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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: **01-07-2021**

SUBJECT: **Aldicarb:** Human Health Risk Assessment in Support of New Uses on Oranges and Grapefruits in Florida.

PC Code: 098301
Decision No.: 549655
Petition No.: NA
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D453397
Registration No.: 87895-2
Regulatory Action: Section 3
Case No.: 0140
CAS No.: 116-06-3
40 CFR: §180.269

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5.0 Executive Summary

The Health Effects Division (HED) has conducted a human health risk assessment to evaluate the proposed registration of the active ingredient (ai) aldicarb [*2-methyl-2-(methylthio)propanal O-[(methylamino)carbonyl]oxime*]**,** a carbamate insecticide used to control soil borne pests including mites, various insects, and nematodes on dry beans, sugar beets, cotton, peanuts, sweet potatoes, and soybeans. This assessment was conducted as part of a new use request for citrus (orange and grapefruit) grown in Florida.

Use Profile
Aldicarb is classified as a Restricted Use Pesticide (RUP) and may be purchased and used only by certified applicators or persons under their direct supervision. The product (EPA Reg No. 87895-4) is available as a granular formulation which contains 15% active ingredient (ai). The substrate for the granular is gypsum or corn grit and these are both thought to reduce the friability compared to a clay substrate (which is used for typical granular formulations). Applications can only be made using motorized ground application equipment followed by immediate soil incorporation. Application of the product with aircraft, backpack spreaders, or push-type spreaders is prohibited. The product is not to be applied within 1,000 feet of any drinking water well on any soil series identified by the United States Department of Agriculture (USDA) Natural Resources Conservation Service as a highly permeable well-drained soil. The proposed product label indicates that the product cannot be applied to citrus more than once per tree per year at a maximum rate of 33 lbs product (4.95 lbs ai) per acre per year, or 2 ounces product/tree (0.019 lb ai/tree).

The product label for the proposed use allows for handlers to use either a closed system or to use an open system with appropriate personal protective equipment (PPE) as noted on the label. If using an open system (for either loading and/or application), all handlers (including mixers, loaders, and applicators) must wear coveralls over long-sleeved shirt, long pants, chemical-resistant gloves, and chemical-resistant footwear. During mixing/loading, handlers must also wear protective eyewear, chemical-resistant apron, and use a filtering face piece, half-face or full-face National Institute for Occupational Safety and Health (NIOSH)-approved respirator.

Exposure Profile
There are no residential uses of aldicarb and non-occupational exposure to aldicarb *via* spray drift is not anticipated. Exposures may occur through food or drinking water as a result of crop treatments. Short- and intermediate-term occupational handler exposures are possible while handling the pesticide prior to or during application. Since aldicarb is applied to crops *via* soil incorporation (generally pre-plant soil incorporation although some crop applications are allowed as a split application at plant and/or post-emergence), occupational post-application exposure is not anticipated.

Hazard Assessment
Aldicarb is a member of the *N*-methyl carbamate (NMC) class of pesticides. Like other NMCs, the initiating event in the adverse outcome pathway (AOP)/mode of action (MOA) for aldicarb involves inhibition of the enzyme acetylcholinesterase (AChE) *via* carbamylation 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. Acetylcholinesterase inhibition (AChEI) is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes.

The toxicology database is complete for human health risk assessment purposes. Appropriate database uncertainty factors are applied to account for the sensitivity seen in pups in the comparative cholinesterase assay (CCA), and the Food Quality Protection Act (FQPA) factor was reduced from 10X to 4.8X based on the results of the acute CCA study showing that postnatal day (PND) 11 pups are 4.8X more sensitive than adults. Section 4.4 addresses the appropriate FQPA safety factor for aldicarb.

RBC AChE is the more sensitive compartment for aldicarb following oral exposure, There are no acceptable data following dermal exposure and there is no available inhalation toxicity study for aldicarb. However, based on a weight-of-evidence (WOE) approach and considering all available aldicarb hazard and exposure information, the Hazard and Science Policy Council (HASPOC) has recommended the requirement for an inhalation study be waived (TXR 0057355, U. Habiba, 03/01/2016). Waiver of the inhalation study was based on a number of factors including its formulation as a granule with limited potential for dust formation, a comparison of acute oral and inhalation studies showing similar toxicity from the two routes, the limited utility of a rat inhalation study when humans are a more sensitive species, as well as other factors. Available dermal toxicity data did not adequately address the most sensitive endpoint, AChEI; therefore, an oral endpoint assuming 100% dermal absorption was used to assess dermal risk.

Aldicarb is classified as Category E, Evidence of Non-Carcinogenicity for Humans, based on the lack of evidence of carcinogenicity in rats and mice studies and the absence of a mutagenicity concern. A quantitative cancer risk assessment is not required. Aldicarb is highly acutely toxic *via* the oral, dermal, and inhalation routes of exposure in the acute lethality studies (Toxicity Category I). It is not considered to be a dermal sensitizer. Immunotoxicity was not observed in the available toxicity data.

Endpoints and Uncertainty Factors for Risk Assessment

The endpoint for all exposure scenarios is RBC AChEI, and points of departure (PODs) were selected from a human oral study. The POD for the acute dietary (all populations) exposure scenario was 0.013 mg/kg/day; no POD was selected for chronic dietary exposure because the magnitude of AChEI does not increase with continued exposure due to the reversibility of AChEI (< 24 hours). There are no chronic toxic effects more sensitive than AChEI. The POD selected for the dermal and inhalation worker scenarios was also 0.013 mg/kg/day based on the same study.

In all exposure scenarios, interspecies (1X) and intraspecies (10X) uncertainty factors were applied since the endpoint selection is based on a human study. As a result, a total uncertainty factor of 10X was applied for all occupational exposure scenarios. Occupational risk estimates for the dermal and inhalation routes of exposure were combined since the level of concern (LOC) values are the same (LOC of 10 for both routes).

For non-occupational (dietary) exposures, an FQPA safety factor (4.8X) has also been retained for all populations including infants and children to account for the sensitivity observed between adult and young animals in the CCA. Since the 4.8-fold increased sensitivity was observed only in pups in the CCA study, not in developing fetuses or in pregnant animals, the factor is only appropriate for children's risk assessments, and was, therefore, not applied as a database uncertainty factor in the occupational assessment to address pregnant workers.

Dietary Exposure Assessment
Refined probabilistic dietary exposure assessments for aldicarb show that food and water exposures do not exceed HED's level of concern for any population subgroup at the 99.9th percentile of exposure, when aldicarb is applied at least 3 inches below the surface in citrus orchards, and following production cap limits for orange and grapefruit. Refinements include the use of residue distributions from monitoring data for citrus, potato, and sweet potato; field trial data for other crops; percent crop treated information; and empirical processing factors where available. These dietary assessments show that the general U.S. population occupies 43% of the acute population adjusted dose (aPAD), while the most highly exposed population subgroup, children 1-2 years old, occupies 95% of the aPAD.

