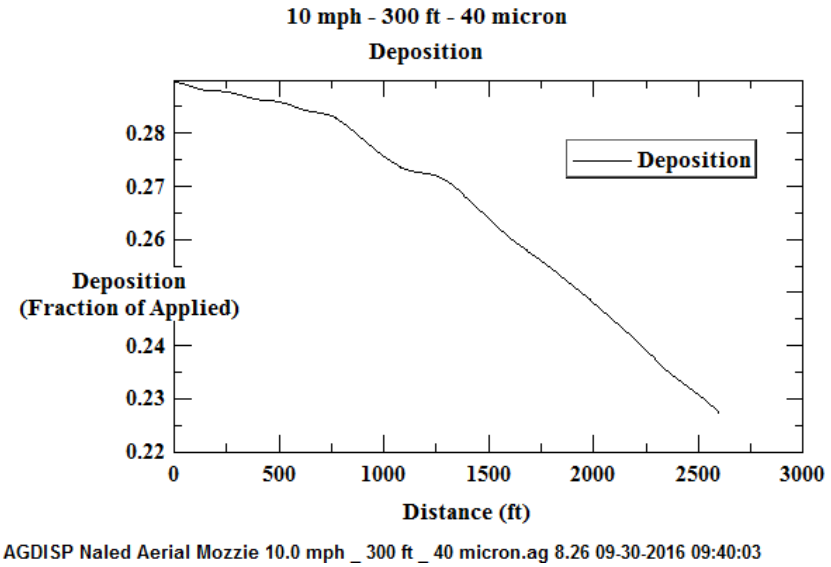


Figure 9.2.1-1. Estimated peak residue deposition downwind from the field edge from aerial treatment at release height of 300 feet (Southern FL Zika transmission prevention parameters). The Distance at 0 feet is equivalent to a swath displacement of 2,822 feet, or the distance at which deposition is the greatest as determined from modeling. Where the fraction of application rate for deposition was determined to be greater than 1, the maximum fraction of 1 will be used for the disposition value.

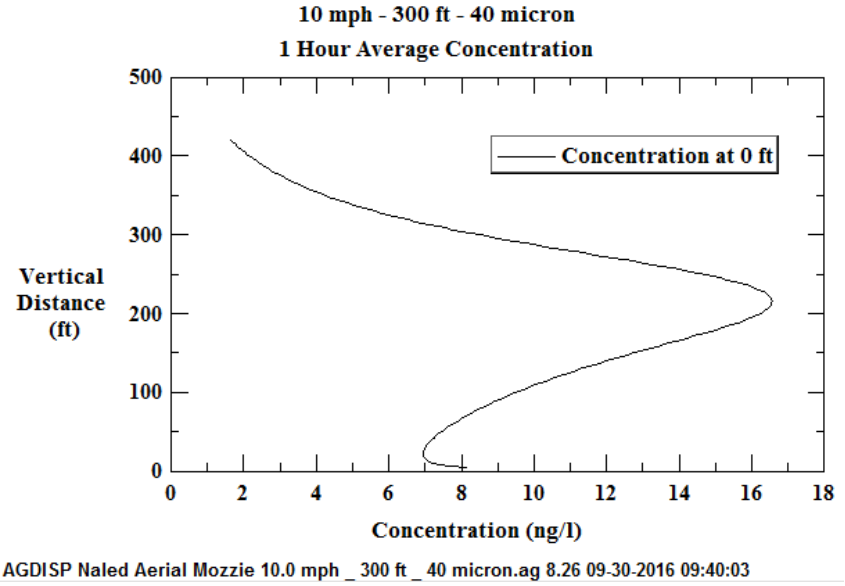


Figure 9.2.1-2. Estimated naled air concentration at the point of peak residue deposition (i.e., swath displacement of 2,822 feet) from aerial treatment at a release height of 300 feet (Southern FL Zika transmission prevention parameters). 7.47 ng/L = 0.00747 mg/m^3 is the concentration at breathing height for adults and children.

Table 9.2.1-2 provides the resulting fractions of application rate for deposition and air concentrations at breathing height resulting from modelling various application conditions. Generally, lower wind speeds, lower release heights, or larger droplet size result in increased residue deposition and higher air concentrations.

Table 9.2.1-2. Fraction of Application Rate for Deposition and Air Concentration at Breathing Height Estimated Based on AgDISP Modeling of Aerial ULV Mosquitocide Application Parameters						
App. Rate (lb ai/A)	**Dv 0.5 < [X] µm**	**Dv 0.9 < [X] µm**	**Release Height (feet)**	**Wind Speed (mph)**	**Fraction of App. Rate for Deposition (unitless)**	**Air Concn at Breathing Height (mg/m^3)**
0.10	40	77	300	10	0.31	0.00747
	60	115	200	5	0.81	0.013
0.075	40	77	300	10	0.31	0.0055
	60	115	200	5	0.81	0.0096
0.05	40	77	300	10	0.31	0.0036
	60	115	200	5	0.81	0.0064

Additionally, based on available air monitoring data, more completely described in Section 9.1 below, as a result of degradation of naled to DDVP, the proportion of the air concentrations immediately following application is assumed to be 70% naled and 30% DDVP. This proportion was applied to the (total) air concentration output from AgDISP model.

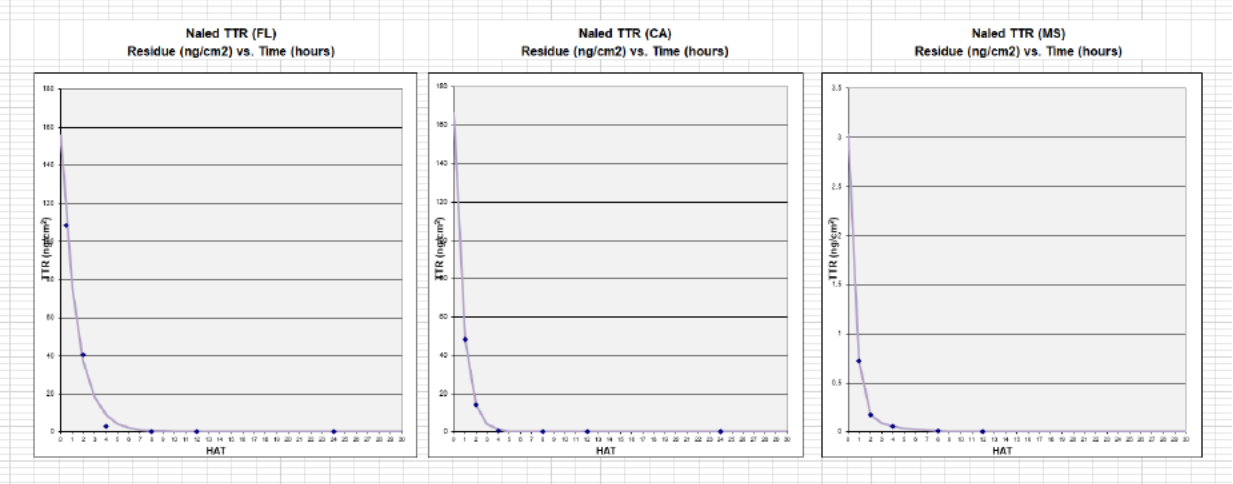
Residue Degradation and Dissipation: Turf transferable residue (TTR) studies were conducted in 2017, measuring transferable residues following experimental mosquitocide applications of Dibrom® Concentrate in California, Mississippi, and Florida. HED finalized review of the studies in 2020 and found them to be acceptable for risk assessment (D445082). The table below provides summary information of the studies' characteristics:

Table 9.2.1-3. Naled TTR Study Design Characteristics							
EPA MRID	**Location**	**Application Method**	**Application Rate (lb ai/acre)**		**Time Range of Samples after application**	**Transferable Residue Method**	**Analytical Method**
			Target	**Actual (measured using deposition pads)**			
50363101	FL	Backpack fogger (Release height of 3 feet)	0.1	0.315	0.5 to 48 hours	Modified CA Roller	LC/MS/MS
50471201 / 50531401	CA	Airplane (Release height of 50 feet)	0.1	0.172	1 to 24 hours		
50471301	MS	Airplane (Release height of 50 feet)	0.1	0.00635	1 to 24 hours		
MRID = Master Record Identification LC/MS/MS = liquid chromatography with tandem mass spectrometry							

As shown in the table above, deposition was measured using cotton percale cloth and the "Modified California Roller" and collected shortly after application. Transferable residue

collection methods and laboratory analytical methods were all procedurally routine for these kinds of studies. Fortification samples (positive control, "spike" samples) were all within acceptable ranges indicating reliable field measurements. A key feature of this study was measurement of the amount deposited and how much of that deposited amount was transferable. Unlike conventional pesticide applications, because the amount deposited from mosquitocide applications is not directly related to the nominal application rate, being able to compare the amount deposited with the amount transferable is valuable information.

Dissipation kinetics were determined by plotting the residues over time. The TTR data demonstrate that both naled and DDVP dissipate extremely rapidly with half-lives on the order of hours, not days. Furthermore, based on a visual inspection of the data, HED fit a simple biphasic function using the SOLVER function in Microsoft Excel (minimizing the sum of squared errors) where, at a particular "knot" or inflection point, the dissipation slows down. These results provide a consistently better visual fit and serve as the basis for determining naled and DDVP residues following application:



9.2.1-4. TTR Study Results								
Location	Application Rate (lb ai/acre)		Biphasic Exponential Model					
			Dissipation Parameters				Initial Transferability	
	Target	Actual	Chemical	Initial Dissipation (per hour)	Inflection Point (time after application)	Final Dissipation (per hour)	C_0 (fitted time-zero value; ng/cm^2)	% of Deposition
FL	0.1	0.315	Naled	51%	8 hours	24%	156	4.4%
			DDVP	70%	2.7 hours	24%	--	--
CA	0.1	0.172	Naled	71%	5.9 hours	11%	166	8.6%
			DDVP	57%	9.2 hours	5%	--	--
MS	0.1	0.00635	Naled	76%	2.2 hours	35%	3	4.3%
			DDVP	69%	2 hours	18%	--	--
As the active ingredient in the products is naled, % of deposition is in terms of naled.								

Finally, the TTR data also characterize the proportion of the residue consisting of naled versus how much has converted to DDVP; this proportion is important because risk estimates from uses of naled will consider exposure to both naled and its degradation to DDVP given that both exhibit similar toxicological effects. In all three locations, as would be expected, the first few hours post-application largely consist of naled (> 95% naled). In the case of Florida, the residues remaining were comprised of naled (> 95%) over the course of sampling, however both the California and Mississippi sites exhibited sizable conversions to DDVP. For example, based on the fitted models, the percentage DDVP of the residue in California exceeds 40% after about 6 hours, before beginning to fall again, while in Mississippi there is a steady conversion for the entire time course (e.g., from 92% naled/8% DDVP after 1 hour to 65% naled/35% DDVP after 8 hours). For simplicity, the initial (time-zero) ratio of naled to DDVP was used in the risk assessment: FL = 99% naled, 1% DDVP; CA = 92% naled, 8% DDVP; and, MS = 94% naled, 6% DDVP.

Additional Exposure Factors: As previously described, in addition to the AgDISP model, standard methods from the 2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment: Lawn/Turf SOP are employed to estimate dermal and incidental oral risk from contact with residues on lawns/turf following wide area public pest control applications via aerial or ground-based vehicles. For assessment of exposures to naled mosquitocides, exposure inputs were used as distributions, rather than point estimates.

These input distributions were used in Crystal Ball[15], a Microsoft Excel compatible software program from Oracle®, to conduct a Monte Carlo-based probabilistic assessment of 10,000 simulations whose output is a distribution of acute (single-day) risk estimates. The distributions are described in the 2012 Residential SOPs, however, they are also summarized below.

Table 9.2.1-5. Input Distributions

Exposure Factor	Lifestage	2012 Residential SOP Recommendations		
		Point Estimate	Distribution	
			Type	Parameters
Transfer Coefficient (cm2/hr)	Adults	180,000	Lognormal	GM = 180,000 GSD = 1.26
	Children (1 < 2 years old)	49,000	Lognormal	GM = 48,000 GSD = 1.26
Daily Exposure Time (hr)	Adults	1.5	Custom	p5 = 0.08, p25 = 0.5, p50 = 1.5, p75 = 3.0, p90 = 5.5; truncated at 5.5
	Children (1 < 2 years old)	1.5	Custom	p5 = 0.42, p25 = 1.0, p50 = 1.5, p75 = 3.0, p90 = 5.1; truncated at 5.1
Bodyweight (kg)	Adult	69	Normal	Mean = 69 SD = 15
	Children (1 < 2 years old)	11	Normal	Mean = 11 SD = 1.5
Fraction of hand mouthed	Children (1 < 2 years old)	0.127	Beta	Max = 0.4 Min = 0.05

[15] Release 11.1.2.4.850 (32-bit) (Build 11.1.4716.0 on 04/18/2017).

Table 9.2.1-5. Input Distributions				
Exposure Factor	Lifestage	2012 Residential SOP Recommendations		
		Point Estimate	Distribution	
			Type	Parameters
				Alpha = 3.7 Beta = 25
Saliva extraction fraction	Children (1 < 2 years old)	0.48	Beta	Max = 0.71 Min = 0.22 Alpha = 7 Beta = 7.6
Hand-to-mouth events (#/hour)	Children (1 < 2 years old)	13.9	Weibull	Location = 1 Scale = 13.8 Shape = 0.98

Though calculation of dermal exposure follows the same general formula as described in the Residential SOPs, in order to incorporate the hourly within-day dissipation of naled/DDVP residue during the time interval in which exposure is occurring, an area under the curve (AUC) methodology was applied as follows:

$$TTR(t) = TTR_0 e^{-kt}$$

$$DE = TC \int_0^{ET} TTR_0 e^{-kt} dt$$

$$DE = \frac{TC \times TTR_0}{k}\left(1 - e^{-k(ET)}\right)$$

Where:

DE = dermal exposure (mg)
TC = transfer coefficient (cm^2/hr)
k = hourly decay constant (hr^{-1})
- CA TTR data: k_{Naled} = 1.23 (71% per hour) and k_{DDVP} = 0.847 (57% per hour)
- FL TTR data: k_{Naled} = 0.715 (51% per hour) and k_{DDVP} = 1.21 (70% per hour)
- MS TTR data: k_{Naled} = 1.43 (76% per hour) and k_{DDVP} = 1.19 (69% per hour)
  - Note: though biphasic models were fit, the combination of the dissipation in the initial phase dissipation with the timing of the inflection point was assumed to render the second phase dissipation superfluous (i.e., for risk assessment purposes, by the time of the inflection point, residues are assumed to be largely dissipated). Thus, for simplicity, only the initial dissipation phase was used/modeled.

t = instantaneous timepoint (hr)
ET = exposure time (hr)

9.2.2 Post-Application Exposure and Risk Estimates

Based on this use pattern and anticipated airborne residue and surface deposition profile, inhalation, dermal, and incidental oral post-application exposures following aerial and ground-

based ULV applications are possible. In all cases exposures are expected to be acute, no repeat or continuous daily exposure is expected due to both the rapid dissipation of naled and DDVP and the retreatment frequency in the same area. Also, as previously described, naled degrades to DDVP and they share a common mechanism of toxicity (AChE inhibition), thus residential post-application risk estimates have been assessed in a manner that represents exposures to both naled and DDVP, accounting for the differential in toxicological PODs as well as their proportions and magnitude in air and surface residues.

Inhalation Exposure

Ground-based Vehicle Fogging

In order to calculate airborne concentrations from ULV truck fogger applications, HED used the 2012 Residential SOPs for Outdoor Fogging/Misting Systems, with minimal modification to the WMB model. The WMB model allows for the estimation of air concentrations in the breathing zones of adults and children for use in calculating the post-application inhalation exposure to individuals residing in areas being treated by ground application of naled. The methodology more accurately accounts for dilution in outdoor air using the WMB model.

The table below shows results for various product application rates to view the range of risk estimates. Exposures are 2-hour time-weighted averages and represent exposure immediately following applications.