Residential Exposure and Risk Assessment
There are currently no registered residential uses of aldicarb; therefore, a quantitative residential handler and post-application assessment was not conducted.

Aggregate Risk Assessment
There are no residential uses of aldicarb. Therefore, aggregate risks include only acute dietary contributions. The acute dietary risk estimates for food plus drinking water are not of concern when aldicarb is applied to citrus at a 3-inch incorporation depth (95% of the aPAD for all infants <1 years old, the most highly exposed population subgroup).

Non-Occupational Spray Drift Assessment
The aldicarb end use product is formulated as a granular and is not anticipated to result in spray drift because of how it is applied (pre-plant/post-emergent soil incorporation).

Cumulative
The FQPA requires the Agency to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. Aldicarb is a member of the NMC common mechanism group. NMCs like aldicarb share the ability to inhibit AChE through carbamylation 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 NMC common mechanism grouping per OPP's *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999). The 2007 Cumulative Risk Assessment (CRA) and the subsequent revision used brain AChEI in female rats as the source of dose response data for the relative potency factors and PODs for each NMC, including aldicarb.

The most recent cumulative risk assessment for the NMC carbamates was issued for comment on September 26, 2007 and is available on the Agency website[1]. Since the proposed use on citrus is

[1] http://itrcweb.org/FileCabinet/GetFile?fileID=6883

similar to the previously registered use, the cumulative exposure to the class of NMC pesticides through food would not be significantly impacted by the proposed citrus use for aldicarb and HED considers the 2007 CRA to still be current.

Occupational Exposure and Risk Assessment
As noted above, the aldicarb product label allows for either open pour/open cab applications (with PPE) or closed loading/closed cab applications (i.e., engineering controls). Also, as noted above, the granular aldicarb products are considered low dust materials due to their substrate and are thought to result in reduced exposure levels. Chemical- and formulation-specific handler exposure data (MRID 43852501) are available in support of open pour/open cab application scenarios for "low dust" aldicarb formulations. HED relied on the chemical-specific data for unit exposures for open pour/open cab applications. For the closed loading/closed cab scenarios, HED relied on available Occupational Pesticide Handler Exposure Data as surrogate data [specifically, the Pesticide Handlers Exposure Database (PHED)].

For the open pour/open cab application scenarios, using chemical-specific unit exposure data, representative of a single layer of clothing, gloves, and, for mixer/loaders only, a standard filtering facepiece respirator, there are no combined dermal and inhalation risk estimates of concern (i.e., margins of exposure (MOEs) are ≥ 10).

For the closed loading/closed cab application scenarios, using available surrogate PHED unit exposure data for engineering controls, all combined dermal and inhalation risk estimates are of concern (i.e., MOEs < 10). Exposure and risk estimates for handlers using closed systems may be considered overestimates as the PHED surrogate unit exposures are not representative of the low dust aldicarb formulations. Furthermore, where risk concerns exist, the combined risk estimates are driven by dermal exposure. It should be noted that an assumption of 100% dermal absorption was used in the dermal exposure/risk calculations since an acceptable dermal absorption study was not submitted. Given that the registered product is a granular formulation, it is unlikely that 100% dermal absorption would occur.

A quantitative occupational post-application dermal assessment has not been conducted for aldicarb because aldicarb is soil incorporated and there is limited potential for worker dermal exposure to soil incorporated pesticides. Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for aldicarb at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for aldicarb.

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

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

6.0 HED Recommendations

HED has examined the toxicology and residue chemistry databases for aldicarb. There are no residue chemistry, dietary, occupational or residential exposure issues that would preclude granting the requested registration of aldicarb on grapefruit and orange in Florida.

6.1 Tolerance Considerations

6.1.1 Enforcement Analytical Method

Adequate analytical enforcement methods are available for aldicarb and its regulated metabolites. The Pesticide Analytical Method (PAM Vol. II) lists a gas-liquid chromatography method using flame photometric detection in the sulfur mode ((GLC/FPD), designated as Method II), as available for the determination of combined residues of aldicarb and its metabolites aldicarb sulfone and aldicarb sulfoxide in plant and livestock commodities. In this method, aldicarb and aldicarb sulfoxide are oxidized to aldicarb sulfone and then total residues of aldicarb sulfone are determined. Although various modifications of Method II exist, the basic method uses an acetone:water (3:1, v:v) extraction with simultaneous oxidation of aldicarb residues of concern using a peracetic acid solution. Residues of aldicarb sulfone are subsequently purified by selective elution from a Florisil column, and the total aldicarb residue is determined as aldicarb sulfone by GLC/FPD. No interference by other sulfur-containing pesticides has been observed with this method, and the method is specific for aldicarb and its regulated metabolites. The limits of detection (LOD) for the method range from 0.01-0.05 ppm.

The 10/97 Food and Drug Administration (FDA) PESTDATA database indicate that residues of aldicarb and aldicarb sulfone are completely recovered (>80%) using multiresidue method PAM Volume I Section 302 (Luke method; Protocol D) and Section 401 (method for *N*-methyl carbamates). Residues of aldicarb sulfoxide are also completely recovered using multiresidue method Section 302 but are only partially recovered (50-80%) using Section 401.

The National Pesticides Standards Repository has supplies of the aldicarb analytical reference standard with the indicated expiration dates in Table 2.1.1 (e-mail from C. Vigo, 12/17/2020):

Table 2.1.1 Analytical Reference Standard Status

Standard	CAS#	Expiration Date
Aldicarb	116-06-3	3/21/2024
Aldicarb sulfoxide	1646-87-3	4/6/2021
Aldicarb sulfone	1646-88-4	3/23/2022; 3/22/2025

6.1.2 Recommended Tolerances

No new tolerances for aldicarb are proposed at this time as the proposed new uses (orange and grapefruit) are currently covered by established tolerances under §180.269 at 0.3 ppm.

6.1.3 International Harmonization

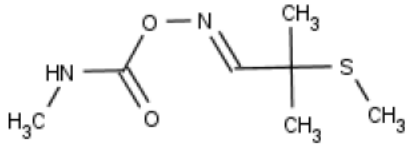
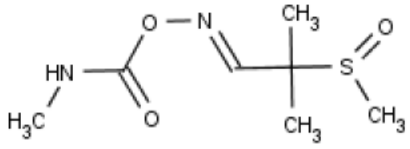
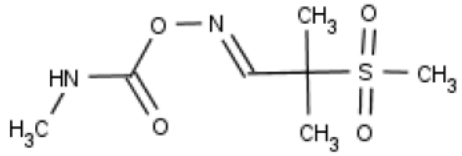
The US tolerance definition is harmonized with the maximum residue limit (MRL) definitions for Canada and Codex: the residues of concern are aldicarb, aldicarb sulfoxide, and aldicarb sulfone. U.S. tolerances (0.3 ppm) and MRLs (Codex at 0.2 ppm) are not harmonized for citrus fruits; differences in typical agricultural practices preclude harmonization of tolerances and MRLs for citrus fruits.

6.2 Label Recommendations

None.

7.0 Introduction

7.1 Chemical Identity

Table 3.1 Chemical Structures and Nomenclature	
Common Name	Aldicarb
Chemical Structure	
Chemical name	2-methyl-2-(methylthio)propanal O-[(methylamino)carbonyl]oxime
CAS Registry Number	116-06-3
Common Name	Aldicarb sulfoxide
Chemical Structure	
Chemical name	2-methyl-2-(methylsulfinyl)propanal O-[(methylamino)carbonyl]oxime
CAS Registry Number	1646-87-3
Common Name	Aldicarb sulfone (Aldoxycarb)
Chemical Structure	
Chemical name	2-methyl-2-(methylsulfonyl)propanal O-[(methylamino)carbonyl]oxime
CAS Registry Number	1646-88-4

7.2 Physical/Chemical Characteristics

A detailed description of the physicochemical properties of aldicarb is provided in Appendix B. Technical aldicarb is a crystalline solid with a melting point of 96-97°C and a slight sulfurous odor. Crystalline aldicarb is heat-sensitive and decomposes above 100°C. Aldicarb is soluble in water (0.6%) and increasingly soluble in the following solvents: hexane (<1%), carbon tetrachloride (4%), benzene (18%), methylethyl ketone (20%), acetone (38%), and chloroform (42%). Based on its log K_{ow} of 1.06, significant bioconcentration is not expected. Aldicarb has a relatively low vapor pressure of 0.9 mPa.

7.3 Pesticide Use Pattern

Aldicarb is classified as a RUP and may be purchased and used only by certified applicators or persons under their direct supervision. The product (EPA Reg No. 87895-4) is available as a granular formulation which contains 15% ai. The substrate for the granular is gypsum or corn grit and these are both thought to reduce the friability compared to a clay substrate (which is used for typical granular formulations). Applications can only be made using motorized ground application equipment followed by immediate soil incorporation. Application of the product with aircraft, backpack spreaders, or push-type spreaders is prohibited. Product is not to be applied within 1,000 feet of any drinking water well on any soil series identified by the USDA Natural Resources Conservation Service as a highly permeable well-drained soil. The proposed product label indicates that the product cannot be applied to citrus more than once per tree per year at a maximum rate of 33 lbs product per acre (4.95 lbs ai/A) per year, or 2 ounces product/tree (0.019 lb ai/tree).

The product label for the proposed use allows for handlers to use either a closed system or to use an open system with appropriate PPE as noted on the label. If using an open system (for either loading and/or application), all handlers (including mixers, loaders, and applicators) must wear coveralls over long-sleeved shirt, long pants, chemical-resistant gloves, and chemical-resistant footwear. During mixing/loading, handlers must also wear protective eyewear, chemical-resistant apron, and use a filtering face piece, half-face or full-face NIOSH approved respirator.

Table 3.3. Summary of Directions for Use of Aldicarb.

Application Timing, Type, and Equipment	Formulation and Percent Active Ingredient (ai) [EPA Reg. No.]	Application Rate	Use Directions and Limitations
Citrus (grapefruit and orange)			
Apply just prior to or during spring flush of foliage growth in a band along the dripline on both sides of tree row. Tractor-drawn spreader	Granular 15% ai [87895-41]	33 lb product/A or 2 oz product/tree (4.95 lb ai/A or 0.019 lb ai/tree)	For use in FL only. Applications with aircraft, backpack spreader or push-type spreader prohibited. To provide maximum performance and to minimize hazard to birds, granules must be placed into bottom

Table 3.3. Summary of Directions for Use of Aldicarb.			
Application Timing, Type, and Equipment	**Formulation and Percent Active Ingredient (ai) [EPA Reg. No.]**	**Application Rate**	**Use Directions and Limitations**
			of furrow and immediately covered with 3 inches or more of soil by mechanical means. Cover granules spilled during loading, at row ends, or elsewhere to ensure the granules are completely covered with at least 3 inches of soil. No more than 1 app per year. Do not apply within 1,000 feet of any drinking water well on any soil series identified by the USDA Natural Resources Conservation Service as a highly permeable well-drained soil such as (but not limited to): Adamsville, Archbold, Astatula, Candler, Cassia, Lake, Neilhurst, Orsino, Palm Beach, Paola, Satellite, St. Lucie, and Tavares.

7.4 Anticipated Exposure Pathways

Humans may be exposed to aldicarb in food and drinking water, since aldicarb may be applied directly to growing crops and application may result in aldicarb reaching surface and ground water sources of drinking water. There are no residential uses of aldicarb and non-occupational exposure to aldicarb *via* spray drift is not anticipated. In an occupational setting, workers may be exposed while handling the pesticide prior to application, as well as during application. Since aldicarb is applied to crops preplant or preemergence and is to be soil incorporated, occupational post-application exposure is not anticipated from the proposed uses.

This risk assessment considers all of the aforementioned exposure pathways based on the proposed new uses of aldicarb, but also considers the existing uses as well, particularly for the dietary exposure assessments.

7.5 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 is also being considered whenever appropriate. 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.

8.0 Hazard Characterization and Dose-Response Assessment

Aldicarb is a member of the NMC class of pesticides. Like other NMCs, the initiating event in the AOP/MOA for aldicarb involves inhibition of the enzyme acetylcholinesterase *via* carbamylation of the serine hydroxyl group located in 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). This MOA is similar to the organophosphate (OP) class of chemicals, as they both result in inhibition of the acetylcholinesterase enzyme. However, they are differentiated by their action upon the active site of the enzyme, which results in clear differences in the timing and duration of inhibition between the two classes.