Table 9.2.2-1. Ground-based Vehicle ULV Fogging – Inhalation Risk Estimates

Application Rate (lb ai/acre)	Air Concentration (mg/m3)		Risk Estimates (MOE) (LOC = 300)		
			Naled	DDVP	Combined
0.1	0.039	70% naled / 30% DDVP	950	320	240
0.075	0.029		1300	430	320
0.05	0.019		1900	640	480

Notes:

- Proportion in air of naled and DDVP estimated from air monitoring results described in Section 9.1.
- MOE = POD / (Air Concentration * Proportion); see Tables 3.3 and 3.6; Naled POD = 25.8 mg/m^3; DDVP POD = 3.7 mg/m^3
- Combined MOE = 1 / [(1/MOE$_{Naled}$) + (1/MOE$_{DDVP}$)]

Aerial ULV Fogging

Air concentrations based on various AgDISP modeling parameters/conditions were previously outlined in Table 9.2.1-2. For example, based on 2016 communication with CDC Southern FL aerial ULV application conditions were modeled: the maximum application rate of 0.1 lbs ai/A; a 300-foot release height; a wind speed of 10 mph; and VMD parameters of Dv 0.5 < 40 µm and Dv 0.9 < 77 µm. Using these parameters with the AgDISP model resulted in an airborne concentration 1 hour following aerial application of 0.00747 mg/m^3. Generally, lower wind speeds, lower release heights, or larger droplet size result in increased residue deposition and higher air concentrations.

The table below summarizes risk estimates for the air concentrations modeled under various application conditions.

Table 9.2.2-2. Aerial ULV Fogging – Inhalation Risk Estimates						
Application Rate (lb ai/acre)	Application Conditions (release hgt / droplet size / wind speed	Air Concentration (mg/m3)		Risk Estimates (MOE) (LOC = 300)		
				Naled	DDVP	Combined
0.1	300 ft / 40 um /10 mph	0.00747	70% naled / 30% DDVP	4900	1700	1200
	200 ft / 60 um / 5 mph	0.0132		2800	930	700
0.075	300 ft / 40 um /10 mph	0.00546		6800	2300	1700
	200 ft / 60 um / 5 mph	0.00961		3800	1300	960
0.05	300 ft / 40 um /10 mph	0.00363		10000	3400	2500
	200 ft / 60 um / 5 mph	0.0064		5800	1900	1400

Notes:

- Proportion in air of naled and DDVP estimated from air monitoring results described in Section 9.1.
- MOE = PoD / (Air Concentration * Proportion); see Tables 3.3 and 3.6; Naled PoD = 25.8 mg/m^3; DDVP PoD = 3.7 mg/m^3
- Combined MOE = 1 / [(1/MOE$_{Naled}$) + (1/MOE$_{DDVP}$)]

Dermal and Incidental Oral Exposure

Ground and Aerial ULV Applications

Because deposition estimates for aerial ULV applications based on AgDISP modeling (e.g., 31% and 81% from Table 9.2.1-2 above) are higher than those for ground-based ULV fogging (8.7% from Section 9.1) – while other exposure factors such as application rate, exposure time, etc. are not different – dermal and incidental oral exposures from aerial ULV treatments are considered sufficiently representative for all naled mosquitocide applications. Additionally, as previously described ground ULV applications were not supported by any of the mosquito control districts present, despite being a labeled application type, since ground applications of naled can corrode the equipment used and cause harm if residues settle on nearby vehicles following application. As described above, a probabilistic approach was used to characterize risks from aerial ULV treatments, with input distributions and software that performs Monte Carlo simulations.

Since dermal and incidental oral exposures for children are expected to coincide, post-application scenarios represent combined dermal and hand-to-mouth exposures. The general formula used to combine risk estimates are shown below; based on toxicity database for the dermal and incidental oral routes of exposure for both naled and DDVP, risk estimates are characterized via comparison to a LOC of 1000 (i.e., MOEs < 1000 represent risk estimates of concern).

$$\textbf{Combined MOE}_{Adult/Child} = \frac{1}{\frac{1}{\left(\frac{Naled\ PoD_{Route\ A}}{Naled\ Dose_{Route\ A}}\right)} + \frac{1}{\left(\frac{DDVP\ PoD_{Route\ A}}{DDVP\ Dose_{Route\ A}}\right)} + \frac{1}{\left(\frac{Naled\ PoD_{Route\ B}}{Naled\ Dose_{Route\ B}}\right)} + \frac{1}{\left(\frac{DDVP\ PoD_{Route\ B}}{DDVP\ Dose_{Route\ B}}\right)} + etc.}$$

Simulations were conducted for a variety of aerial application parameters and application rates. A summary of the distribution of risks using each residue study and various AgDISP modeling parameters are presented in Table 9.2.2-3 and 9.2.2-4 below. Results in this table represent only

those exposures that occur immediately following residue deposition on the day-of-application; under those conditions, compared with the LOC of 1000 for MOE estimates, risk estimates are largely of concern. Subsequent risk characterization is provided regarding the effect of residue dissipation both in terms of risks on the day-of-application as well as the risks when considering all potential days of exposure, not just those on the day-of-application.

Table 9.2.2-3. Aerial ULV Wide Area Public Pest Control - Summary of Acute Risk Estimates														
TTR Data Location	Application Parameters					Day-of-application MOE at Select Exposure Percentiles (LOC=1000)								
	Droplet size (µm)		Release Ht (feet)	Wind Speed (mph)	App. Rate (lb ai/acre)	Adult (Dermal)								
						99th			95th			75th		
	Dv50	Dv90				Naled	DDVP	Total	Naled	DDVP	Total	Naled	DDVP	Total
FL	40	77	300	10	0.1	370	27000	360	500	36000	490	760	53000	750
					0.075	490	36000	490	670	48000	660	1030	72000	1020
					0.05	730	54000	720	990	71000	980	1500	106000	1500
	60	115	200	5	0.1	140	9900	140	190	14000	190	290	20000	290
					0.075	190	14000	180	260	19000	250	390	27000	390
					0.05	280	20000	280	370	27000	370	580	40000	580
CA	40	77	300	10	0.1	320	1300	250	430	1700	340	640	2600	520
					0.075	420	1700	330	560	2300	450	840	3400	670
					0.05	640	2500	520	850	3400	680	1300	5200	1020
	60	115	200	5	0.1	120	490	99	160	650	130	240	990	200
					0.075	165	650	130	220	860	170	320	1300	260
					0.05	240	960	190	330	1300	260	490	2000	390
MS	40	77	300	10	0.1	700	4400	600	940	6000	810	1400	12000	1200
					0.075	950	6000	820	1300	8000	1100	1900	12000	1600
					0.05	1400	8800	1200	1900	12000	1600	2800	18000	2400
	60	115	200	5	0.1	270	1700	230	360	2300	310	540	3400	460
					0.075	370	2300	320	490	3100	420	720	4600	620
					0.05	530	3400	460	730	4600	630	1100	6800	930
Calculations and results summarized in 18 separate Excel files, covering each residue study and droplet size/release height/wind speed combination. Filename structure example: "Naled2020_mosquito_0.1_CA_200-60-5_1 app.xls".														

Table 9.2.2-4. Aerial ULV Wide Area Public Pest Control - Summary of Acute Risk Estimates																				
TTR Data Loc.	Application Parameters					Day-of-application MOE at Select Exposure Percentiles (LOC=1000)														
	Droplet size (µm)		Release Ht (feet)	Wind Speed (mph)	App. Rate (lb ai/acre)	Child (1< 2 years) (Dermal + Inc. Oral)														
						99th					95th					75th				
						Naled		DDVP		Total	Naled		DDVP		Total	Naled		DDVP		Total
	Dv50	Dv90				D	IO	D	IO		D	IO	D	IO		D	IO	D	IO	
FL	40	77	300	10	0.1	260	5900	19000	440000	250	330	8800	23000	660000	310	460	21000	32000	1500000	440
					0.075	350	8000	26000	610000	340	440	12000	31000	890000	420	620	27000	42000	1900000	590
					0.05	510	12000	37000	890000	490	650	18000	47000	1300000	630	930	42000	64000	3000000	890
	60	115	200	5	0.1	99	2300	7200	180000	95	125	3300	9000	250000	120	180	7800	12000	550000	170
					0.075	130	3100	9700	230000	130	170	4500	12000	340000	160	240	11000	16000	770000	230
					0.05	200	4400	14000	340000	190	250	6700	18000	510000	250	360	16000	25000	1100000	350
CA	40	77	300	10	0.1	230	5300	900	20000	180	280	7700	1100	30000	220	380	17000	1600	70000	300
					0.075	290	7300	1200	28000	230	370	11000	1500	41000	290	510	24000	2100	95000	400
					0.05	450	11000	1800	41000	350	560	16000	2200	60000	440	770	35000	3100	140000	600
	60	115	200	5	0.1	87	2000	340	7600	67	110	3000	430	12000	85	150	6700	590	27000	120
					0.075	120	2700	460	10000	89	140	4000	570	16000	110	200	9000	780	36000	150
					0.05	170	4000	680	16000	140	210	6000	850	23000	170	290	14000	1200	55000	230
MS	40	77	300	10	0.1	500	12000	3200	77000	430	630	18000	4000	112000	530	850	39000	5400	250000	720
					0.075	670	16000	4200	100000	570	830	24000	5300	150000	700	1100	52000	7100	330000	950
					0.05	1000	24000	6400	150000	850	1200	35000	7800	220000	1040	1700	76000	11000	490000	1400
	60	115	200	5	0.1	200	4500	1300	28000	170	240	6800	1500	42000	200	320	15000	2000	94000	270
					0.075	260	6100	1600	38000	220	320	9100	2000	57000	270	430	20000	2700	120000	360
					0.05	390	9100	2400	56000	330	480	14000	3000	86000	410	650	30000	4100	190000	560
Calculations and results summarized in 18 separate Excel files, covering each residue study and droplet size/release height/wind speed combination. Filename structure example: "Naled2020_mosquito_0.1_CA_200-60-5_1 app xls".																				

As can be seen by the summary, risk estimates are sensitive to a variety of application parameters and exposure inputs. Generally, reduced wind speeds, lower release heights, or larger droplet size result in increased residue deposition which in turn lead to increased risks. Risk is proportional to residue which is in turn proportional to the application rate, such that reducing the application rate or a reduction in residue due to dissipation corresponds to a proportional reduction in risk. Of the other factors, exposure time is generally the most sensitive variable.

As residue is an important factor for risk, the particularly fast dissipation of naled and DDVP residues also means that the timing of contact with deposited residue relative to the application can also have a large effect. For example, the available residue data suggests a half-life for each chemical on grass of approximately 30-60 minutes (see Table 9.2.1-4). According to the AMCA, efficacious aerial applications of naled are those that occur early in the morning (dawn) or later in the evening (dusk). Though information on whether exposure occurs immediately following application or sometime thereafter is unavailable, given the early-morning and evening application timings and the short dissipation half-lives, it is likely that contact with naled/DDVP residues on lawns for most people occurs after significant residue dissipation – not necessarily immediately following deposition.

Using examples from the day-of-application risk estimates (Table 9.2.2-4 above) can provide a simple demonstration of this effect. Shown in the table below (using MS TTR data as an example), one can think of an application occurring at dawn (6 am), and exposure beginning 30 minutes ("1 half-life") later at 6:30 am, or 1 hour ("2 half-lives") later at 7 am. Since risk is assumed to be directly proportional to residue, one can observe the effect of the elapsed time-to-exposure through simple consideration of the residue half-life. In other words, all else equal, if exposure is assumed to begin one half-life after residues are deposited, corresponding risk estimates will be reduced by half as well. Table 9.2.2-5 below shows the approximate elapsed time post-application after which risk estimates are not of concern (i.e., MOE $\geq$ 1000).

Table 9.2.2-5. Effect of Elapsed Time-to-Contact and Residue Dissipation on Day-of-application Exposures [Combined (Naled + DDVP), Child (1< 2 years), Dermal + Inc. Oral]

Residue Data Location	Application Parameters						Elapsed time (hours) post-application to reach MOE=1000		
	Droplet size (µm)		Release Ht (feet)	Wind Speed (mph)	Application Rate (lb ai/acre)	Residue Half life			
	Dv50	Dv90					99th	95th	75th
FL	40	77	300	10	0.1	1 hour	2	1.7	1.2
					0.075		1.6	1.3	0.8
					0.05		1	0.7	0.2
	60	115	200	5	0.1		3.4	3.1	2.6
					0.075		2.9	2.6	2.1
					0.05		2.4	2	1.5
CA	40	77	300	10	0.1	34 minutes	1.4	1.2	1
					0.075		1.2	1	0.7
					0.05		0.9	0.7	0.4
	60	115	200	5	0.1		2.2	2	1.7
					0.075		2	1.8	1.6
					0.05		1.6	1.4	1.2

Table 9.2.2-5. Effect of Elapsed Time-to-Contact and Residue Dissipation on Day-of-application Exposures [Combined (Naled + DDVP), Child (1< 2 years), Dermal + Inc. Oral]

Residue Data Location	Application Parameters						Elapsed time (hours) post-application to reach MOE=1000		
	Droplet size (µm)		Release Ht (feet)	Wind Speed (mph)	Application Rate (lb ai/acre)	Residue Half life	99th	95th	75th
	Dv50	Dv90							
MS	40	77	300	10	0.1	30 minutes	0.6	0.5	0.2
					0.075		0.4	0.3	0.04
					0.05		0.1	0	0
	60	115	200	5	0.1		1.3	1.2	0.9
					0.075		1.1	0.9	0.7
					0.05		0.8	0.6	0.4

$\text{Elapsed time}_{MOE=LOC} = [\ln(MOE_{t=0}/MOE_{LOC})/\ln(0.5)] * \text{Half-life}$

See Table 5.1.3-3 for $MOE_{t=0}$

Example (FL, 60/115/200/5, 0.1 lb ai/acre, 99th percentile):

$\text{Elapsed time}_{MOE=1000} = [\ln(350/1000)/-0.693] * 60$ mins

$\text{Elapsed time}_{MOE=1000} \approx 3.4$ hours

Thus far risk estimates have been presented in the context of exposures that occur on the day-of-application only. Conceptually, one can think of day-of-application exposures as a sub-set of all possible exposure days. Though information on whether most exposures occur on the day-of-application or whether most occur on subsequent days after application is unavailable, an example can help characterize risks across all exposure days, not just on the day-of-application. If naled applications are assumed to occur once per week, and the probability of exposure is (for example) assumed equal across all days, individuals in the exposed population have a 1 out of 7 chance, or 14% probability, of experiencing exposure on the day-of-application, a 14% probability of experiencing exposure on the day after application, a 14% probability of experiencing exposure two days after application, etc. Monte Carlo simulations were conducted assuming this equal daily exposure probability and factoring in daily residue dissipation.

Additionally, because the AMCA indicated that high pest pressure events can require two applications on successive nights, simulations were conducted to reflect that scenario as well. In that case, a 7-day period essentially will have two day-of-application exposures – thus day of application exposures rise to a 28% probability of occurring. The table below summarizes risk estimates for some example scenarios.

Table 9.2.2-6. Risk Summary - All Exposure Days

Residue Data Location	Application Parameters					Exposure Percentile	Child (1< 2 years) Combined (Naled + DDVP; dermal + incidental oral) MOE (LOC=1000)	
	Droplet size (µm)		Release Ht (feet)	Wind Speed (mph)	Application Rate (lb ai/acre)		Weekly application regimen	
	Dv50	Dv90					1 application	2 applications, on successive days
FL	40	77	300	10	0.1	99	330	300
						95	510	410
						75	40000	1200
	60	115	200	5	0.1	99	130	120
						95	200	190
						75	17000	450

Table 9.2.2-6. Risk Summary - All Exposure Days								
Residue Data Location	Application Parameters					Exposure Percentile	Child (1< 2 years) Combined (Naled + DDVP; dermal + incidental oral) MOE (LOC=1000)	
	Droplet size (µm)		Release Ht (feet)	Wind Speed (mph)	Application Rate (lb ai/acre)		Weekly application regimen	
	Dv50	Dv90					1 application	2 applications, on successive days
CA	40	77	300	10	0.1	99	230	210
						95	330	270
						75	20500	670
	60	115	200	5	0.1	99	90	80
						95	120	110
						75	7900	260
MS	40	77	300	10	0.1	99	570	510
						95	790	660
						75	47000	1500
	60	115	200	5	0.1	99	220	190
						95	300	250
						75	20000	550
Calculations and results summarized in 12 separate Excel files, covering each residue study and droplet size/release height/wind speed combination. Filename structure example: "Naled2020_mosquito_0.1_CA_200-60-5_1app_all days.xls".								