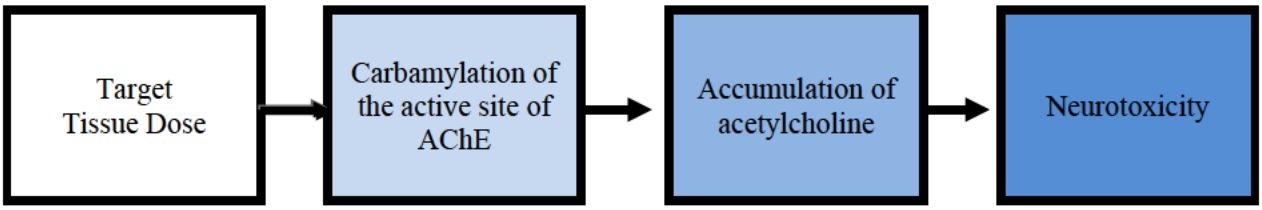


Figure 1. Adverse outcome pathway for NMCs

In the OP MOA, inhibition of acetylcholinesterase occurs *via* phosphorylation, as opposed to carbamylation with NMCs. Phosphorylation results in an irreversible binding and a permanent inhibition of the bound enzyme. Inhibition occurs within a few hours and continues until new, uninhibited enzymes are produced. This results in the OPs exhibiting a phenomenon known as steady-state cholinesterase inhibition. After repeated dosing with an OP at the same dose level, the degree of cholinesterase inhibition comes into equilibrium with the production of new, uninhibited enzyme. At this point, the amount of AChEI at a given dose remains consistent across duration. Therefore, acute and steady state exposure durations are of concern for OPs.

The NMCs react differently in that carbamylation of the serine hydroxyl group results in a reversible binding process thus allowing for rapid reactivation of the enzyme. The NMCs, therefore, have a unique MOA that results in rapid onset and recovery of the enzyme. The time to peak inhibition for NMCs is typically between 15 to 45 minutes while complete recovery of the enzyme is achieved within minutes to hours (USEPA 2007 Revised NMC Cumulative Risk Assessment). Therefore, for NMCs, repeated daily exposure does not result in an increased inhibition of AChE since enzyme recovery is complete before the next acute exposure, and only acute exposure durations are of concern for NMCs, including aldicarb.

For aldicarb, AChEI is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. NMC specific cholinesterase studies are available that support aldicarb time to peak inhibition as well as recovery. Cholinesterase inhibition is the focus of this hazard characterization; the availability of reliable AChEI dose-response data is one of the key determinants in evaluating the toxicology database.

4.1 Toxicology Studies Available for Analysis

The toxicology database for aldicarb is complete, as described in 40 CFR, Part 158. No new toxicity and/or metabolism data have been received since the last risk assessment (D424564, S. Dobreniecki, 03/25/2016). However, based on a WOE approach and considering all available aldicarb hazard and exposure information, the HASPOC has recommended the requirement for acute inhalation and dermal studies be waived (TXR 0057355, U. Habiba, 03/01/2016).

The following animal toxicology studies have been submitted in support of the registered uses of aldicarb. Additionally, there is an intentional dosing acute oral study in humans in which clinical signs and RBC cholinesterase activity were monitored.

- Subchronic oral toxicity study (dog)
- Subchronic dermal toxicity studies (rat)
- Developmental (rat and rabbit) and reproductive toxicity (rats) studies
- Comparative Cholinesterase Assay (time to peak, dose-response, and recovery)
- Chronic oral toxicity studies (rat and dog)
- Carcinogenicity studies (rat and mouse)
- Metabolism studies (rat)
- Acute and subchronic neurotoxicity studies (rat)
- Developmental neurotoxicity study (rat)
- Immunotoxicity study (mice)
- Mutagenicity battery

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

Aldicarb is rapidly absorbed, widely distributed, and rapidly excreted, with more than 90% excreted in the urine within 24 hours after either acute or repeated oral doses. A minor part is also subject to biliary elimination and, consequently, to enterohepatic recycling. Aldicarb does not accumulate in the body. It is metabolized primarily to aldicarb sulfoxide, with a smaller amount then slowly converted into aldicarb sulfone. These three moieties (aldicarb, sulfoxide, and sulfone) may then be further metabolized to oximes and nitriles. Both the sulfoxide and the

sulfone are also potent cholinesterase inhibitors. The sulfone is less toxic following an acute oral exposure than either the parent compound or the sulfoxide. The sulfoxide shows comparable acute oral toxicity to the parent, based on results of median lethal dose studies.

4.2.1 Dermal Absorption

There are no acceptable dermal absorption studies for aldicarb; a dermal absorption factor is needed for risk assessment since the route-specific aldicarb dermal toxicity studies in rats did not provide adequate information on the most sensitive endpoint (AChEI). Therefore, a dermal absorption factor of 100% is assumed.

4.3 Toxicological Effects

Aldicarb is an NMC pesticide that exerts its pesticidal activity and elicits adverse toxic effects by inhibition of cholinesterase activity, which has been demonstrated in whole blood, plasma, RBC, and brain of rats, mice, and dogs following acute, subchronic, and chronic exposure and in plasma and RBC in humans following acute oral exposure.

The time to peak AChEI as well as the recovery of RBC and brain AChE is well understood for aldicarb. In a special time to peak and recovery study, peak brain inhibition occurred within 40 minutes in adults and within 60 minutes in PND 11 pups. For RBC AChE, peak inhibition occurred within 20 minutes in adults and 40 minutes in PND 11 pups (Table 4.3.1).

Cholinesterase inhibition was also measured at several time points post exposure, thus generating an enzyme reactivation or recovery profile. In the recovery phase of the study, aldicarb had an enzyme recovery half-live of 50-55 minutes in male pups and adults and 10 minutes in female pups. These data demonstrate that enzyme recovery is complete by the time the next exposure may occur the following day, 24 hours later. Therefore, only AChE data that is measured within minutes to an hour of the last exposure are appropriate for inclusion in the risk assessment.

Table 4.3.1. Results of Benchmark Dose (BMD) Modeling (mg/kg) for RBC Cholinesterase (Oral Dosing Studies)

Study	Time to peak effect (TOPE)	BMD_{10}[1]	$BMDL_{10}$[2]
MRID 47994305[A] Acute CCA Adult Male Adult Female	20-40 minutes[B]	0.0228 0.0242	0.0153 0.0144
MRID 47994305[A] Acute CCA PND 11 Male PND 11 Female	40-60 minutes[B]	0.00477 0.00731	0.00294 0.00387
MRID 45068601[C] Acute (Moser) PND 17 PND 27 PND 67	60 minutes 60 minutes 60 minutes	0.03	0.02
MRID 43442301[D] Acute Neurotoxicity Adult	45 minutes		

Table 4.3.1. Results of Benchmark Dose (BMD) Modeling (mg/kg) for RBC Cholinesterase (Oral Dosing Studies)			
Study	**Time to peak effect (TOPE)**	**BMD_{10}[1]**	**$BMDL_{10}$[2]**
MRID 43829602 Subchronic Neurotoxicity Adult	45 minutes		
MRID 42373001 Human study Adult	60 minutes	0.02	0.01

[1] The BMD_{10} is the estimated dose where AChE is inhibited by 10% compared to background.
[2] The $BMDL_{10}$ is the lower confidence bound on the BMD_{10}
[A] D379831, B. Sarkar, dated 7/1/2010.
[B] D380046. B. Sarkar and P. Villanueva, dated 7/14/2010.
[C] MRID 45079705.
[D] MRIDs 43442302, 43442305.

RBC and brain AChE data are available from several studies, and RBC AChE is the more sensitive compartment for aldicarb following oral exposure. Clinical signs associated with cholinesterase inhibition include tremors, salivation, lacrimation, lethargy, and prostration in rats and diarrhea and mucoid and/or soft stool in dogs. Other effects observed in rats following repeat exposure (decreased body weight and eye effects (ectopic pupil and damage to the iris)) were observed at dose levels 3-fold higher than those producing cholinesterase inhibition. Immunotoxicity was not observed. There are no acceptable data for cholinesterase inhibition following dermal exposure, and there is no inhalation toxicity study for aldicarb with which to assess cholinesterase activity.

The aldicarb database for neurotoxicity is complete, with acceptable acute, subchronic, and developmental neurotoxicity studies. Both the acute and subchronic rat neurotoxicity studies show a variety of typical clinical signs of acetylcholinesterase inhibition after oral exposures, including decreased motor activity, lacrimation, tremors, salivation, pinpoint pupils, and decreased grip strength, as well as significant decreases in RBC and brain cholinesterase activity. In the developmental neurotoxicity study in rats, AChEI and associated clinical signs, i.e., tremors, salivation, lacrimation, ataxia, miosis, and hunched posture, were observed in the dams at the same dose levels where decreased motor activity was observed in the pups in the absence of AChEI. No neuropathological effects related to exposure were seen in any of the acute, subchronic, chronic, or neurotoxicity studies.

The aldicarb database has multiple studies for informing susceptibility at different lifestages. There was no indication of increased susceptibility of fetuses in rat or rabbit developmental toxicity studies, including a rat developmental neurotoxicity study, and no increased susceptibility of the offspring in the rat reproduction study. In the developmental toxicity study in rabbits, no developmental effects were observed at any dose level, but maternal toxicity was observed, as evidenced by decreased body weight, pale kidneys, and hydroceles on the oviducts. In the developmental toxicity study in rats, the developmental effects, ecchymosis (hemorrhagic spots) of the trunk, occurred at the same dose level as the maternal effects, although the findings in the maternal rat are minimal (decreased body-weight gain and food consumption). Although cholinesterase activity was not monitored in this study, it is likely that cholinesterase inhibition occurred at all dose levels, based on the acute neurotoxicity study where RBC cholinesterase inhibition was observed following oral gavage (0.05, 0.1, and 0.5 mg/kg) at dose levels lower

than the dose levels used in this developmental rat study (0.125, 0.25, and 0.5 mg/kg/day). Death and signs of cholinesterase inhibition, including hypoactivity, ataxia, tremors, lacrimation, loose feces, and cold extremities were observed in the high dose maternal rats. In the reproduction study, the effects on the offspring (reduced survival on PND 4, decreased body weight, and signs of debilitation) were observed only at the highest dose tested (1.4 mg/kg/day) where parental toxicity also occurred, as evidenced by RBC cholinesterase inhibition and decreased body weight. In this study, the NOAEL for maternal toxicity was lower than the NOAEL for offspring toxicity.

Juvenile rat data are available for aldicarb at both the PND 11 and PND 17 lifestages. A CCA for aldicarb provides AChE data in both the adult and the PND 11 pup to determine if the young are more sensitive than adults to aldicarb. In this study, PND 11 pups were more sensitive for both RBC (3.3-4.8X) and brain (3.7-4.5X) AChEI compared to adults. A published acute oral exposure study (Moser, 1999)[3] demonstrated that PND 17 pups were also more sensitive (2X) than adults (brain only). In that study, decreased motor activity was observed only in the adult animals, and clinical signs of AChEI occurred more frequently in (and recovery was prolonged in) the adult compared to the PND 17 rats. The juvenile rat data available for aldicarb demonstrate that PND 11 pups are the most sensitive, as compared to PND 17 pups, as compared to adult rats.

As for the fetal lifestage, there is no indication in the toxicity database that the fetus is more sensitive than pups to aldicarb. The Agency notes, however, that there is an article in the open literature (Cambon, et al., 1979[4]) suggesting the fetus to be more susceptible than the rat dam. However, this article is not considered reliable and scientifically robust since cholinesterase inhibition in the fetus and dam was reported at time points (5 hours and 24 hours) well beyond the known time frame for cholinesterase inhibition and recovery for aldicarb and any of the NMCs.

An acute oral exposure study on aldicarb involving direct dosing of adult humans provides the timing and magnitude of plasma and RBC cholinesterase inhibition and clinical signs. Aldicarb treatment of both males and females resulted in statistically significant inhibition of both red blood cell and plasma cholinesterases at the two common dose levels. The results of the acute oral human study suggest a two-fold difference in toxic responses between animals and humans, with humans being more sensitive. This human study was reviewed by EPA's Human Studies Review Board (HSRB), as required by EPA's Human Subjects Protections rule, 40 CFR Part 26 (effective April 7, 2006), who concluded that use of the human study endpoint was appropriate for human health risk assessment. Because these human data are considered reliable, and the study is considered scientifically valid, the human study is regarded as the most suitable for this single-chemical risk assessment.

Aldicarb is highly acutely toxic *via* the oral, dermal, and inhalation routes of exposure in the acute lethality studies required for labeling (Toxicity Category I). It is not considered to be a

[3] Moser, V.C. (1999). Comparison of aldicarb and methamidophos neurotoxicity at different ages in the rat: behavioral and biochemical parameters. Toxicol Appl Pharmacol. 157(2):94-106

[4] Cambon et al. (1979). Toxicology and Applied Pharmacology. (49): 203-208.

dermal sensitizer; dermal and eye irritation studies were waived due to severe effects (death) following corneal and dermal dosing.

More detail concerning the characterization and quantification of the toxic effects of aldicarb is provided in Appendix A.2. A toxicity profile table can be found in Appendix A.2 (Table A.2.2). A table of the benchmark modeling results is also provided in Appendix A.2 (Table A.2.3). Complete BMD modeling and data has been previously published (USEPA 2007 Revised NMC Cumulative Risk Assessment) and can be accessed as indicated within the appendix of the NMC Cumulative Risk Assessment.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)[5]

As previously described, the Agency has non-guideline CCA studies in the rat that directly compare the timing and magnitude of cholinesterase inhibition in the young (PND 11) as compared to adults. The Agency is also relying on RBC AChEI data from adult human subjects. Therefore, for the protection of infants and children, the Agency is relying on the CCA studies to derive an aldicarb data-derived FQPA Safety Factor of 4.8X (BMD adult/ BMD pup). Because of the rapid onset and recovery of the enzyme following carbamate exposure, in contrast to the irreversible binding and permanent inhibition of the bound enzyme that occurs following OP exposure, an additional safety factor is not warranted for the carbamate aldicarb based on the following considerations:

- The toxicity database for aldicarb is complete and evaluates all relevant lifestages in the rat.
- There is no evidence of increased susceptibility or sensitivity in guideline studies in rats or rabbits to pre- and/or post-natal exposure to aldicarb.
- Acute, subchronic, and developmental neurotoxicity studies are available.
- Developmental neurotoxicity was not observed.
- Dose-response AChE data are available for comparison of inhibition between adult rats and PND 11 rat pups.
- The endpoint used for the dietary assessment is based on the species of concern (humans).
- The POD is based on the lower limit or $BMDL_{10}$ of the central estimate (BMD_{10}) for 10% cholinesterase inhibition and is health protective.
- The FQPA safety factor accounts for and is based on the sensitivity observed in the same compartment as the endpoint of concern, namely RBC cholinesterase inhibition response (endpoint of concern) between adult and young animals observed in the CCA study. See section 4.4.3 for additional detail on the sensitivity and susceptibility identified in the CCA study.