In the case of naled and DDVP, due to rapid residue dissipation, exposures on days after application do not have risks of concern – as seen previously in the consideration of the within-day effect of half-life. In the examples here, the risk distribution is different from the distribution of risks of day-of-application exposures because the "all exposure days" distribution now includes exposures on days after the application which do not have risks of concern due to residue dissipation. It follows that other examples where daily exposure probabilities are changed or where the application regimen is assumed once every 14 or 21 days would have correspondingly different risk distributions.

Combining Exposure and Risk Estimates

All routes of exposure for naled share a common toxicological endpoint (AChE inhibition) and should be combined where applicable. In the previous section this was conducted for dermal and incidental oral exposure routes, with those risk estimates compared to the LOC of 1000. In the case of combining with inhalation exposure however, the LOC for naled and DDVP is 300 therefore a total ARI would be used and compared with a LOC of 1 (i.e., ARIs < 1 are of concern). Quantification of ARIs for all exposure routes was not conducted – as risk estimates are of concern for dermal and incidental oral exposures, it follows that ARIs would also be of concern.

10.0 Cumulative Exposure/Risk Characterization

OPs, such as naled, share the ability to inhibit AChE through phosphorylation of the serine residue on the enzyme leading to accumulation of acetylcholine and ultimately cholinergic neurotoxicity. This shared MOA/AOP is the basis for the OP common mechanism grouping per

OPP's *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999). The 2002 and 2006 CRAs used brain AChE inhibition in female rats as the source of dose response data for the relative potency factors and PODs for each OP, including naled. Prior to the completion of Registration Review, OPP will update the OP CRA on AChE inhibition to incorporate new toxicity and exposure information available since 2006.

As described in Section 4.5, OPP has retained the FQPA Safety Factor for OPs, including naled, due to uncertainties associated with neurodevelopmental effects in children and exposure to OPs. There is a lack of an established MOA/AOP for the neurodevelopment outcomes which precludes the agency from formally establishing a common mechanism group per the *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999) based on that outcome. Moreover, the lack of a recognized MOA/AOP and other uncertainties with exposure assessment in the epidemiology studies prevent the agency from establishing a causal relationship between OP exposure and neurodevelopmental outcomes. The agency will continue to evaluate the epidemiology studies associated with neurodevelopmental outcomes and OP exposure prior to the release of the revised DRA. During this period, the agency will determine whether or not it is appropriate to apply the draft guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* for the neurodevelopment outcomes.

11.0 Occupational Exposure/Risk Characterization

Given the uses of naled described in Section 3, exposures are anticipated for both workers who mix, load, and apply naled products (i.e., handler exposure) and who contact residues following naled applications (i.e., post-application exposure). Handler risks are estimated for naled exposure only, while, due to degradation of naled to DDVP, post-application risks are estimated for exposure to both naled and DDVP.

11.1 Short-/Intermediate-Term Occupational Handler Exposure and Risk Estimates

Naled is a restricted use pesticide, which requires applications to be performed by or under the supervision of certified applicators. All products are required to utilize engineering controls in the form of closed mixing/loading systems and enclosed-cabs for vehicle-based applications, with exception of aerial applications for wide area public pest control. Where engineering controls are not applicable handlers are required to wear long pants, long-sleeved shirt, and PPE including coveralls, chemical-resistant gloves, footwear, and headgear (for overhead exposure), and a respirator.

Based on the use profile outlined in Section 3.0 above, the quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

- Outdoor agricultural uses (field and orchard/vineyard crops)
    - Aerial applications
    - Ground-based vehicles: groundboom, airblast, truck-mounted foggers
- Non-crop trees and ornamentals (forest/shade trees, shrubs/bushes, flowering plants

  - Ground-based vehicles (airblast, groundboom)
  - Mechanically-pressurized handgun
- Livestock feedlots/pastures/rangelands
  - Aerial applications
  - Truck-mounted fogger
- Bait traps (applications to wicks or fiber blocks or inside jars which are placed on non-food trees, telephone/light poles or other inanimate objects or applied directly to non-food tree trunks or limbs)
  - Handheld spray or brush applications
- Wide area public pest control (e.g., mosquito adulticides)
  - Aerial
  - Truck-mounted foggers
  - Backpack and mechanically-pressurized handgun sprayers
- Indoor/outdoor commercial areas (food processing plants, refuse areas, loading docks)
  - Manually- and mechanically-pressurized hand sprayers
- Greenhouse hot plate/vaporization
  - Handlers pour the recommended amount of product into a metal pan on a hot plate.
  - Workers then vacate the greenhouse and activate the hot plate with an automatic timer.
  - The greenhouse remains closed for at least 3 hours during treatment, followed by ventilation according to the Agency's Worker Protection Standard (WPS) requirements.

*Handlers pour the recommended amount of product into a metal pan on a hot plate.
Workers then vacate the greenhouse and activate the hot plate with an automatic timer.
The greenhouse remains closed for at least 3 hours during treatment, followed by ventilation according to the Agency's WPS requirements.

As dermal and inhalation exposures share a common toxicological endpoint (i.e., AChE inhibition), dermal and inhalation exposures are combined for risk assessment purposes. A total ARI was used since the LOCs for dermal exposure (1000) and inhalation exposure (300) are different. The target ARI is 1; therefore, ARIs of less than 1 indicate risk estimates of concern. The ARI was calculated as follows:

$$ARI = \frac{1}{\frac{LOC_{Derm}}{\left(\frac{PoD_{Derm}}{Dose_{Derm}}\right)} + \frac{LOC_{Inh}}{\left(\frac{PoD_{Inh}}{Dose_{Inh}}\right)}}$$

Based on the levels of concern for dermal (MOEs < 1000) and inhalation exposure (MOEs < 300), many handler exposure scenarios for naled have risk estimates of concern (ARIs < 1). Scenarios with risk estimates of concern are predominantly large-scale use patterns such as the agricultural uses and wide area public pest control where workers are assumed to handle a substantial amount of active ingredient; the combination of relatively high exposure potential with relatively high potency and uncertainty regarding naled's toxicity results in risk estimates of

concern even with the use of engineering controls or maximum levels of PPE such as coveralls and half-face respirators. Table 11.2.1 presents detailed exposure and risk calculations.

Notably, current product labels require enclosed cockpits for aerial applications, except for public pest control uses, which are exempt from that requirement. Risk estimates for all aerial application scenarios are based on exposure data for applicators in enclosed cockpits and are the only data available; data for open cockpit aerial applications would be needed to appropriately assess risk for open-cockpit exposures. Note, however, that for some use patterns current risk estimates for aerial applicators of naled in enclosed cockpits are of concern.

Table 11.11. Summary of Occupational Handler Risk Estimates for Naled

Use Site Category		Exposure Scenario		Application Rate[1]	Amount Handled/ Area Treated[2]	Unit Exposure (ug/lb ai)[3,4] (PPE designation)		MOE[5]		ARI[6] (LOC = 1)
						Dermal	Inhalation	Dermal (LOC = 1000)	Inhalation (LOC = 300)	
Indoor/ outdoor commercial areas	Food processing facilities	Manually-pressurized handwand		0.04 lb ai/gallon solution	40 gallons of solution	6200 (DL/G)	110 (PF10)	180	23	0.054
		Mechanically-pressurized handgun			1000 gallons of solution	1360 (DL/G)	0.87 (PF10)	34	120	0.031
	Loading docks, refuse areas, etc	Manually-pressurized handwand			40 gallons of solution	365 (DL/G)	3 (PF10)	3100	850	1.5
		Mechanically-pressurized handgun			1000 gallons of solution	1360 (DL/G)	0.87 (PF10)	34	120	0.031
Field crops	Safflower	Aerial	Mix/ load	2.1 lb ai/acre	1200 acres	8.6 (EC)	0.083 (EC)	85	19	0.036
			Apply			2.08 (EC)	0.0049 (EC)	350	330	0.27
		Ground boom	Mix/ load		200 acres	8.6 (EC)	0.083 (EC)	510	120	0.22
			Apply			5.1 (EC)	0.043 (EC)	860	230	0.41
	High-acreage crops	Aerial	Mix/ load	1.4 lb ai/acre	1200 acres	8.6 (EC)	0.083 (EC)	130	29	0.055
			Apply			2.08 (EC)	0.0049 (EC)	530	500	0.4
		Ground boom	Mix/ load		200 acres	8.6 (EC)	0.083 (EC)	760	180	0.34
			Apply			5.1 (EC)	0.043 (EC)	1300	340	0.61

Table 11.11. Summary of Occupational Handler Risk Estimates for Naled

Use Site Category		Exposure Scenario		Application Rate[1]	Amount Handled/ Area Treated[2]	Unit Exposure (ug/lb ai)[3,4] (PPE designation)		MOE[5]		ARI[6] (LOC = 1)
						Dermal	Inhalation	Dermal (LOC = 1000)	Inhalation (LOC = 300)	
		Aerial	Mix/ load	0.9 lb ai/acre	1200 acres	8.6 (EC)	0.083 (EC)	200	45	0.086
			Apply			2.08 (EC)	0.0049 (EC)	820	770	0.62
		Ground boom	Mix/ load		200 acres	8.6 (EC)	0.083 (EC)	1200	270	0.51
			Apply			5.1 (EC)	0.043 (EC)	2000	530	0.94
	Typical-acreage crops	Aerial	Mix/ load	1.9 lb ai/acre	350 acres	8.6 (EC)	0.083 (EC)	320	74	0.14
			Apply			2.08 (EC)	0.0049 (EC)	1300	1300	1
		Ground boom	Mix/ load		80 acres	8.6 (EC)	0.083 (EC)	1400	320	0.61
			Apply			5.1 (EC)	0.043 (EC)	2400	620	1.1
		Aerial	Mix/ load	1.4 lb ai/acre	350 acres	8.6 (EC)	0.083 (EC)	440	100	0.19
			Apply			2.08 (EC)	0.0049 (EC)	1800	1700	1.4
		Ground boom	Mix/ load		80 acres	8.6 (EC)	0.083 (EC)	1900	4400	0.83
			Apply			5.1 (EC)	0.043 (EC)	3200	840	1.5
		Mix/load solution		0.017 lb ai/bait	600 baits	8.6 (EC)	0.083 (EC)	21000	4800	9.1

Table 11.11. Summary of Occupational Handler Risk Estimates for Naled

Use Site Category	Exposure Scenario		Application Rate[1]	Amount Handled/ Area Treated[2]	Unit Exposure (ug/lb ai)[3,4] (PPE designation)		MOE[5]		ARI[6] (LOC = 1)
					Dermal	Inhalation	Dermal (LOC = 1000)	Inhalation (LOC = 300)	
Bait traps in/on trees, poles, other inanimate objects	Pour on application		0.1 lb ai/acre	350 acres	29.1 (DL/G)	0.0219 (PF10)	6200	18000	5.6
	Trigger spray bottle application				1110 (DL/G)	6.12 (PF10)	160	65	0.092
	Manually pressurized handwand application				365 (DL/G)	3 (PF10)	490	130	0.23
	Brush/roller application				22000 (DL/G)	28 (PF10)	8.2	14	0.007
Livestock feedlots/ pastures/ rangelands	Aerial	Mix/ load			8.6 (EC)	0.083 (EC)	6100	1400	2.6
		Apply			2.08 (EC)	0.0049 (EC)	25000	24000	19
	Truck-mounted fogger	Mix/ load			8.6 (EC)	0.083 (EC)	6100	1400	2.6
		Apply			14.6 (EC)	0.068 (EC)	3600	1700	2.2
Greenhouse hot plate vaporization	Pour formulation in metal pan on hot plate; automatic timer application required		0.06 lb ai/10,000 ft3	595,000 ft3	29.1 (DL/G)	0.0219 (PF10)	18000	52000	26
	Airblast	Mix/ load	0.9 lb ai/acre	20 acres	8.6 (EC)	0.083 (EC)	12000	2700	5.1

Table 11.11. Summary of Occupational Handler Risk Estimates for Naled									
Use Site Category	Exposure Scenario		Application Rate[1]	Amount Handled/ Area Treated[2]	Unit Exposure (ug/lb ai)[3,4] (PPE designation)		MOE[5]		ARI[6] (LOC = 1)
					Dermal	Inhalation	Dermal (LOC = 1000)	Inhalation (LOC = 300)	
Non-crop trees, shrubs/bushes, and ornamentals		Apply			14.6 (EC)	0.068 (EC)	7000	3300	4.3
	Ground boom	Mix/ load		60 acres	8.6 (EC)	0.083 (EC)	4000	910	1.7
		Apply			5.1 (EC)	0.043 (EC)	6700	1800	3.2
	Mechanically-pressurized handgun		0.0094 lb ai/gallon solution	1000 gallons of solution	1360 (DL/G)	0.87 (PF10)	140	500	0.13
Orchard/Vineyard crops	Aerial	Mix/ load	1.9 lb ai/acre	350 acres	8.6 (EC)	0.083 (EC)	320	74	0.14
		Apply			2.08 (EC)	0.0049 (EC)	1300	1300	1
	Airblast or Truck-mounted Fogger	Mix/ load		40 acres	8.6 (EC)	0.083 (EC)	2800	650	1.2
		Apply			14.6 (EC)	0.068 (EC)	1700	790	1
	Aerial	Mix/ load	0.9 lb ai/acre	350 acres	8.6 (EC)	0.083 (EC)	680	160	0.3
		Apply			2.08 (EC)	0.0049 (EC)	2800	650	1.2
	Airblast or Truck-	Mix/ load		40 acres	8.6 (EC)	0.083 (EC)	5900	1400	2.6

Table 11.11. Summary of Occupational Handler Risk Estimates for Naled									
Use Site Category	Exposure Scenario		Application Rate[1]	Amount Handled/ Area Treated[2]	Unit Exposure (ug/lb ai)[3,4] (PPE designation)		MOE[5]		ARI[6] (LOC = 1)
					Dermal	Inhalation	Dermal (LOC = 1000)	Inhalation (LOC = 300)	
	mounted Fogger	Apply			14.6 (EC)	0.068 (EC)	3500	1700	2.2
Wide area public pest control	Aerial	Mix/ load	0.1 lb ai/acre	7500 acres	8.6 (EC)	0.083 (EC)	280	65	0.12
		Apply			2.08 (EC)	0.0049 (EC)	1200	1100	0.9
		Mix/ load	0.05 lb ai/acre	7500 acres	8.6 (EC)	0.083 (EC)	570	130	0.25
		Apply			2.08 (EC)	0.0049 (EC)	2400	2200	1.8
	Truck-mounted Fogger	Mix/ load	0.1 lb ai/acre	3000 acres	8.6 (EC)	0.083 (EC)	710	160	0.3
		Apply			14.6 (EC)	0.068 (EC)	420	200	0.26
		Mix/ load	0.05 lb ai/acre	3000 acres	8.6 (EC)	0.083 (EC)	1400	330	0.62
		Apply			14.6 (EC)	0.068 (EC)	840	400	0.52
	Backpack sprayer		0.1 lb ai/acre	5 acres	4120 (DL/G)	0.258 (PF10)	890	32000	0.88
			0.05 lb ai/acre	5 acres	4120 (DL/G)	0.258 (PF10)	1800	63000	1.8

Table 11.11. Summary of Occupational Handler Risk Estimates for Naled

Use Site Category	Exposure Scenario	Application Rate[1]	Amount Handled/ Area Treated[2]	Unit Exposure (ug/lb ai)[3,4] (PPE designation)		MOE[5]		ARI[6] (LOC = 1)
				Dermal	Inhalation	Dermal (LOC = 1000)	Inhalation (LOC = 300)	
	Mechanically-pressurized handgun	0.1 lb ai/acre	5 acres	1360 (DL/G)	0.87 (PF10)	2700	9400	2.5
		0.05 lb ai/acre	5 acres	1360 (DL/G)	0.87 (PF10)	5400	19000	5

1 Based on registered labels outlined in Table 3.3.
2 Based on Exposure Science Advisory Council Policy #9.1.
3 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (November 2016). Though a more recent version was available (June 2018) at the time of this assessment, no updates in the newer version effect the naled risk assessment therefore the assessment was not conducted using the June 2018 version. Finally, the assessment pre-dated the most recent March 2020 updates.
4 DL/G = Double-layer (single-layer plus coveralls) + chemical resistant gloves; PF10 = "Protection Factor 10" indicating a respirator that reduces exposure by 90% such as a filtering facepiece respirator or half-face elastomeric respirator. EC = engineering control (closed mixing/loading system or enclosed cab/cockpit).
5 MOE = POD (mg/kg/day) ÷ [(Unit Exposure (mg/lb ai) × Application Rate (e.g., lb ai/acre or gal) × Area Treated or Amount Handled (e.g., acre/day or gallons/day) ÷ BW (69 kg))].
6 ARI = $1/[(Dermal_{LOC}/Dermal_{MOE})+(Inhalation_{LOC}/Inhalation_{MOE})]$

11.2 Short-/Intermediate-Term Post-Application Exposure and Risk Estimates

Based on the use pattern for naled, occupational post-application exposures are anticipated for activities throughout the growing seasons of the various crops registered for naled. Additionally, given the degradation to DDVP and common mechanism of toxicity for naled and DDVP, risk estimates are provided separately and for the combination of exposure to both chemicals

11.2.1 Dermal Post-Application Risk

Based on the registered uses of naled, including the direct agricultural uses and wide area public pest control applications that can be made over agricultural areas, standard values recommended for use in predicting post-application exposure that are used in this assessment, known as "transfer coefficients", were used to represent a variety of crop/crop groups: strawberry, hop, alfalfa, dry beans and peas, snap beans, sugar beets, green peas, safflower, cotton, greenhouse roses/ornamentals, grapefruit, lemon, tangerine, orange, walnuts, non-crop trees/bushes/ornamentals, carrot, turnip, cantaloupe, summer squash, eggplant, peppers, broccoli, brussels sprouts, cabbage, cauliflower, celery, collards, kale, swiss chard, and grapes. These standard values from ExpoSAC Policy 3 can be found at the Agency website[16].

Furthermore, the following chemical-specific dislodgeable foliar residue data are available for naled, including measurements of its degradate DDVP:

- Grapes (two sites in California) (MRID 43223904)
- Oranges (one site in each Florida and California) (MRID 45276801)
- Broccoli (one site in each California, North Carolina, Ontario, Canada) (MRID 45276803)
- Cotton (one site in each Mississippi and California) (MRID 45276802)

All studies have been previously reviewed (Leighton, T., 09/19/2001, D273305) and remain acceptable for use in risk assessment. A summary of the results for naled and DDVP is provided in Table 11.2.1 below.

Table 11.2.1.1. Summary of Available Naled/DDVP Dislodgeable Foliar Residue Data

Crop	Study Appl. Rate (lb ai/acre)	Day-of-application DFR (ug/cm2)				Dissipation				Study used for the assessment of …
		Measured		Predicted		Half-life (days)		% per day		
		Naled	DDVP	Naled	DDVP	Naled	DDVP	Naled	DDVP	
Grapes (CA site 1)	0.9	0.226	0.053	0.255	0.034	0.4	0.6	82%	70%	Grapes, Greenhouse roses/ornamentals
Oranges (CA)	1.875	0.476	0.035	0.317	0.041	1.4	0.7	40%	63%	Hop, Tree fruits, Nuts

[16] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

Table 11.2.1.1. Summary of Available Naled/DDVP Dislodgeable Foliar Residue Data										
Crop	Study Appl. Rate (lb ai/acre)	Day-of-application DFR (ug/cm2)				Dissipation				Study used for the assessment of …
		Measured		Predicted		Half-life (days)		% per day		
		Naled	DDVP	Naled	DDVP	Naled	DDVP	Naled	DDVP	
Broccoli (CA)	1.875	0.597	2.48	0.387	0.439	0.3	0.2	87%	96%	Strawberry, Non-crop Trees/Ornamentals, Cucurbits, Fruiting Vegetables, Brassica, Leafy Vegetables
Cotton (CA)	0.9375	1.07	0.129	0.206	0.109	0.2	0.2	94%	99%	Cotton, Beans, Peas, Alfalfa, Safflower

A comparison of these results shows that both naled and DDVP dissipate very quickly and, though variable, the proportion of the total residue immediately following application is approximately 80% naled/20% DDVP. Given the variability in degradation and dissipation, study- and chemical-specific predicted "time zero" residues and dissipation constants were applied to calculate exposure. In all cases, use of the DFR data includes a proportional adjustment to current application rates from the applied rates in the studies. For assessment of crops without chemical-specific data, as shown in the table, the available DFR data are used as a surrogate based on the same criteria (application equipment, etc.) used in previous naled risk assessments. Additionally, consistent with previous use of the data, studies done in California are utilized for their representativeness and potential worst-case climatic conditions.

For re-entry exposure to greenhouse roses and other ornamentals, the grape DFR data are normalized to an application rate of 3.8 lb ai/acre assuming the hot plate/vaporization application rate of 0.06 lb ai/10,000 ft^3 is applied to an 85,000 ft^3 greenhouse with floor dimensions of 120 ft x 48 ft. This is consistent with the assessment for the 2006 naled re-registration eligibility decision (RED). Additionally, because the application is as a vapor not a spray, the 2006 assessment assumed that only 10% of the application rate would be deposited on the foliage, the remainder would remain airborne and exit the greenhouse during ventilation. While it is reasonable to assume there would be a difference in residue deposition between a vapor application and a foliar spray application, this difference would be better demonstrated by greenhouse crop -and application-specific transferable residue data. Thus, the assumption of 10% deposition is not incorporated in this risk assessment.

Transferable residue data on cotton bolls are not available for the assessment of cotton harvesting applicable to the SLN registration for use on cotton after bolls have opened up to 4 days prior to harvest (SLN CA050011). Therefore, the ExpoSAC Policy 3 default value of 2 µg/gm per lb ai/acre is applied to the existing cotton application rate of 1.4 lb ai/acre to estimate an initial ("time zero") transferable cotton boll residue of 2.8 ug naled/gm cotton boll[17]. Based on the available residue data, a "time zero" assumption of 80% naled/20% DDVP is used – that is, of the 2.8 µg naled/gm cotton boll transferable residue on the day of application, 2.24 µg is assumed naled and 0.56 µg is assumed DDVP. For dissipation, the most conservative (i.e., slowest) dissipation results (from the study on oranges in California) are used: 40% per day for naled and 63% per day for DDVP, instead of the default estimate of 10% daily dissipation.

[17] 1.4 lb ai/acre * (2 µg/gm cotton boll / lb ai/acre) = 2.8 µg ai/gm cotton boll

For the purposes of assessing occupational post-application exposures following wide area public pest control applications an additional factor is applied for the fraction of the application rate that is deposited on crops. Unlike direct applications to agricultural crops, wide area public pest control applications are not always assumed to deposit residues such that the surface concentration is equivalent to the application rate. Due to the nature of these wide area treatments, modeling that accounts for wind speed, droplet size, etc. can demonstrate that only a fraction of the application rate will actually deposit on the treated area. As described in Section 9.2 above, based on modeling done in AgDISP (v8.2.6), deposition fractions of 100% and 31% are used to bracket the possibilities for various application types.

As both naled and DDVP share a common mechanism of toxicity (i.e., AChE inhibition), exposures from contact with residues of both (as demonstrated in the available residue studies) are combined for risk assessment purposes. Risk estimates (MOEs) are calculated for each naled and DDVP (using their chemical-specific toxicological PODs), then aggregated using the following formula:

$$MOE = \frac{1}{\frac{1}{\left(\frac{Naled\ PoD_{Dermal}}{Naled\ Dose_{Dermal}}\right)} + \frac{1}{\left(\frac{DDVP\ PoD_{Dermal}}{DDVP\ Dose_{Dermal}}\right)}}$$

With the exception of activities related to cotton harvesting, no occupational post-application dermal risks of concern were identified beyond label-specified REIs of 24, 48, or 72 hours. Risk estimates as a result of wide area public pest control over agricultural areas are also presented with select scenarios shown to bracket the range of possible scenarios across all crops and activities. Following wide area public pest control applications, dermal risks of concern were identified on the day-of-application for some activities that involve high contact with residues, including mechanically harvesting of cotton and grape cane turning. On the other hand, low contact activities, such as orchard fruit hand weeding, do not result in risk estimates of concern. Unlike direct agricultural uses, these risks have not been characterized in terms of REIs as it is unclear whether an REI is a feasible option for wide area public pest control uses. Because of the nature of these applications, the application timing, from which a re-entry period would be calibrated, is likely unknown. Table 11.2.1-2 provides more detail on the risk estimates

Table 11.2.1-2. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Naled Uses											
Crop	Application Rate (lb ai/acre)	DFR_0 (ug/cm^2 or ug/gm)[1]		Dissipation (% per day)		TC (cm^2/hr or gm/hr)	Re-entry Worker Activities	Risk Characterization[2]			
								MOE on Day-of-application			Day when Combined MOE > LOC (1000)
		Naled	DDVP	Naled	DDVP			Naled	DDVP	Combined	
Strawberry	0.9	0.19	0.21	87%	96%	1100	Hand harvesting	1100	160	140	1
						230	Transplanting	5400	750	660	1
						210	Scouting	5900	820	720	1
						70	Hand weeding, Canopy management	18000	2500	2200	0
						No TC	Irrigation (non-hand set), Mechanical weeding	>1000			0
Hop	0.9	0.15	0.02	40%	63%	1900	Irrigation (hand set)	790	970	440	2
						1400	Mechanically-assisted harvesting	1100	1300	600	1
						640	Stripping, Scouting, Hand weeding, Tying/training	2400	2900	1300	0
						230	Transplanting	6500	8000	3600	0
						No TC	Mechanical harvesting, Irrigation (non-hand set), Mechanical weeding, Discing, Ditching	>1000			0

Table 11.2.1-2. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Naled Uses											
Crop	Application Rate (lb ai/acre)	DFR_0 (ug/cm^2 or ug/gm)[1]		Dissipation (% per day)		TC (cm^2/hr or gm/hr)	Re-entry Worker Activities	Risk Characterization[2]			
								MOE on Day-of-application			Day when Combined MOE > LOC (1000)
		Naled	DDVP	Naled	DDVP			Naled	DDVP	Combined	
Alfalfa, dry beans and peas, snap beans, sugar beets, green peas, safflower	1.4	0.31	0.16	94%	99%	1900	Irrigation (hand set)	390	120	92	1
						1100	Scouting, Hand harvesting	680	200	150	1
						210	Scouting	3500	1100	840	1
						70	Hand weeding, Thinning	11000	3200	2500	0
						No TC	Irrigation (non-hand set), Mechanical Harvesting, Fertilizing, Mechanical Swathing, Mechanical Weeding, Mechanical Knifing,	>1000			0
Cotton	1.4	2.24 ug/gm cotton boll	0.56 ug/gm cotton boll	40%	63%	5050 gm/hr	Mechanical Harvesting (tramper)	20	13	7.9	8
						2400 gm/hr	Mechanical Harvesting (Picker Operator)	43	27	17	7
						2400 gm/hr	Mechanical Harvesting (Raker)	43	27	17	7
						900 gm/hr	Mechanical Harvesting (Module Builder Operator)	110	72	44	5

Table 11.2.1-2. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Naled Uses											
Crop	Application Rate (lb ai/acre)	DFR_0 (ug/cm^2 or ug/gm)[1]		Dissipation (% per day)		TC (cm^2/hr or gm/hr)	Re-entry Worker Activities	Risk Characterization[2]			
								MOE on Day-of-application			Day when Combined MOE > LOC (1000)
		Naled	DDVP	Naled	DDVP			Naled	DDVP	Combined	
	0.9	0.20	0.10	94%	99%	210	Scouting	5500	1700	1300	0
						70	Hand weeding	17000	5000	3900	0
						No TC	Irrigation (non-hand set), Mechanical weeding	>1000			0
Greenhouse roses/ ornamentals	3.8	1.07	0.15	82%	70%	4800	Hand harvesting	44	52	24	3
						1900	Irrigation (hand-set)	110	130	60	2
						230	Container moving, pinching, hand pruning, hand weeding, scouting, transplanting	930	1100	500	1
						No TC	Irrigation (non-hand set), Mechanical weeding	>1000			0
Grapefruit, Lemon, Tangerine, Orange	1.9	0.32	0.04	40%	63%	1400	Hand harvesting	510	620	280	2
						580	Scouting, Hand pruning	1200	1500	670	1
						230	Transplanting	3100	3800	1700	0
						100	Orchard maintenance, Hand weeding, Baiting/Trapping	7100	8700	3900	0

Table 11.2.1-2. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Naled Uses											
Crop	Application Rate (lb ai/acre)	DFR_0 (ug/cm^2 or ug/gm)[1]		Dissipation (% per day)		TC (cm^2/hr or gm/hr)	Re-entry Worker Activities	Risk Characterization[2]			
								MOE on Day-of-application			Day when Combined MOE > LOC (1000)
		Naled	DDVP	Naled	DDVP			Naled	DDVP	Combined	
						No TC	Irrigation (non-hand set), Mechanical weeding, Mechanical pruning	>1000			0
Walnut	1.9	0.32	0.04	40%	63%	580	Scouting	1200	1500	670	1
						230	Transplanting	3100	3800	1700	0
						190	Mechanical harvesting	3800	4600	2100	0
						100	Orchard maintenance, Poling, Hand weeding	7100	8700	3900	0
						No TC	Irrigation (non-hand set), Mechanical weeding	>1000			0
Non-crop trees/ bushes/ ornamentals	0.9	0.19	0.21	87%	96%	1900	Irrigation (hand set)	650	90	79	1
						1400	Harvesting Seed Cones (Conifers)	880	120	110	1
						580	Hand pruning, Scouting	2100	300	260	1

Table 11.2.1-2. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Naled Uses											
Crop	Application Rate (lb ai/acre)	DFR_0 (ug/cm^2 or ug/gm)[1]		Dissipation (% per day)		TC (cm^2/hr or gm/hr)	Re-entry Worker Activities	Risk Characterization[2]			
								MOE on Day-of-application			Day when Combined MOE > LOC (1000)
		Naled	DDVP	Naled	DDVP			Naled	DDVP	Combined	
						230	Transplanting, Hand Harvesting, Hand Pruning, Scouting, Container Moving, Hand Weeding, Transplanting, Grafting Hand Harvesting, Propagating, Hand Pruning, Pinching, Tying/Training	5400	750	660	1
						100	Hand weeding	12000	1700	1500	0
						No TC	Mechanical Harvesting, Mechanical Weeding, Burndown, Fertilizing, Irrigation (non-hand set), Spreading Bins	>1000			0
Carrot, Turnip	1.4	0.29	0.33	87%	96%	1900	Irrigation (hand set)	420	58	51	2
						1100	Hand Harvesting	720	100	88	1
						210	Scouting	3800	530	470	1
						70	Hand weeding, Thinning plants	11000	1600	1400	0

Table 11.2.1-2. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Naled Uses											
Crop	Application Rate (lb ai/acre)	DFR_0 (ug/cm^2 or ug/gm)[1]		Dissipation (% per day)		TC (cm^2/hr or gm/hr)	Re-entry Worker Activities	Risk Characterization[2]			
								MOE on Day-of-application			Day when Combined MOE > LOC (1000)
		Naled	DDVP	Naled	DDVP			Naled	DDVP	Combined	
						No TC	Irrigation (non-hand set), Mechanical harvesting, Mechanical weeding	>1000			0
Cantaloupe, Summer Squash	0.9	0.19	0.21	87%	96%	1900	Irrigation (hand set)	650	90	79	2
						550	Hand Harvesting, Mechanically-assisted Harvesting, Turning, Training	2200	310	270	1
						230	Transplanting	5400	750	660	1
						90	Scouting, Hand weeding, Hand pruning, Thinning fruit	14000	900	1700	0
						No TC	Irrigation (non-hand set), Mechanical weeding	>1000			0
Eggplant, Peppers	1.9	0.39	0.45	87%	96%	1900	Irrigation (hand set)	310	43	38	2
						1100	Hand Harvesting, Tying/Training	530	74	65	1
						550	Hand Harvesting, Tying/Training	1100	150	130	1
						230	Transplanting	2500	350	310	1