[5] 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).

4.4.1 Completeness of the Toxicology Database

The database of toxicology studies for aldicarb is complete and includes developmental toxicity studies in the rat and rabbit, a reproductive toxicity study in the rat, acute and subchronic neurotoxicity studies in the rat, a developmental neurotoxicity study in the rat, and an acute comparative cholinesterase study in adult rats and PND 11 pups. Additionally, there are AChE data in the open literature and unpublished data that assess sensitivity of the adult rat, pregnant rats, and the young (fetuses, PND 11, 17, and PND 27) with respect to cholinesterase inhibition and lethal doses. Immunotoxicity data are also available. Also available is an acute oral exposure study involving direct dosing of adult humans, which provides an appropriate endpoint for human health risk assessment and is regarded as the most suitable for this single-chemical risk assessment.

4.4.2 Evidence of Neurotoxicity

Aldicarb is an NMC with an established neurotoxic AOP. AChEI is the most sensitive effect in all species, routes, and lifestages and is being used in deriving the PODs.

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

Based on the guideline studies, there is no evidence of increased susceptibility or sensitivity in rats or rabbits to pre- and/or post-natal exposure to aldicarb. However, these studies did not include data comparing cholinesterase inhibition in young and adult animals.

In the CCA, evidence of sensitivity was observed in the young animal (PND 11) compared to the adult for both RBC and brain compartments. Additionally, there was some evidence for increased susceptibility in terms of lethal doses and brain cholinesterase inhibition in an unpublished EPA study in adult rats and PND 17 pups and PND 27 rats.

Although the cholinesterase inhibition was greater in PND 11 pups than in adults in the CCA study, the points of departure for risk assessment are health protective. The oral point of departure is based on the most sensitive compartment, RBC AChE, and based on the species of concern, namely humans. Further, an FQPA Safety Factor of 4.8X is applied, which is based on the most sensitive juvenile data (PND 11) and therefore is health protective of all lifestages.

The data-derived FQPA factor of 4.8, based on a comparison of the adult and PND 11 male RBC data (0.0228 mg/kg/0.00477mg/kg = 4.8; see table below), was selected for use in dietary risk assessment. It is noted that the RBC compartment is more sensitive than the brain compartment for both the adults and PND 11 pups. Since the point of departure for risk assessment is from an adult human RBC cholinesterase study, application of an FQPA factor based on the RBC cholinesterase rodent data is necessary to account for the additional sensitivity seen in the pups.

Table 1. FQPA Factor Estimates Based on the PND 11 CCA Study				
Sex	**Compartment**	**Adult BMD_{10} [1]**	**PND 11 Pups BMD_{10} [1]**	**FQPA Factor [2]**
Male	Brain	0.0535	0.0143	3.7
	RBC	0.0228	0.00477	**4.8**
Female	Brain	0.0615	0.0136	4.5
	RBC	0.0242	0.00731	3.3

[1] BMD_{10} is defined as the estimated dose at which 10% cholinesterase inhibition would be observed.
[2] The FQPA factor is calculated by dividing the BMD_{10} for the adults by the BMD_{10} of the pups for the same sex and compartment. The FQPA factor must be derived from the same compartment as that relied upon for the point of departure, i.e. RBC.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. The food exposure assessment was based on maximum percent crop treated estimates, and Pesticide Data Program (PDP) monitoring data supplemented by field trial data, as appropriate. Water estimates were based on modeling programs designed to provide high-end water values.

4.5 Toxicity Endpoint and Point of Departure Selections

There have been no changes since the last dose-response assessment and no changes to the prior recommendations for combining routes of exposure or cancer classification (D424564, S. Dobreniecki, 03/25/2016). Table 4.3.1 summarizes the benchmark dose analyses considered in selecting aldicarb endpoints, and Table 4.5.4.1 summarize the aldicarb toxicity endpoints, uncertainty factors, and points of departure. A more detailed description of the studies used as a basis for the selected endpoints are presented in the toxicity profile table (Table A.2.2) in Appendix A.

As discussed previously, since peak inhibition of cholinesterase occurs rapidly (within 20-60 minutes) with recovery occurring within minutes to hours (recovery half-lives of 10-50 minutes), the daily exposure to aldicarb is the toxicological duration of concern. This is supported by the toxicity database for aldicarb, which indicates that the most sensitive toxicological effect is inhibition of AChE following acute exposure. As discussed above, the magnitude of AChEI does not increase over repeated administration. Therefore, based on this mode of action and time course for inhibition and recovery, the endpoints selected are protective for the acute and repeat exposure assessment.

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}s and $BMDL_{10}$s. 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). All BMD/BMDL modeling was completed using USEPA BMD Software, version 2.4; an exponential model or Hill model was used to fit the data.

Acute Dietary Exposure (All populations including females 13+):
The Agency evaluated the toxicity profile for aldicarb and considered the human acute oral study to be appropriate for assessment of the acute dietary exposure and risks. A $BMDL_{10}$ POD of 0.013 mg/kg was selected from the acute human oral study and was associated with RBC cholinesterase inhibition. Data from the human oral study are appropriate for acute POD derivation, since effects were observed after a single exposure and the endpoint is the most sensitive adverse response in all populations (infant and children, females 13+, and adults). An uncertainty factor of 48X (1X interspecies extrapolation, 10X for intraspecies variation, and a 4.8X for FQPA safety factor (see Section 4.4)) is applied to the $BMDL_{10}$ to obtain an acute population adjusted dose (aPAD) of 0.00027 mg/kg for dietary exposure scenarios for all populations, including infants and children.

Chronic Dietary Exposure (All population including females 13+):
A chronic dietary assessment was not conducted since recovery data demonstrate that the rapid recovery of cholinesterase following acute exposure to aldicarb prevents increased toxicity with longer exposure duration; consequently, longer-term exposures are considered a series of acute exposures. A chronic assessment is, therefore, not considered appropriate for aldicarb. Aldicarb has been classified as Category E, Evidence of Non-Carcinogenicity for Humans, therefore; a cancer dietary assessment was not required.