Table 11.2.1-2. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Naled Uses											
Crop	Application Rate (lb ai/acre)	DFR_0 (ug/cm^2 or ug/gm)[1]		Dissipation (% per day)		TC (cm^2/hr or gm/hr)	Re-entry Worker Activities	Risk Characterization[2]			
								MOE on Day-of-application			Day when Combined MOE > LOC (1000)
		Naled	DDVP	Naled	DDVP			Naled	DDVP	Combined	
						210	Scouting	2800	390	340	1
						90	Scouting, Hand weeding, Hand pruning, Thinning fruit	6500	900	790	1
						70	Hand weeding, Hand pruning	8400	1200	1100	0
						No TC	Irrigation (non-hand set), Mechanical harvesting, Mechanical weeding	>1000			0
Broccoli, Brussels sprouts, Cabbage, Cauliflower	1.9	0.39	0.45	87%	96%	4200	Hand harvesting, Scouting, Hand weeding, Topping, Tying/Training	140	19	17	2
						1900	Irrigation (hand set)	310	43	38	2
						1400	Hand weeding, Scouting, Hand Harvesting, Mechanically-assisted harvesting	420	58	51	2
						330	Scouting, Thinning plants	1800	250	220	1
						230	Transplanting	2500	350	310	1

Table 11.2.1-2. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Naled Uses											
Crop	Application Rate (lb ai/acre)	DFR_0 (ug/cm^2 or ug/gm)[1]		Dissipation (% per day)		TC (cm^2/hr or gm/hr)	Re-entry Worker Activities	Risk Characterization[2]			
								MOE on Day-of-application			Day when Combined MOE > LOC (1000)
		Naled	DDVP	Naled	DDVP			Naled	DDVP	Combined	
						No TC	Mechanical weeding, Irrigation (non-hand set), Injection Fertilizing,	>1000			0
Celery, Collards, Kale, Swiss Chard	1.4	0.29	0.33	87%	96%	1900	Irrigation (hand set)	420	58	51	2
						1100	Hand Harvesting	720	100	88	1
						230	Transplanting	3500	480	420	1
						210	Scouting	3800	530	470	1
						70	Hand weeding, Thinning plants	11000	1600	1400	0
						No TC	Irrigation (non-hand set), Mechanical harvesting, Mechanical weeding	>1000			0
Grapes	0.9	0.25	0.03	82%	70%	19300	Girdling, Turning (table grapes)	47	55	25	3
						10100	Hand harvesting, Tying/Training, Leaf pulling (juice/wine grapes)	89	100	47	3

Table 11.2.1-2. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Naled Uses														
Crop		Application Rate (lb ai/acre)		DFR$_0$ (ug/cm^2 or ug/gm)[1]		Dissipation (% per day)		TC (cm^2/hr or gm/hr)	Re-entry Worker Activities	Risk Characterization[2]				
										MOE on Day-of-application			Day when Combined MOE > LOC (1000)	
				Naled	DDVP	Naled	DDVP			Naled	DDVP	Combined		
								5500	Hand Harvesting, Tying/Training, Leaf pulling (table/raisin grapes)	160	190	87	2	
								1900	Irrigation (hand set)	470	550	250	1	
								640	Scouting, Hand Pruning, Hand weeding, Propagating, Bird Control, Trellis Repair, Hand pruning	1400	1600	750	1	
								No TC	Irrigation (non-hand set), Mechanical harvesting, Mechanical weeding, Burndown, Ditching, Mechanical pruning	>1000			0	
All crops via wide area public pest control	Tree fruits & nuts	0.1	100% deposition	0.02	0.0022	40%	63%	100	Orchard maintenance, Hand weeding, Baiting/Trapping, Poling	140000	170000	77000	0	
			31% deposition	0.01	0.0007					440000	530000	240000	0	
	Head and	0.1	100% deposition	0.02	0.02	87%	96%	4200	Hand harvesting, Scouting, Hand	2600	370	320	1	

Table 11.2.1-2. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Naled Uses

Crop		Application Rate (lb ai/acre)		DFR_0 (ug/cm^2 or ug/gm)[1]		Dissipation (% per day)		TC (cm^2/hr or gm/hr)	Re-entry Worker Activities	Risk Characterization[2]			
										MOE on Day-of-application			Day when Combined MOE > LOC (1000)
				Naled	DDVP	Naled	DDVP			Naled	DDVP	Combined	
	Stem Brassica		31% deposition	0.01	0.01				weeding, Topping, Tying/Training	8500	1200	1100	0
	Cotton	0.1	100% deposition	0.16	0.04	40%	63%	5050 gm/hr	Mechanical Harvesting (tramper)	280	180	110	4
			31% deposition	0.05	0.01					920	580	360	2
	Grapes	0.1	100% deposition	0.03	0.0038	82%	70%	19300	Girdling, Turning (table grapes)	420	490	230	2
			31% deposition	0.01	0.0012					1400	1600	750	1

1. DFR_0 (ug/cm2) = (Study DFR_0/Study Application Rate) * Application Rate. For contact with cotton bolls an estimate of "dislodgeable boll residue" (DBR_0, ug/gm cotton boll) is used.
2. MOE = PoD (mg/kg/day) / [DFR_0 x (1-Dissipation)^t x TC x 0.001 mg/ug x 8 hrs/day / BW (kg)]. Combined MOE = $1/[(1/MOE_{Naled} + MOE_{DDVP})]$
3. Unlike direct application to agricultural crops, wide area public pest control applications over agricultural areas are not always assumed to deposit residues equivalent to the application rate. Thus, for naled, in addition to assuming 100% deposition, risk estimates are also presented assuming only 31% deposition as described in Section 9.2 above.

Restricted Entry Interval

Naled is classified as Toxicity Category II via oral, dermal, and inhalation exposure routes and Toxicity Category I for eye and skin irritation potential. It is a weak skin sensitizer. Under 40 CFR 156.208 (c)(2), active ingredients classified as Category I for dermal toxicity, eye irritation or skin irritation effects are assigned a 48-hour REI. Additionally, according to 40 CFR 156.208 (c)(2), products containing naled, as an organophosphate pesticide, are required to have an REI of "72 hours in outdoor areas where average annual rainfall is less than 25 inches per year".

The dermal risk assessment demonstrated that most steady-state post-application risk estimates – considering exposures from both naled and DDVP – were not of concern after 48 or 72 hours, therefore, the [156 subpart K] Worker Protection Statement interim REI of 48 hours (or 72 hours, where applicable) is adequate. However, activities related to harvesting cotton had post-application risk estimates of concern beyond 48 or 72 hours:

- Mechanical harvesting
  - Conventional Module
    - Picker Operator (MOE ≥ 1000 on Day 7)
    - Raker (MOE ≥ 1000 on Day 7)
    - Module Builder Operator (MOE ≥ 1000 on Day 5)
  - Trailer
    - Picker Operator (MOE ≥ 1000 on Day 7)
    - Raker (MOE ≥ 1000 on Day 7)
    - Tramping (MOE ≥ 1000 on Day 8)

11.2.2 Inhalation Post-Application Risk

Agricultural Use

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010[18]. The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis[19]. During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for naled.

In addition to the volatilization screening tool, a post-application inhalation exposure assessment was conducted for naled utilizing currently available inhalation toxicity and air monitoring data. As previously described in Section 9.1, air monitoring following an application of naled (including measurements of DDVP) is available (Tulare, CA in 1995), as is route-specific

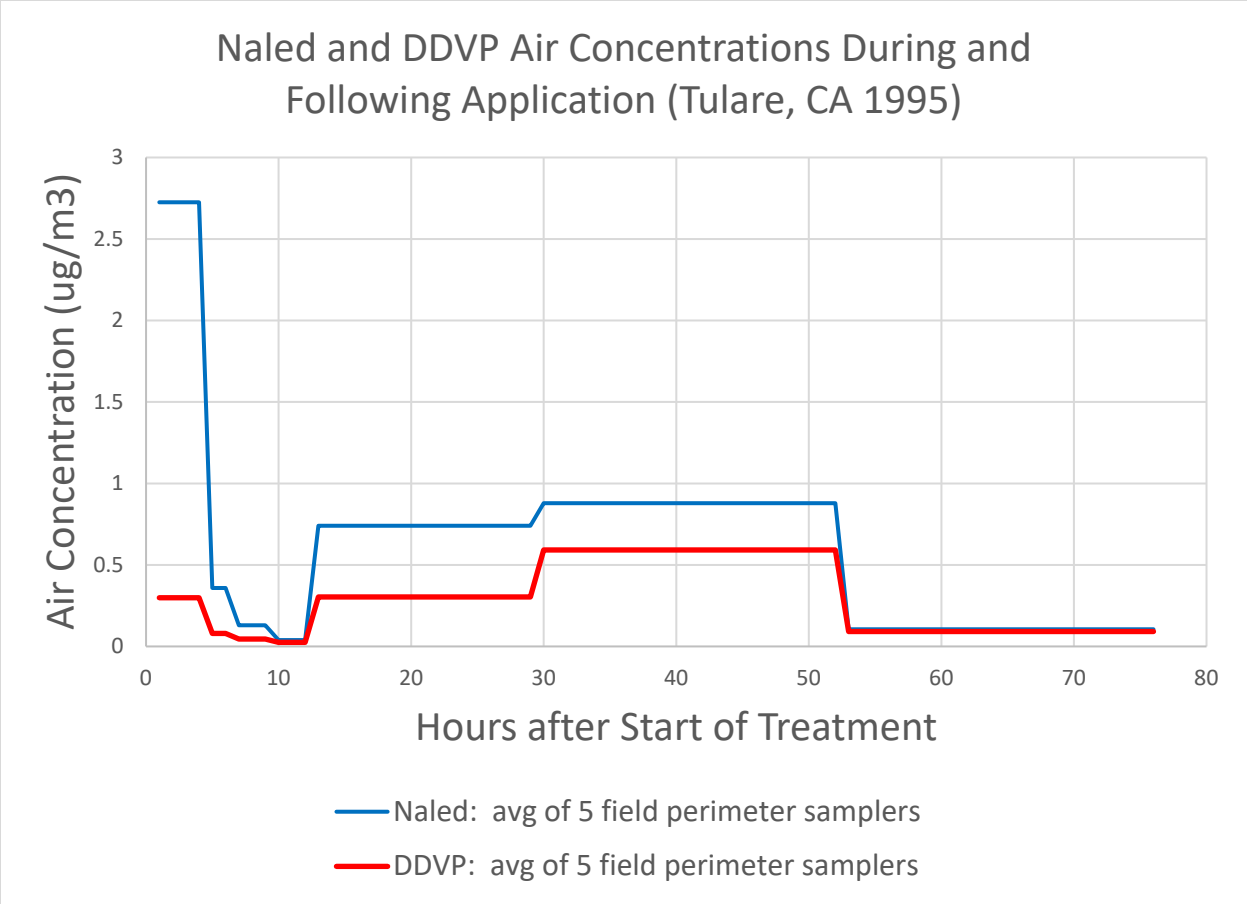
[18] http://www regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037
[19] http://www regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219

inhalation toxicity data available that can be used for occupational post-application inhalation risk assessment.

The data applicable for post-application occupational inhalation risk assessment was conducted in Tulare, CA in 1995[20]. It involved air monitoring around the perimeter of a 20-acre orange grove during the application and up to 72 hours post-application. Section 9.1 provides more specifics on the details of the study. The maximum concentration for naled was 6.3 ug/m^3, found in a 4-hour sample taken during application and the maximum DDVP sample was 0.994 ug/m^3 found in a 11-hour sample taken 24-48 hours after application. Samples during application, likely reflecting unsettled spray droplets, show proportions of between 70-90% of the total (naled + DDVP) as naled and 10-30% of the total as DDVP. Days after application the proportion changes to approximately 50% naled/50% DDVP.

The plot below presents the naled and DDVP data – the average of the 5 perimeter samples is represented by the horizontal lines whose length corresponds to the sample's duration. A dissipation pattern is not immediately clear from the data: there was a decrease following application for about 10 hours post-application, then an increase over the course of 40 hours, followed by another decrease again after about 50 hours post-application. Sampling beyond 72 hours might have made evident additional decreases in air concentrations around the treated field.

[20] http://www.cdpr.ca.gov/docs/emon/pubs/tac/tacpdfs/nalapsi.pdf



An aggregate risk index (ARI) approach was used since naled and DDVP share a common toxicological endpoint (AChE inhibition) and the LOCs for each chemical are different. The LOC is an ARI of 1; therefore, ARIs of less than 1 indicate risk estimates of concern. The aggregate risk index (ARI) was calculated as follows:

$$ARI = \frac{1}{\frac{Naled\ LOC_{Inhalation}}{\left(\frac{Naled\ PoD_{Inhalation}}{Naled\ Dose_{Inhalation}}\right)} + \frac{DDVP\ LOC_{Inhalation}}{\left(\frac{DDVP\ PoD_{Inhalation}}{DDVP\ Dose_{Inhalation}}\right)}}$$

Table 11.3.2-1 provides risk estimates based on the air concentrations after the application. Risk estimates are shown based on steady-state toxicology given workers may experience repeat exposures during agricultural work seasons. Steady-state risk estimates are of concern based on various estimates of average air concentrations following application; the 3000-fold uncertainty factors for DDVP inhalation toxicity are a significant factor in these risk estimates. Because a dissipation pattern was not completely evident, modeling and estimation of risk beyond 72 hours was not conducted. However, risk estimates based on only those samples taken 48-72 hours post-application – as if the workers "re-entered" 3 days after application – were of concern.

Table 11.2.2. Summary of Air Monitoring Results for Occupational Post-application Inhalation Risk Assessment						
Monitoring Type	Location/Year	Sampling Time/Result Presentation	Chemical	Concentration (ng/m^3)	Risk Characterization Steady State	
					MOE[1] (LOC_{Naled}=300) (LOC_{DDVP}=3000)	ARI[2]
Application	Tulare, CA 1995 (all pre-application "background" samples were non-detects)	Average of all samples following application (72-hour time-weighted average)	Naled	508	1200	0.04
			DDVP	296	140	
		Average of only those samples taken 2-3 days after application (24-hour time-weighted average)	Naled	136	4600	0.12
			DDVP	111	360	

1. Steady-state MOE = Acute or Steady-state HEC (ng/m3) / Study air concentration (ng/m^3). See Section 4 for HECs.
2. ARI = $1/[(LOC_{Naled}/MOE_{Naled})+(LOC_{DDVP}/MOE_{DDVP})]$

Greenhouse Use

The Worker Protection Standard (WPS) contains requirements for protecting workers from inhalation exposures during and after greenhouse applications through the use of ventilation requirements [40 CFR 170.110, (3) (Restrictions associated with pesticide applications)]. The WPS requires any one of the following ventilation criteria: (1) ten air exchanges completed; (2) two hours of mechanical ventilation; (3) four hours of passive ventilation; (4) eleven hours with no ventilation followed by one hour of mechanical ventilation; (5) eleven hours with no ventilation followed by two hours of passive ventilation, or (6) twenty-four hours with no ventilation.

Current labels for greenhouse uses require users to follow the WPS ventilation criteria, therefore re-entry inhalation risks are not of concern. Additionally, the label requires supplied air respirators or SCBA for pre-ventilation emergency re-entry during the treatment process as well as an organic vapor cartridge respirator during early re-entry prior to expiration of any applicable REI.

11.2.3 Combined Dermal and Inhalation Occupational Post-application Exposure/Risk Estimates

Because dermal and inhalation exposures share a common toxicological endpoint, occupational post-application risks can be estimated based on both the estimated inhalation risks and dermal risks previously presented. In the case of dermal exposure, as shown in Section 11.1, some risk estimates were of concern out to a number of days following application and, as shown in

Section 11.2, inhalation risk estimates were of concern at the limit of available sampling (72 hours post-application).

Based on inhalation risk estimates of concern 72 hours post-application, it follows that combined dermal and inhalation risk estimates would also be of concern during that timeframe. Additionally, as previously described, an air concentration dissipation pattern for naled and DDVP was not apparent from the available data, and estimation of inhalation risk was not conducted based on modeling beyond the available data out to 72 hours. Therefore, REIs outlined above in relation to dermal risk estimates should be considered with the inhalation risk estimates outlined in Section 11.2. Additional post-application air monitoring or reduction in the uncertainty for inhalation toxicity would enable refinement of estimation of both inhalation-specific and combined dermal and inhalation risks

12.0 Incident and Epidemiological Data Review

For this naled Tier II Incident and Epidemiology Report, HED found that overall, there were few naled incidents reported to the databases reviewed (Recore, S. *et al*., 04/02/2020, D456232). All of the reported incidents were classified as low to moderate severity. The symptoms include gastrointestinal, neurological, respiratory, dermal and ocular. HED did not identify any aberrant effects outside of those anticipated from naled exposure. Based on the continued low frequency and mostly low severity of naled incidents reported to Incident Data System (IDS), National Institute of Occupational Safety and Health (NIOSH) Sentinel Event Notification System for Occupational Risk (SENSOR)- Pesticides, National Pesticide Information Center (NPIC), and California Pesticide Illness Surveillance Program (PISP), there does not appear to be a concern at this time. Epidemiological studies investigating the association between naled and health outcomes available in the open literature were reviewed. Overall, in the studies reviewed, there was insufficient evidence to suggest a clear associative or causal relationship between naled exposure and the health outcomes investigated (infant motor function, infant sensory function, and Parkinson's disease).. The Agency will continue to monitor the epidemiology data, and -- if a concern is triggered -- additional analysis will be conducted.

13.0 References

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Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.500) for food use for naled are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test		Technical	
		Required	Satisfied
870.1100	Oral Toxicity	yes	yes
870.1200	Dermal Toxicity	yes	yes
870.1300	Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation	yes	yes
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5900	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5300	Mutagenicity—Other Genotoxic Effects	yes	yes
870.5550	Mutagenicity—Unscheduled DNA synthesis	yes	yes
870.6100a	Delayed Neurotox. (hen)	yes	yes
870.6100b	90-Day Neurotoxicity (hen)	no	no
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b	90-Day Neuro. Screening Battery (rat)	yes	yes
870.6300	Developmental Neurotoxicity	yes	yes
870.7485	General Metabolism	yes	yes[a]
870.7600	Dermal Penetration	yes	yes
870.7800	Immunotoxicity	yes	yes
Special Studies for Comparative Cholinesterase			
	Oral Acute (rat)	yes	yes
	Oral Repeat Dose (rat)	yes	yes

a = The metabolism requirement relies on that of DDVP.

A.2 Toxicity Profile

Table A.2.1 Acute Toxicity of Naled				
Guideline No.	**Study Type**	**MRID #**	**Results**	**Toxicity Category**
870.1100	Acute Oral Toxicity – rat TXR 0004170	00142660 (1984)	Corn oil: LD_{50} = 325 mg/kg (M) LD_{50} = 230 mg/kg (F) Carboxymethy-cellulose: LD_{50} = 191 mg/kg (M) LD_{50} = 92 mg/kg (F)	II
	Acute Oral Toxicity – rat TXR 4001914	45193201 (2000)	LD_{50} > 50 mg and < 500 mg/kg (M & F)	II
870.1200	Acute Dermal Toxicity – rat TXR 0004838	00146493 (1985)	LD_{50} = 390 mg/kg (M) LD_{50} = 360 mg/kg (F)	II
	Acute Dermal Toxicity – rat TXR 4001914	45193202 (2000)	LD_{50} = 3627 mg/kg (M) LD_{50} = 4492 mg/kg (F) LD_{50} = 4037 mg/kg (C)	III
870.1300	Acute Inhalation Toxicity – rat TXR 0004838	00146494 (1985)	LC_{50} = 0.20 mg/L (M) LC_{50} = 0.19 mg/L (F)	II
	Acute Inhalation Toxicity – rat TXR 4001914	45193203 (2000)	LC_{50} = 1.40 mg/L (M) LC_{50} = 1.50 mg/L (F) LC_{50} = 1.42 mg/L (C)	III
870.2400	Acute Eye Irritation – rabbit	00074826 (1974)	Severe irritant	I
	Acute Eye Irritation – rabbit TXR 4001914	45193204 (2000)	Self-Validated	I
870.2500	Acute Dermal Irritation – rabbit	00074825 (1974)	Corrosive (escharotic)	I
	Acute Dermal Irritation – rabbit TXR 4001914	45193205 (2000)	Moderately irritating	III
870.2600	Skin Sensitization - guinea pig TXR 0003285	00074657 (1978)	Weakly positive	NA
	Skin Sensitization - guinea pig TXR 4001914	45193206 (2000)	Self-Validated – Skin sensitizer	NA

[1]A preliminary study to a cytogenetics assay obtained somewhat lower oral LD_{50} values of 85.1 mg/kg/day for male rats and 81.2 mg/kg/day for females using CMC as the vehicles (MRID 00142665)
OPIDN = OP-induced delayed neuropathy

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile - Naled		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/TXR No./ Classification /Purity/Doses**	**Results**
870.3100 28- day Oral Subchronic Range-Finding Sprague Dawley Rat	00088871, 00246496 (1981) TXR 0001460 **Acceptable/Guideline** Oral (gavage) doses: 0, 0.25, 1, 10, 100 mg/kg/day	NOAEL = 1 mg/kg/day LOAEL = 10 mg/kg/day based on cholinergic effects (26%↓ and 28%↓ RBC ChEI, males and females, respectively. 53%↓ and 52%↓ brain ChEI, males and females, respectively. 0.25 mg/kg/day did not result in a minimum of 10% ChEI for either compartment.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile - Naled		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/TXR No./ Classification /Purity/Doses**	**Results**
870.3200 28-Day Dermal Toxicity Rat	MRID 00160750 (1986) TXR 0005774 **Acceptable/Guideline** Doses Tested: 0, 1, 20, 80 mg/kg/day	Systemic and ChEI NOAEL = 1 mg/kg/day Systemic and ChEI LOAEL = 20 mg/kg/day based on findings of dermal irritation, reduced weight gain and ChE (60%↓ brain ChEI, 25% RBC ChEI).
870.3200 28-Day Dermal Toxicity Female Crl:CD (SD) BR Rat	MRID 45222001 (2000) TXR 0014436 **Acceptable/Guideline** Doses Tested: 0, 5, 10, 40, 80 mg/kg/day	Systemic and ChEI NOAEL = 10 mg/kg/day Systemic and ChEI LOAEL = 40 mg/kg/day based on minimal kidney effects (increased relative weight and hydronephrosis) in males and decreased brain ChE activity in females and RBC and plasma ChE activity in both sexes.
870.3465 90-Day Inhalation Fischer-344 Rat	MRIDs 00164224, 00265678, 00265680 (1986) TXR 0005784 **Acceptable/Guideline** Concentrations Tested: 0, 0.2, 1.2, 6 µg/L	NOAEL was not established LOAEL was 0.23 µg/L based on 17% inhibition of RBC cholinesterase activity. Portal of entry histology/pathology was examined and did not report any treatment-related effects.
870.3465 21-Day Inhalation Fischer-344:CDF Rat	MRIDs 40087201, 00148978 (1988) TXR 0006709 **Supplementary/Non-Guideline** Concentrations Tested: 0, 4, 8, 16 µg/L	NOAEL was not established LOAEL was 3.4 µg/L based on inhibition of brain, RBC, and plasma cholinesterase activity and nasal epithelial lesions.
870.3700 Developmental Toxicity Rat	MRIDs 00138682 TXR 0003815, 0004170 MRID 00144026 (1984) TXR 0005000 **Acceptable/Guideline** Doses Tested (gavage): 0, 2, 10, 40 mg/kg/day	NOAEL = 10 mg/kg/day LOAEL = 40 mg/kg/day based on maternal clinical signs (tremors hypoactivity, discharge from mouth and eyes, dyspnea) and weight loss. No developmental toxicity identified related to treatment.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile - Naled		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/TXR No./ Classification /Purity/Doses**	**Results**
870.3700 Developmental Toxicity Rabbit	MRID 00146496 (1985) TXR 0005332 **Acceptable/Guideline** Doses Tested (gavage): 0, 0.2, 2, 8 mg/kg/day	NOAEL = 8 mg/kg/day LOAEL was not established
870.3800 Two-Generation Reproductive Toxicity Rat	MRID 00146498 (1985) TXR 0005000 **Acceptable/Guideline** Doses Tested (gavage): 0, 2, 6, 18 mg/kg/day	Parental NOAEL = 6 mg/kg/day Parental LOAEL = 18 mg/kg/day based on based on decreased body weight gain in both parental generations. Reproductive NOAEL = 18 mg/kg/day Reproductive LOAEL was not established
870.4100a, 870.4200a Chronic Toxicity/Carcinogenicity Rat	MRIDs 00128701, 00141784 (1984), 40418901 (1983) MRID 00088871 TXR 0002997, 0004521, 0004521, 0006711 **Acceptable/Guideline** Doses Tested (gavage): 0, 0.2, 2, 10 mg/kg/day for 2 years	NOAEL = 0.2 mg/kg/day LOAEL = 2 mg/kg/day based on decreased RBC (4-33%), plasma (54-60%, and brain (24%) ChE activity.
870.4100b 1-year chronic toxicity Beagle dog	MRID 00160751 (1986) TXR 0005774 **Acceptable/Guideline** Doses Tested (gavage): 0, 0.2, 2, 20 mg/kg/day for 1-yr	NOAEL = 0.2 mg/kg/day LOAEL = 2 mg/kg/day based on decreased RBC (43-58%), plasma (24-48%, and brain (17%) ChE activity, and decreased hemoglobin and hematocrit values for both sexes.
870.4200b Carcinogenicity Mice	MRIDs 00141785, 00148569 (1984) TXR 0004128, 0004521 **Acceptable/Guideline** Doses Tested (gavage): 0, 3, 15, 75 (later became 50) mg/kg/day for 89 weeks	No neoplastic finders were related to treatment. Cholinesterase was not measured.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile - Naled		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/TXR No./ Classification /Purity/Doses**	**Results**
870.5200 *In vivo* Mouse gene mutation	MRID 00141571 (1984)	An in vivo gene mutation study (mouse spot test) was conducted with pregnant C57BL/6 mice given 0, 3, 20, or 150 mg/kg/day of naled by gavage for four days of gestation (days 8-12). Litters were scored for coat color mutations ("spots") on post-partum days 12 and 28. The test was presumably indicative of mutation events consisting of intragenic base-pair changes, deletions and somatic crossing-over. The high dose of naled was very toxic producing maternal mortality, decreased maternal body weight and decreased pup survival. Naled exhibited no potential to induce coat color spots
870.5500 *Salmonella typhimurium* gene mutation	MRID 00142662 (1983) **Acceptable**	(Ames Assay) Concentrations tested: DMSO, 0.5, 1, 2 µM Highest dose tested was toxic in absence of metabolic activation. 1 µM was positive both with and without metabolic activation. Lowest dose tested was marginally positive (less than 2-fold that of control).
870.5500 Bacterial DNA damage and repair (*Proteus mirabilis*)	MRID 00142662 (1983) **Acceptable**	Naled was tested for DNA damage in *Proteus mirabilis* strains PG273 (wild type) and PG713 (thr-, rec-, hcr-). Naled was negative in both strains at inhibitory concentrations of 10 and 40 µM.
Cytogenetics in mouse bone marrow	00146497 (1984) **Acceptable**	Naled was tested for cytogenetic effects in vivo in the mouse bone marrow micronucleus assay. Naled was administered to male and female Swiss mice as a single oral dose by gavage. Dose levels were 0, 55, 110, or 220 mg/kg for males and 0, 55, 110, or 290 mg/kg for females. Dose selection was based on preliminary studies indicating oral LD50 values of 257 mg/kg for males and 336 mg/kg for females. Bone marrow cells were harvested 24, 48 and 72 hours after treatment. The highest dose produced mortality (16-24%) and clinical signs of toxicity. Naled had no cytotoxic effect on bone marrow at these dose levels and produced no nuclear anomalies.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile - Naled		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/TXR No./ Classification /Purity/Doses**	**Results**
Cytogenetics and Clastogenicity in rat bone marrow	00142665 (1983) **Acceptable**	In an *in vivo* cytogenetics study, male and female Sprague Dawley rats were administered naled as a single oral dose by gavage. Dose levels were 0, 3.88, 12.93, or 38.80 mg/kg for males and 0, 6.17, 20.57, or 61.70 mg/kg for females. Dose selection was based on preliminary studies conducted at the same laboratory indicating oral LD_{50} values of 85.1 mg/kg for males and 81.2 mg/kg for females. Bone marrow cells were harvested 6, 24 and 48 hours after treatment. High dose females showed signs of toxicity including ataxia, dyspnea and oral exudate. Cytotoxicity in bone marrow was not evident at any dose level. Naled had no clastogenic effect. The highest dose was considered to be near a maximum tolerated dose based on the clinical signs observed in females and the results of preliminary studies indicating the high dose for males was approximately one-half the oral LD_{50}
870.6100a Acute Delayed Neurotoxicity (hen)	MRID 41630701 (1990) TXR 0008325 **Acceptable/Guideline** Doses Tested: (set 1) 42 mg/kg; (set 2) 8, 42 mg/kg	All hens in set 1 showed clinical signs of neurotoxicity (subdued, unsteady). Axonal degeneration in the spinal cord was increased. Brain ChE decreased 50% at 42 mg/kg. No frank delayed neurotoxicity, but degenerative neuronal effect manifested in the spinal cord.
870.6100b 28-Day Delayed Neurotoxicity (hen)	MRID 43223903 (1994) TXR 0011374 **Acceptable/Guideline** Doses tested (oral): 0, 0.4, 2.0, 4.0 mg/kg/day.	Minimal body weight decrease at high dose and significant brain ChE inhibition at 2 and 4 mg/kg/day. No treatment related clinical or delayed neuropathy.
870.6200a Acute Neurotoxicity (rat)	42861301 (1993) TXR 0012054, 0011228 **Acceptable/Guideline** Doses Tested (gavage): 0, 25, 100, 400 mg/kg	NOAEL was 25 mg/kg LOAEL was 100 mg/kg based on marked effects in the functional observational battery on the day of treatment (convulsions, tremors, increased secretions, exophthalmos, respiratory changes, reduce muscle strength, and slow response to stimuli). Total motor activity was also reduced. Cholinesterase was not measured.
870.6200b Subchronic Neurotoxicity Rat	43223901 (1994) TXR 0011374 **Acceptable/Guideline** Doses Tested (gavage): 0, 0.4, 2.0, 10 mg/kg/day.	NOAEL = 2 mg/kg/day LOAEL = 10 mg/kg/day based on sporadic occurrences of tremors (forelimb, hindlimb and/or whole body). Cholinesterase was not measured.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile - Naled		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/TXR No./ Classification /Purity/Doses**	**Results**
870.6300 Developmental Neurotoxicity Screening Study Rat	MRIDs 46153102 46153101 (2003) TXR 0052378 **Acceptable/Non-Guideline** Doses tested (gavage): 0, 0.4, 2, or 10 mg/kg/day during gestation day 7 to lactation day 7. F1 pups were dosed via gavage with same doses on postnatal days 8-22.	Maternal NOAEL = 10 mg/kg/day Maternal LOAEL = not established Offspring NOAEL = 0.4 mg/kg/day Offspring LOAEL = 2 mg/kg/day based on decreased total motor activity in males at PND 14 and 18 and decreased subsession motor activity in males in the 41-45 minute interval on PND 18. A preliminary report was also submitted in which cholinesterase parameters were measured. Doses tested (gavage): 0, 3, 10, 30 mg/kg/day Maternal ChEI NOAEL not established Maternal ChEI LOAEL = 3 mg/kg/day based on brain and RBC ChEI (brain: 16%↓ postpartum day 22; RBC: 27%↓ gestation day 22, 25%↓ postpartum day 22) Fetus ChEI NOAEL not established Fetus ChEI LOAEL = 3 mg/kg/day based on brain ChEI (9%↓) decreases in males Pup ChEI NOAEL not established Pup ChEI LOAEL = 3 mg/kg/day based on brain ChEI on PND 15 (11%↓) for males and PND 8 (10%↓) for females and based on RBC ChEI on PND 15 (14%↓) for males and PND 22 (11%↓) for females.
870.7485 Metabolism Study Rat	(DDVP metabolite studies) MRID 41228701 TXR 0008132 MRID 41839901 TXR 0008444 **Acceptable**	The requirement for a metabolism study on naled was waived since metabolism data from DDVP, a more toxic metabolite, can be used to substitute. The overall metabolic profile for DDVP suggests the involvement of the one-carbon pool biosynthetic pathway as evidenced by the presence of a relatively large amount of radioactivity in the form of expired $^{14}CO_2$ and the presence of dehalogenated metabolites as well as urea and hippuric acid.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile - Naled		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/TXR No./ Classification /Purity/Doses**	**Results**
870.7600 Dermal Penetration Male Sprague-Dawley Rat	MRID 45099301 (1999) D265852; TXR 0014339 **Acceptable/Guideline** Young male rats (4/dose/exposure duration) received single application of ^{14}C-naled EC formulation on a 10 cm^2 shaven dorso-lumbar area at 0.045, 0.19, 0.52, or 4.2 mg/rat for durations of 0.5, 1, 2, 4, 10 or 24 hours.	The mean percentage of absorbed radioactivity at the three lower doses was 2-3 times higher than that absorbed at the high dose during the first 10 hours of exposure (7.7-21.45% vs 3.25-10.20%) indicating a saturation of absorption at this dose. At 420 µg/cm^2 , the absorbed radioactivity peaked at 20.69% after 24 hours of exposure. The majority of the unabsorbed radioactivity remained on the skin surface and was removed by skin washing. It gradually decreased (84.74% at 0.5 hours to 38.29% at 24 hours) in the 420 µg/cm^2 dosed group and at all lower dose levels with increasing exposure duration. In conclusion, the test material, naled is moderately absorbed through the skin at peak levels of 23% after 24 hours of exposure.
870.7800 Immunotoxicity Study Sprague Dawley Rat	MRID 48777301 (2012) TXR 0056394 **Acceptable/Guideline** Doses tested (gavage): 0, 0.4, 2, 10 mg/kg/day for 4 weeks	The systemic toxicity NOAEL is 0.4 mg/kg bw/day The systemic toxicity LOAEL is 2 mg/kg bw/day based on reduced erythrocyte and brain acetylcholinesterase activity The immunotoxicity NOAEL is 10 mg/kg/day The immunotoxicity LOAEL is not established
Special Study Dermal penetration – *in vitro* Rat and Human Epidermal Membranes	MRID 45099302 (2000) TXR 0014340 **Acceptable/nonguideline** Dilutions of the Dibrom-8® emulsion equivalent to 426-430, 47.3-54.3, 19.5-20.6, or 4.46-5.04 µg naled/cm^2 of skin for 0.5, 1, 2, 4, 10 or 24 hours (skin washed at the end of exposure period)	The results obtained in this *in vitro* study suggest that naled applied in a spray emulsion is absorbed faster and more in the rat epidermis than in the human epidermis. The maximum amount absorbed by the human epidermis was 18% at 1/1000 dilution application compared to 85% of the applied dose in the rat at 1/80 dilution. More radioactivity volatilized from the human skin than in the rat. Also, the rat skin retained more radioactivity in the epidermis than in the human epidermis. Although there are differences in the *in vitro* absorption behavior of naled from rat and human epidermis, no conclusions can be derived from these results regarding the *in vivo* absorption of this chemical.
Special Study Acute Oral Cholinesterase Inhibition Study (time-course) Rat	MRID 46153103 TXR 0053710 **Acceptable/Non-Guideline** Single oral dose at 0, 100 mg/kg to 25 female Wistar rats/dose, sacrificed at 1, 3, 8, 24 or 72-hour post dosing.	Peak ChE activity inhibition occurred at 1-3 hours post dosing.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile - Naled		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/TXR No./ Classification /Purity/Doses**	**Results**
Special Study Acute Oral Cholinesterase Inhibition Study Pre-weaning Rat	MRID 46153105 TXR 0053710 **Acceptable/Non-Guideline** Single oral dose of 0, 5, 25 or 100 mg/kg to post-natal day 8, 15, or 22 Wistar rats, 5 rats/sex/dose and sacrificed at 1 hr post dosing.	Acute LOAEL was 5 mg/kg based on 10% ChE inhibition in brain and RBC in PND 15 pups. Acute NOAEL was not established.
Special Study Acute Oral Cholinesterase Inhibition Study Adult Rat	MRID 46153107 TXR 0053710 **Acceptable/Non-Guideline** Single oral dose of 0, 5, 25 or 100 mg/kg to adult Wistar rats, 5 rats/sex/dose/time point and sacrificed at 1 hr, day 8 and day 15 post dosing.	Acute LOAEL was 5 mg/kg based on 10% ChE inhibition in RBC in females. Acute NOAEL was not established.
Special Study Acute Oral Cholinesterase Inhibition Study Adult Rat	MRID 46153106 TXR 0053710 **Acceptable/Non-Guideline** Single oral dose of 0, 5, 25 or 100 mg/kg to adult Sprague Dawley rats, 5 rats/sex/dose/time point and sacrificed at 1 hr, day 8 and day 15 post dosing.	Acute LOAEL was 5 mg/kg based on 10% ChE inhibition in brain and RBC in females. Acute NOAEL was not established.
Special Study Repeat Oral Dose Cholinesterase Inhibition Study Pre-weaning and Young Adult Rat	MRID 46153104 TXR 0053710 **Acceptable/Non-Guideline** Oral doses of 0, 0.4, 2, 10 and 30 mg/kg/day in the diet for 7 days to PND 12 or young adults (PND 42) Wistar rats.	LOAEL was 2 mg/kg based on 10% ChE inhibition in RBC in males. NOAEL was 10 mg/kg/day.
Special Study Repeat (90-day) Oral Dose Cholinesterase Inhibition Study with recovery Adult Rat	MRID 46153108 TXR 0053710 **Acceptable/Non-Guideline** Oral doses of 0, 0.4, 2, or 10 mg/kg/day in the diet of adult Sprague Dawley rats for 90 days. 10/sex/group were retained for 8 weeks without exposure.	LOAEL was 2 mg/kg based on 10% ChE inhibition in RBC in males. NOAEL was 10 mg/kg/day.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile - Naled		
Guideline No./ Study Type/Animal Species and Strain	**MRID No. or Study Authors (year)/TXR No./ Classification /Purity/Doses**	**Results**
Special Study In Vivo Single Dose Dermal Toxicity Study Female Sprague Dawley (Crl:SD) rats	MRID 50795201 TXR 0057864 **Acceptable/Non-Guideline** Doses of 0, 12.5, 25, 50, or 100 mg/kg was applied as a single dermal dose to a clipped area of skin.	The systemic LOAEL was not determined. The systemic NOAEL is 100 mg/kg. The neurotoxicity LOAEL is 50 mg/kg based on inhibition of RBC ChE activity at 2 h for adult female rats. The neurotoxicity NOAEL is 25 mg/kg.
Special Study Single Dose Inhalation Toxicity Study Female Sprague Dawley (Crl:SD) rats	MRID 50823901 TXR 0057864 **Acceptable/Non-Guideline** Nose-only inhalation at target concentrations of 0, 1, 15, or 30 µg/L (equivalent to 0, 0.001, 0.015, and 0.030 mg/L; achieved concentrations of 0, 0.981, 15.8, and 27.0 µg/L).	The systemic LOAEC was not determined. The systemic NOAEC is 30 µg/L (achieved mean concentration of 27.0 µg/L). The inhalation LOAEC is 15 µg/L (achieved mean concentration of 15.8 µg/L) based on ulceration, inflammatory cell infiltration, epithelial regeneration, and necrosis of the respiratory epithelium at the base of the epiglottis, arytenoids, and ventral cartilage of the larynx and inflammation of the squamous epithelium of the nasal turbinates. The inhalation NOAEC is 1 µg/L (achieved mean concentration of 0.981 µg/L).