Dermal Exposure (short and intermediate term durations):
A POD of 0.013 mg/kg/day was selected from the human acute oral study, based on RBC cholinesterase inhibition. The endpoint/POD is applicable to short- and intermediate-term dermal exposures. In the case of aldicarb, the magnitude of AChEI does not increase with continued exposure, and AChEI is generally reversible within 24 hours. As discussed in Section 4.0, acute inhibition of acetylcholinesterase is the main exposure duration of concern. Short- and intermediate-term exposures can be considered a series of acute exposures, with regard to AChEI. A total uncertainty factor of 10X is appropriate for occupational dermal exposures since exposures are expected for adults only, not children (1X for interspecies extrapolation, 10X for intraspecies variation, resulting in an LOC of 10). There are no acceptable dermal absorption studies for aldicarb. A 100% dermal absorption factor is assumed.

Inhalation Exposure (short and intermediate term durations):
A POD of 0.013 mg/kg/day was selected from the human acute oral study, based on RBC cholinesterase inhibition. The endpoint/POD is applicable to short- and intermediate-term inhalation exposures. Based on a WOE approach and considering all available aldicarb hazard and exposure information, the HASPOC has recommended the requirement for acute inhalation study be waived (TXR 0057355, U. Habiba, 03/01/2016) based on the following: (1) aldicarb is a Restricted Use Pesticide and exposure to aldicarb is to granules, which are soil-incorporated; (2) humans are 2X more sensitive to aldicarb than rats; (3) the POD is based on human (oral) data; (4) the acute rat inhalation study does not involve a detailed toxicological examination of the respiratory system; (5) aldicarb is extremely toxic *via* the oral, dermal, and inhalation routes (Toxicity Category 1); (6) based on a comparison of doses (oral vs. inhalation) that result in 50% deaths (on a mg/kg basis), the oral and inhalation doses in the rat are similar and likely the result of cholinesterase inhibition. An inhalation study with rats would not be expected to provide a lower point of departure than the one based on the human data. The total uncertainty factor of

10X is appropriate for occupational inhalation exposures (1X for interspecies extrapolation, 10X for intraspecies variation, resulting in an LOC of 10).

4.5.1 Recommendation for Combining Routes of Exposures for Risk Assessment

As part of conducting a human health risk assessment, HED considers risks from individual routes of exposure (oral, dermal, and inhalation) as well as combined risks from multiple routes, if appropriate. The endpoints identified for each route of exposure are examined to determine whether it is appropriate to combine across routes of exposure. In the case of aldicarb, the dermal, inhalation and oral routes are based on the same effects and can be combined.

4.5.2 Cancer Classification and Risk Assessment Recommendation

There are acceptable genotoxicity studies for all three required categories of mutagenic effects: gene mutations, chromosomal aberrations, and other genotoxic effects. The results of these studies are all negative. In accordance with the Agency's 2005 Guideline for Carcinogen Risk Assessment, aldicarb is classified as Category E, Evidence of Non-Carcinogenicity for Humans, based on the lack of evidence of carcinogenicity in studies in rats and mice and the absence of a mutagenicity concern (TXR 0012871, W. Sette, 09/15/1998).

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

Table 4.5.3.1 Summary of Toxicological Doses and Endpoints for Aldicarb for Use 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 (General Population, including Infants and Children)	$BMDL_{10}$ = 0.013 mg/kg	UF_H = 10X UF_A= 1X FQPA SF = 4.8X	Acute RfD = 0.0013 mg/kg/day aPAD = 0.00027 mg/kg/day	Human oral study MRIDs 43829602, 45068601, 43442302, 43442305, 42373001 BMD_{10} = 0.02 mg/kg, based on RBC cholinesterase inhibition
Chronic Dietary (All Populations)	A quantitative chronic assessment was not conducted because the toxicity database for aldicarb indicates that the magnitude of AChEI does not increase with continued exposure, due to the reversibility of AChEI (< 24 hours). There are no chronic toxic effects more sensitive than AChEI.			
Cancer (oral, dermal, inhalation)	Classification: Aldicarb is classified as Category E, Evidence of Non-Carcinogenicity for Humans, based on the lack of evidence of carcinogenicity in studies in rats and mice and the absence of a mutagenicity concern.			

AChEI = acetylcholinesterase inhibition. 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). BMD_{10} = Benchmark Dose; dose that corresponds to 10% response in AChEI. $BMDL_{10}$ = Benchmark Dose estimate based on the lower 95% confidence interval where 10% AChEI would be observed. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose. a = acute. RfD = reference dose.

Table 4.5.3.2 Summary of Toxicological Doses and Endpoints for Aldicarb for Use in Occupational Human Health Risk Assessments.				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Exposures (Short- and Intermediate-Term)	$BMDL_{10}$ = 0.013 mg/kg DAF = 100%	UF_A=1X UF_H=10X	Occupational LOC for MOE = 10	Human oral study MRIDs 43829602, 45068601, 43442302, 43442305, 42373001 BMD_{10} = 0.02 mg/kg, based on RBC cholinesterase inhibition
Inhalation Exposures (Short- and Intermediate-Term)	$BMDL_{10}$ = 0.013 mg/kg	UF_A=1X UF_H=10X	Occupational LOC for MOE = 10	Human oral study MRIDs 43829602, 45068601, 43442302, 43442305, 42373001 BMD_{10} = 0.02 mg/kg, based on RBC cholinesterase inhibition
Cancer (oral, dermal, inhalation)	Classification: Aldicarb is classified as Category E, Evidence of Non-Carcinogenicity for Humans, based on the lack of evidence of carcinogenicity in studies in rats and mice and the absence of a mutagenicity concern.			

DAF = dermal absorption factor. 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). BMD_{10} = Benchmark Dose; dose that corresponds to 10% response in AChEI. $BMDL_{10}$ = Benchmark Dose estimate based on the lower 95% confidence interval where 10% AChEI would be observed. MOE = margin of exposure. LOC = level of concern.

9.0 Dietary Exposure and Risk Assessment

9.1 Residues of Concern Summary and Rationale

The residues of concern for dietary risk assessment and the tolerance expression are summarized in Table 5.1. Aldicarb, aldicarb sulfoxide, and aldicarb sulfone are the residues of concern for tolerance enforcement and risk assessment. No new metabolism data were submitted in support of the current registration action. Further information on the metabolism and degradation of aldicarb may be found in the aldicarb risk assessment dated 02/26/2007 (D336910, F. Fort et al.).