A.3 HEC/HED Calculations

1) Single Dose (Acute)

The route specific single dose inhalation study in rats was selected to evaluate single dose (acute) inhalation exposures. The BMD_{10} of 15.2 mg/m^3 (0.0152 mg/L) is based on RBC AChE inhibition in adult females; $BMDL_{10}$ = 9.9 mg/m^3 (0.0099 mg/L). Human equivalent concentrations (HECs) were derived using the $BMDL_{10}$ and the regional deposited dose ratio (RDDR). The RDDR accounts for the particle diameter [mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD)] and estimates the different dose fractions deposited along the respiratory tract. The RDDR also accounts for interspecies differences in ventilation and respiratory tract surface areas. For the single dose inhalation toxicity study with naled, a RDDR was estimated at 2.606 based on a MMAD of 1.0 μm and GSD of 1.63.

Human equivalent doses (HEDs) were subsequently calculated from the HECs for residential and occupational handler scenarios. HEC and HED calculations are summarized in Table A.3.1. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 3X due to the calculation of HECs accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. The intraspecies uncertainty factor remains at 10X.

a. Human Equivalent Concentration (HEC)

Acute exposure is 2 h/day based on acute inhalation study duration and anticipated acute inhalation exposure scenarios therefore both the daily duration adjustment and the weekly duration adjustment are = 1 (no duration adjustment).

$HEC = NOAEL_{study}$ * (daily duration of $exposure_{animal}$/daily duration of $exposure_{human}$) * (days/week of $exposure_{animal}$/days/week of $exposure_{human}$) * RDDR

HEC = 0.0099 mg/L * (1[no adjustment]) * (1[no adjustment]) * 2.606 = 0.026 mg/L.

a. Route-to-Route Extrapolation

HED's route-to-route extrapolation converts human and animal values from mg/L concentrations to mg/kg oral equivalent doses. The equation uses a single conversion factor to account for default body weights and respiratory volumes.

Using the HEC calculated, a conversion of the inhalation concentration to a dose (mg/L to mg/kg/day) was conducted as follows:

Human-Equivalent Dose (HED, mg/kg/day) = Dose (HEC value, mg/L) x A x CF (L/h/kg) x D (hours) = mg/kg

Where:
A = absorption: ratio of deposition and absorption in respiratory tract compared to absorption by the oral route (1).

CF = conversion Factor; a L/h/kg factor which accounts for respiratory volume and body weight for a given species and strain (11.8).
D = duration; duration of daily animal or human exposure (hours).

Therefore, the occupational human equivalent dose for naled is calculated as follows:

Occupational Handler HED:
0.026 mg/L x 1 x 11.8 L/h/kg x 8 h = 2.441 mg/kg/day

Residential Handler and Indoor Post-Application HED:
0.026 mg/L x 1 x 11.8 L/h/kg x 2 h = 0.610 mg/kg/day

Residential Outdoor Post-application:
0.026 mg/L x 1 x 11.8 L/h/kg x 2.3 h = 0.702 mg/kg/day

HEC and HED calculations are summarized in Table A.3.1. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 3X due to the calculation of HECs accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. The intraspecies uncertainty factor remains at 10X.

a. Summary

Table A.3.1. Human Equivalent concentrations (HECs) and Human Equivalent Doses (HEDs) Based on Acute Inhalation Study MRID 50823901 and RDDR Methodology

Population	Scenario	Tox duration adjustment		HEC		HED (mg/kg-day)
		Daily	Weekly	mg/L	mg/m^3	
Occupational	Handler	1	1	0.026	25.799	2.441
Residential	Handler	NA	NA	0.026	25.799	0.610
	Outdoor post-application	NA	NA	0.026	25.799	0.702
	Indoor Post-application	NA	1	0.026	25.799	0.610
	Bystander	1	1	0.026	25.799	NA

2) Steady-state

The route specific repeat dose inhalation study in rats was selected to evaluate steady state inhalation exposures. The BMD_{10} of 0.3 mg/m^3 (0.0003 mg/L) is based on RBC AChE inhibition in adult males and females; $BMDL_{10}$ = 0.2 mg/m^3 (0.0002 mg/L). HECs were derived using the $BMDL_{10}$ and the RDDR. For the repeated dose inhalation toxicity study with naled, a RDDR was estimated at 4.176 based on a MMAD of 1.80 µm and GSD of 1.00.

HEDs were subsequently calculated from the HECs for residential and occupational handler scenarios. HEC and HED calculations are summarized in Table A.3.2. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 3X due to the calculation of HECs accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. The intraspecies uncertainty factor remains at 10X.

a. Human Equivalent Concentration (HEC)

Animal study was conducted for 6 hrs/day and 5 days/week.
Assume occupational handler exposure for 8 hrs/day and 5 days/week.
Assume residential bystander exposure for 24 hrs/day and 7 days/week.
For residential handler and outdoor post-application exposure, there are no daily or weekly duration adjustments.
For residential indoor post-application exposure, there is no daily duration adjustment.

HEC = $NOAEL_{study}$ * (daily duration of $exposure_{animal}$/daily duration of $exposure_{human}$) * (days/week of $exposure_{animal}$/days/week of $exposure_{human}$) * RDDR

Occupational Handler HEC = 0.0002 mg/L * (6/8) * (5/5) * 4.176 = 0.001 mg/L.
Residential Handler and Outdoor Post-Application HEC = 0. 0002 mg/L * 4.176 = 0.001 mg/L.
(Expected exposure is less than the duration of the available inhalation toxicity studies; downward adjustments are not permitted)
Residential Indoor Post-application HEC = 0. 0002 mg/L* (5/7) * 4.176 = 0.001 mg/L.
(Expected daily exposure is less than the duration of the available inhalation toxicity studies; downward adjustments are not permitted)
Residential Bystander HEC = 0. 0002 mg/L* (6/24) * (5/7) * 4.176 = 0.0001 mg/L.

b. Route-to-Route Extrapolation

HED's route-to-route extrapolation converts human and animal values from mg/L concentrations to mg/kg oral equivalent doses. The equation uses a single conversion factor to account for default body weights and respiratory volumes.

Using the HEC calculated, a conversion of the inhalation concentration to a dose (mg/L to mg/kg/day) was conducted as follows:

Human-Equivalent Dose (HED, mg/kg/day) = Dose (HEC value, mg/L) x A x CF (L/h/kg) x D (hours) = mg/kg

Where:
A = absorption: ratio of deposition and absorption in respiratory tract compared to absorption by the oral route (1).
CF = conversion Factor; a L/h/kg factor which accounts for respiratory volume and body weight for a given species and strain (11.8).
D = duration; duration of daily animal or human exposure (hours).

Therefore, the occupational human equivalent dose for naled is calculated as follows:

Occupational Handler HED:
0.001 mg/L x 1 x (11.8 L/h/kg) x (8 h) = 0.059 mg/kg/day

Residential Handler HED:
0.001 mg/L x 1 x (11.8 L/h/kg) x (2 h) = 0.020 mg/kg/day

Residential Outdoor Post-application:
0.001 mg/L x 1 x (11.8 L/h/kg) x (2.3 h) = 0.023 mg/kg/day

Residential Indoor Post-application:
0.001 mg/L x 1 x (11.8 L/h/kg) x (2. h) = 0.014 mg/kg/day

HEC and HED calculations are summarized in Table A.3.2. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 3X due to the calculation of HECs accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. The intraspecies uncertainty factor remains at 10X.

b. Summary

Table A.3.2. Human Equivalent concentrations (HECs) and Human Equivalent Doses (HEDs) Based on Repeat Inhalation Study MRID 00265680 and RDDR Methodology

Population	Scenario	Tox duration adjustment		HEC		HED (mg/kg-day)
		Daily	Weekly	mg/L	mg/m^3	
Occupational	Handler	0.75	1	0.001	0.626	0.059
Residential	Handler	NA	NA	0.001	0.835	0.020
	Outdoor post-application	NA	NA	0.001	0.835	0.023
	Indoor Post-application	NA	0.71	0.001	0.597	0.014
	Bystander	0.25	0.71	0.000	0.149	NA

A.4 Summary of OPP's ChE Policy and Use of BMD Modeling

The Office of Pesticide Program's (OPP) ChE policy (USEPA, 2000[21]) describes the manner in which ChE data are used in human health risk assessment. The following text provides a brief summary of that document to provide context to points of departure selected.

ChEI can be inhibited in the central or peripheral nervous tissue. Measurements of AChE or ChE inhibition in peripheral tissues (e.g., liver, diaphragm, heart, lung, etc.) are rare. Experimental laboratory studies generally measure brain (central) and blood (plasma and RBC) ChE. Blood measures do not represent the target tissue, but are instead used as surrogate measures for peripheral toxicity in studies with laboratory animals or for peripheral and/or central toxicity in humans. In addition, RBC measures represent AChE, whereas plasma measures are predominately butyryl-ChE (BuChE). RBC AChE data are expected to provide a better representation of the inhibition of AChE in target tissues. As part of the dose response assessment, evaluations of neurobehavior and clinical signs are performed to consider the dose response linkage between ChEI and apical outcomes.

Refinements to OPP's use of ChE data have come in the implementation of BMD approaches in dose response assessment. Beginning with the OP CRA, OPP has increased its use of BMD modeling to derive PODs for AChE inhibiting compounds. Most often, the decreasing exponential empirical model has been used.

OPP does not have a defined benchmark response (BMR) for OPs. However, the 10% level has been used in the majority of dose response analyses conducted to date. This 10% level represents a 10% reduction in AChE activity (i.e., inhibition) compared to background (i.e., controls). Specifically, the BMD_{10} is the estimated dose where ChE is inhibited by 10% compared to background. The $BMDL_{10}$ is the lower confidence bound on the BMD_{10}.

The use of the 10% BMR is derived from a combination of statistical and biological considerations. A power analysis was conducted by the Office of Research and Development (ORD) on over 100 brain AChE datasets across more than 25 OPs as part of the OP CRA (USEPA, 2002). This analysis demonstrated that 10% is a level that can be reliably measured in the majority of rat toxicity studies. In addition, the 10% level is generally at or near the limit of sensitivity for discerning a statistically significant decrease in ChE activity in the brain compartment and is a response level close to the background brain ChE level. With respect to biological considerations, a change in 10% brain ChEI is protective for downstream clinical signs and apical neurotoxic outcomes. With respect to RBC ChEI, these data tend to be more variable than brain AChE data. OPP begins its BMD analyses using the 10% BMR for RBC ChEI, but BMRs up to 20% could be considered on a case by case basis as long as such PODs are protective for brain ChEI, potential peripheral inhibition, and clinical signs of neurotoxicity.

The BMD modeling process for naled involved a complete review of all the available studies that included ChE data. Data were analyzed from rats in an acute comparative cholinesterase assay

[21] USEPA (2000) Office of Pesticide Programs, US Environmental Protection Agency, Washington DC 20460. August 18, 2000 Office of Pesticide Programs Science Policy of The Use of Data on Cholinesterase Inhibition for Risk Assessments of Organophosphorous and Carbamate Pesticides.

(CCA; MRIDs 46153105 and 46153107), repeated dose CCA (MRID 46153104), 90-day oral toxicity study (MRID 46153108), 2-year chronic toxicity/carcinogenicity study (MRID 00141784), 28-day dermal toxicity studies (MRIDs 00160750 and 45222001), and inhalation toxicity study (MRID 00265680). All data from these studies were considered; however, some data were not amenable to BMD analysis. The tables below summarize the findings from the BMD modeling. Toxicity studies with AChE data were analyzed using the most recent version of EPA's Benchmark Dose Software (Version 2.4). Full results and technical details for these analyses can be found in the BMD memo (Bever, R., 08/23/2016, TXR 0057475).

Tables A.4 Results of the BMD Modeling for the Naled (Bever, R., 08/23/2016, TXR 0057475)

Table A.4.1. Results of BMD Modeling (mg/kg) for Brain and RBC ChE Data on Naled, Acute Oral Dosing Studies in Rats.

Study	Age Sex	Brain BMD_{10}	Brain $BMDL_{10}$	RBC BMD_{10}	RBC $BMDL_{10}$
MRID 46153105 Acute CCA	PND 8 Male	5.3	3.8	7.5	5.5
MRID 46153105 Acute CCA	PND 8 Female	7.2	5.5	---	---
MRID 46153105 Acute CCA	PND 15 Male	7.0	5.8	6.5	4.9
MRID 46153105 Acute CCA	PND 15 Female	---	---	7.9	5.6
MRID 46153105 Acute CCA	PND 22 Male	6.8	5.6	5.0	3.5
MRID 46153105 Acute CCA	PND 22 Female	4.8	3.6	4.2	3.2
MRID 46153107 Acute CCA	Adult Male	---	---	---	---
MRID 46153107 Acute CCA	Adult Female	---	---	10.0	5.4

--- = No model fit, either by statistical tests or visual fit or by comparison of results to empirical data, typically due to a lack of dose-response and/or extreme variation
CCA = Comparative Cholinesterase Assay

Table A.4.2. Results of BMD Modeling (mg/kg/day) for Brain and RBC ChE Data on Naled, Repeated Oral Dosing Studies in Rats.

Study (dosing days)	Age Sex	Brain BMD_{10}	Brain $BMDL_{10}$	RBC BMD_{10}	RBC $BMDL_{10}$
MRID 46153104 Repeated Dose CCA (7)	PND 18 Male	1.5	0.9 [a]	---	---
MRID 46153104 Repeated Dose CCA (7)	PND 18 Female	---	---	---	---
MRID 46153104 Repeated Dose CCA (7)	Adult Male	---	---	2.2	1.7

Table A.4.2. Results of BMD Modeling (mg/kg/day) for Brain and RBC ChE Data on Naled, Repeated Oral Dosing Studies in Rats.

Study (dosing days)	Age Sex	Brain BMD_{10}	Brain $BMDL_{10}$	RBC BMD_{10}	RBC $BMDL_{10}$
MRID 46153104 Repeated Dose CCA (7)	Adult Female	---	---	---	---
MRID 46153108 90D Oral Toxicity (90)	Adult Male	NE		1.8	0.4
MRID 46153108 90D Oral Toxicity (90)	Adult Female	NE		1.6	0.9 [a]
MRID 00141784 Carc (25/26W)	Adult Male	NE		---	---
MRID 00141784 Carc (25/26W)	Adult Female	NE		---	---
MRID 00141784 Carc (102/106W)	Adult Male	0.8	0.6	NE	
MRID 00141784 Carc (102/106W)	Adult Female	0.7	0.6	NE	

--- = No model fit, either by statistical tests or visual fit or by comparison of results to empirical data, typically due to a lack of dose-response and/or extreme variation

a After visual inspection of the plots and comparison of the predicted BMD with the results of empirical evidence (ground-truthing), Model 4 was chosen as the most accurate fit, even though other model(s) had a lower AIC.

W = weeks

CCA = Comparative Cholinesterase Assay

NE = Not evaluated

Carc = Carcinogenicity

Table A.4.3. Results of BMD Modeling (mg/kg/day) for Brain and RBC ChE Data on Naled, Dermal Toxicity in Rats.

Study (dosing days)	Age Sex	Brain BMD_{10}	Brain $BMDL_{10}$	RBC BMD_{10}	RBC $BMDL_{10}$
MRID 00160750 28-Day Dermal Tox (28)	Adult Male	---	---	4.0	0.8
MRID 00160750 28-Day Dermal Tox (28)	Adult Female	---	---	1.4	0.5
MRID 45222001 28-Day Dermal Tox (28)	Adult Male	---	---	---	---
MRID 45222001 28-Day Dermal Tox (28)	Adult Female	---	---	9.7	6.9 [a]

a According to standard protocol, Model 4 would be chosen (BMD 9.7, BMDL 4.0) based on the lower BMDL. However, the empirical data indicates that inhibition is 7% at 10. Model 4 provides an overly conservative value based on empirical data. High variability was noted for the low- and high-doses.

--- = No model fit, either by statistical tests or visual fit or by comparison of results to empirical data, typically due to a lack of dose-response and/or extreme variation
NE = Not evaluated

Table A.4.4. Results of BMD Modeling (mg/L/day) for Brain and RBC ChE Data on Naled, Inhalation Toxicity in Rats. [a]

Study (dosing weeks)	Age Sex	Brain BMD_{10}	Brain $BMDL_{10}$	RBC BMD_{10}	RBC $BMDL_{10}$
MRID 00265680 Inhalation Tox (7W)	Adult Male	NE		0.00026	0.00019
MRID 00265680 Inhalation Tox (7W)	Adult Female	NE		0.00025	0.00020 [a]

a The exposure period consisted of six-hours/day, 5 days/week, whole body exposures for 13 weeks.
b According to standard protocol, Model 5 would be chosen (BMD 0.00051, BMDL 0.00023) based on the AIC (-9.3 vs -9.0; negligible difference). However, the empirical data indicates that inhibition is already 13% at 2, so Model 4 provides a more accurate estimate.
NE = Not evaluated

A.5 Literature Search for Naled

Date and Time of Search: 11/21/2019; 12:30 pm

Search Details:
((Naled or "1,2-Dibromo-2,2-dichloroethyl dimethyl phosphate")) AND (rat OR mouse OR dog OR rabbit OR monkey OR mammal)

Citations Identified in PubMed*: 39

SWIFT-Review**Tags:

28 for Animal

26 for Human (11 that lack animal(all) tag)

0 for NO TAG

11 studies are human only; 28 are animal all tags for total of 39 publications reviewed

All studies identified in the PubMed search were screened when the citation list was $\leq$100. Screening of larger citations lists (>100 citations) was conducted after prioritization in SWIFT-Review and focused on studies identified with the "Animal" and/or "Human" tag.

Conclusion of Literature Search: Following title/abstract and/or full text screening, no studies were identified as containing potentially relevant information (either quantitative or qualitative) for the naled human health registration review risk assessment.

*PubMed is a freely available search engine that provides access to life science and biomedical references predominantly using the MEDLINE database.
**SWIFT-Review is a freely available software tool created by Sciome LLC that assists with literature prioritization. SWIFT-Review was used to prioritize studies identified in the PubMed search based on the model of interest in the study (e.g. human, animal, *in vitro*, etc.).
Studies could have resulted in multiple tags which would account for citations identified in PubMed not matching the number of tagged citations.

Appendix B. Physical/Chemical Properties

Table B.1.1 Summary of Physical-Chemical Properties of Naled

Parameter	Value[1]			Reference/ Study Classification/ Comment
Molecular Weight (g/mole)	380.84			MRID 00152133
Water Solubility at 20°C mg/L	< 1 mg/l			MRIDs 00152133
Vapor Pressure (torr) 20 °C	2×10^{-4}			MRID 45088902
Henry's Law constant at 20°C (atm-m^3/mole)	9.22×10^{-3}			Product Chemistry
Log Dissociation Constant (pKa)	Not expected to ionize in natural waters			
Octanol-water partition coefficient (K_{ow}) at 25°C (unitless)	25 (log K_{OW}=1.4)			PUBCHEM
Air-water partition coefficient (K_{AW}) (unitless)	1.66×10^{-3} (log K_{AW} = -2.8)			Estimated[1] from vapor pressure and water solubility at 20°C.
Soil-Water Distribution Coefficients (Kd in L/kg-soil or sediment) Organic carbon normalized distribution coefficients (Koc in L/kg-organic carbon)	**Soil/Sediment**	**K_d**	**K_{OC}**	MRID 40279201 Acceptable Moderately Mobile (FAO classification system)
	sandy loam, pH 5.6	1.3	160	
	clay loam, pH 7.2	3.6	93	
	loam sand, pH 7.3	1.8	222	
	Clay, pH 4.5	3.6	259	
	Mean	2.6	183	
	CV	47%	40%	

[1]All estimated values were calculated according to "*Guidance for Reporting on the Environmental Fate and Transport of the Stressors of Concern in Problem Formulations for Registration Review, Registration Review Risk Assessments, Listed Species Litigation Assessments, New Chemical Risk Assessments, and Other Relevant Risk Assessments*" (USEPA, 2010a).

Table B.1.2. Summary of Physico-Chemical Properties of DDVP

Parameter	Value	Reference
Molecular Weight	220.97 g/mole	Product Chemistry
Boiling point/range	117°C at 10 mm Hg	MRID 40798103
pH	~ 4 as 1% aqueous solution	MRID 40798103
Density (25°C)	1.424 g/mL	MRID 40798103
Water solubility (20°C)	~1.5 g/100 g	MRID 40798103
Solvent solubility (temperature not specified)	~0.5% in glycerine Miscible with aromatic hydrocarbons, chlorinated hydrocarbons, alcohols, ketones, and esters. Essentially insoluble in kerosene and aliphatic hydrocarbons	MRID 40798103
Vapor pressure (25°C)	0.018 mm Hg	MRID 40798103
Dissociation constant, pKa	N/A	
Octanol/water partition coefficient, log K_{OW} (25°C)	K_{OW} = 38.4 log K_{OW} = 1.58	MRID 40798103
UV/visible absorption spectrum	N/A	
Hydrolysis half-life	11.6 days at pH 5 5.2 days at pH 7 21 hours at pH 9	MRID 41723101
Photolysis half-life[1]	Aquatic:10.18 days Soil: 15.5 hours	Wente, S., 06/17/2020, D433560
Soil Metabolism half-life	Aerobic: 2.3-8 hours Anaerobic: 6.2 days	Wente, S., 06/17/2020, D433560
Aquatic Metabolism half-life	Aerobic: 10.6-16.6 hours Anaerobic:4.5 days	Wente, S., 06/17/2020, D433560

[1]Aquatic dark control = 8.9 days; Soil dark control = 16.6 hours

Appendix C: Human Studies Review

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from the Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1); the Agricultural Handler Exposure Task Force (AHETF) database; the Agricultural Reentry Task Force (ARTF) database; the Outdoor Residential Exposure Task Force (ORETF) database; the Residential SOPs (Lawns/Turf); and other registrant-submitted exposure studies (MRIDs 44459801, 41054701, 44739301, 44339801), are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[22].

[22] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

Appendix D. International Residue Limit Status Sheet.

Naled (PC Code 034401)

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition: Tolerances are established for residues of the insecticide naled (1,2-dibromo-2,2-dichloro-ethyl dimethyl phosphate) and its conversion product 2,2-dichlorovinyl dimethyl phosphate, expressed as naled, resulting from the application of the pesticide to growing crops or from direct application to livestock and poultry, in or on the following raw agricultural commodities: The tolerance expression should be revised to read: Tolerances are established for residues of the insecticide naled (1,2-dibromo-2,2-dichloroethyl dimethyl phosphate) and its conversion product 2,2-dichlorovinyl dimethyl phosphate (DDVP), expressed as naled, <u>including its metabolites and degradates</u>, resulting from the application of the pesticide to growing crops or from direct application to livestock and poultry, in or on the following food commodities in the table below. <u>Compliance with the tolerance levels specified below, is to be determined by measuring only naled and DDVP.</u>				
US		Canada	Mexico[1]	Codex
40 CFR: 180.215 Naled		None		None
Commodity	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[1]	Codex
Almond, hulls	0.5			
Almond	0.5			
Bean, dry, seed	0.5	0.5 (Beans)		
Bean, succulent	0.5	0.5 (Beans)		
Beet, sugar, roots	0.5			
Beet, sugar, tops	0.5			
Broccoli	1	1		
Brussels sprouts	1	1		
Cabbage	1	1		
Cauliflower	1	1		
Celery	3			
Collards	3			
Cotton, undelinted seed	0.5			
Cucumber	0.5	0.5		
Eggplant	0.5	0.5		
Grape	0.5			
Grapefruit	3	3 (Citrus fruits)		
Grass, forage	10			
Hop, dried cones	0.5			
Kale	3			
Legume, forage	10	3		
Lemon	3	3 (Citrus fruits)		
Melon	0.5	0.5		

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition: Tolerances are established for residues of the insecticide naled (1,2-dibromo-2,2-dichloro-ethyl dimethyl phosphate) and its conversion product 2,2-dichlorovinyl dimethyl phosphate, expressed as naled, resulting from the application of the pesticide to growing crops or from direct application to livestock and poultry, in or on the following raw agricultural commodities: The tolerance expression should be revised to read: Tolerances are established for residues of the insecticide naled (1,2-dibromo-2,2-dichloroethyl dimethyl phosphate) and its conversion product 2,2-dichlorovinyl dimethyl phosphate (DDVP), expressed as naled, <u>including its metabolites and degradates</u>, resulting from the application of the pesticide to growing crops or from direct application to livestock and poultry, in or on the following food commodities in the table below. <u>Compliance with the tolerance levels specified below, is to be determined by measuring only naled and DDVP.</u>				
US		Canada	Mexico[1]	Codex
40 CFR: 180.215 Naled		None		None
Commodity	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[1]	Codex
Orange, sweet	3	3 (Citrus fruits)		
Peach	0.5			
Pea, succulent	0.5	0.5 (Peas)		
Pepper	0.5	0.5		
Pumpkin	0.5	0.5		
Safflower, seed	0.5			
Spinach	3	3		
Squash, summer	0.5	0.5		
Squash, winter	0.5	0.5		
Strawberry	1	1		
Swiss chard	3	3		
Tangerine	3	3 (Citrus fruits)		
Tomato	0.5	0.5		
Turnip, greens	3	3		
Walnut	0.5			
A tolerance of 0.5 part per million is established for the pesticide naled in or on all raw agricultural commodities, except those otherwise listed in this section, from use of the pesticide for area pest (mosquito and fly) control.				
MRLs without a corresponding US Tolerance				
		Rice 0.5 Dry Soybeans 0.5 Lettuce 1		

[1] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.