Table 5.1. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression.			
Matrix		**Residues Included in Risk Assessment**	**Residues Included in Tolerance Expression**
Plants	Primary Crop	Aldicarb, aldicarb sulfoxide and aldicarb sulfone	Aldicarb, aldicarb sulfoxide and aldicarb sulfone
	Rotational Crop		
Livestock	Ruminant		
	Poultry		
Drinking Water			Not Applicable

9.2 Food Residue Profile

No new residue data were submitted as part of this registration request as adequate residue chemistry data are available to support the current tolerances for aldicarb, including those for orange and grapefruit (both at 0.3 ppm). Residues are considered systemic, being taken up from plant roots. Residues are generally low, as reflected by tolerance levels ranging from 0.02 – 1

ppm. In general, aldicarb per se is not detected in plants; residues of aldicarb sulfoxide tend to be detected more often and at higher levels than aldicarb sulfone. Stability of residues in frozen storage is dependent on the crop or livestock matrix and may be limited. Residues typically reduce upon processing but may concentrate in some dried matrices.

Consideration of potential residues in citrus dried pulp does not change the conclusions of the most recent evaluation of aldicarb residues in meat, milk, poultry, and egg (MMPE) commodities (D425180, W. Donovan, 02/18/2016), where HED concluded that residues in livestock commodities are classified under 40 CFR §180.6(a)(3), i.e., there is no reasonable expectation of finite residues.

As oranges and grapefruit are perennial crops, rotational crop considerations do not apply to these crops.

9.3 Water Residue Profile

Drinking water residue estimates have been provided by the Environmental Fate and Effects Division (EFED) in the following memorandum: "Aldicarb: Drinking Water Exposure Assessment (DWA) for Proposed New Use on Citrus Grown in Florida" (D460216, J. Lim, 01/07/2021).

For the current assessment, HED included the contribution of potential residues in drinking water through a timeseries of daily averages of estimated aldicarb concentrations as generated and provided by EFED. Specifically, EFED provided 4 files of surface water estimates for 2 and 3 inch application depths reflecting both Texas and Florida percent crop treated refinements as follows: 1) 2" FL percent crop area (PCA), 2) 2" TX PCA, 3) 3" FL PCA, and 4) 3" TX PCA. These files, with water concentrations expressed in ppm, were converted to residue distribution files for analysis using the Dietary Exposure Evaluation Model (DEEM) program. As the current registration action is limited to use of aldicarb in/on orange and grapefruit in Florida, no results pertaining to Texas are included in the dietary assessment section of this risk assessment.

EFED noted that ground water estimates are highly dependent on well setback distances. As the orange/grapefruit proposed use specifies 1000' well setbacks, it is appropriate to include surface water estimates in the dietary assessment as these concentrations are protective for residues from ground water sources. With 300' well setbacks, the ground water concentrations are expected to be higher than those from surface water and the contributions are expected to be similar at well setbacks of approximately 500'.

9.4 Dietary Risk Assessment

9.4.1 Description of Residue Data Used in Dietary Assessment

Aldicarb acute dietary exposure assessments were conducted using the DEEM-FCID, Version 3.16, which incorporates 2003-2008 consumption data from USDA's NHANES/WWEIA. The data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food

commodities (e.g., apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/Agricultural Research Service (ARS) and EPA. For acute exposure assessment, consumption data are retained as individual consumption events.

For an acute exposure assessment, individual one-day food consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a deterministic exposure assessment, or "matched" in multiple random pairings with residue values and then summed in a probabilistic assessment. The resulting distribution of exposures is expressed as a percentage of the aPAD on both a user (i.e., only those who reported eating relevant commodities/food forms) and a per-capita (i.e., those who reported eating the relevant commodities as well as those who did not) basis. In accordance with HED policy, per capita exposure and risk are reported for analyses performed at all levels of refinement. However, for deterministic assessments, any significant differences in user vs. per capita exposure and risk are specifically identified and noted in the risk assessment.

The acute adverse effect of red blood cell cholinesterase inhibition tends to reverse itself within 2 hours following exposure to aldicarb. Since the food diaries used by DEEM-FCID (Version 3.16) Model are based on total daily intake, the estimated risks produced by this software are overestimates, to the extent that foods and drinking water are consumed throughout the day, rather than during only one event. To provide a better approximation of the potential exposure leading to peak RBC ChE inhibition, potential exposure from food and/or water to aldicarb was computed incrementally throughout the day. This computation was made by incorporating information on the time of day and amounts consumed during each occasion from the USDA NHANES/WWEIA food diaries. The potential for accumulation of toxicity was accounted for by computing the degree to which exposures could be discounted between exposure occasions, assuming a two-hour half-life. Further discussion of the methodology used to compute the exposure based on the eating and drinking occasions may be found in a 2006 memo by S. Nako (D299889, 11/01/2006).

USDA PDP monitoring data were used for residues of aldicarb and its metabolites in/on sweet potato and citrus (orange, lemon, lime and grapefruit). Field trial data provided in previous dietary assessments (D299883, C. Olinger, 08/16/2010; and D430197, I. Negron-Encarnacion, 03/28/2016) were used for soybean, dry beans, pecan, cottonseed, and peanut. Residue distribution files (RDFs) were constructed for drinking water based on timeseries residue distributions provided by EFED.

HED considers the current aldicarb dietary assessment to be highly refined. Further refinements would be possible if PDP monitoring data become available for soybean, dry beans, pecan, cottonseed and/or peanut. Additionally, refinement of the 100 percent crop treated assumption for lime may be possible. However, such refinements are not likely to result in a significant reduction of exposures and risk levels as none of these crops are risk drivers in these assessments.

9.4.2 Percent Crop Treated Used in Dietary Assessment

The Biological Economic Analysis Division (BEAD) provided projected percent of crop treated estimates for orange, orange juice, grapefruit, and grapefruit juice in the following memorandum: "Aldicarb Use on Oranges and Grapefruit: Benefits, Estimated Percent Crop Treated (PCT) for use in Risk Assessments, and Anticipated Impacts of Mitigation" (D454270, J. Hansel, R. Waterworth, and L. Hendrick, 01/07/2021). Percent crop treated estimates for other registered crops were as used in the previous dietary assessment (D444345, W. Donovan, 11/28/2017). The projected percent crop treated estimates for orange, orange juice, grapefruit and grapefruit juice took into account production cap limits proposed by the registrant.

The following maximum percent crop treated estimates (Updated Screening Level Usage Analysis (SLUA) Report for Aldicarb, PC Code 098301; 12/18/2014) were used in the acute dietary risk assessment: cotton, 35%; dry bean, 2.5%; grapefruit, 13%; grapefruit juice, 16%; lemon, 10%; orange, 13%; orange juice, 63%; pecan, 58%; peanut, 45%; processed potato, 4%; soybean, 2.5%; and sweet potato, 34%. The remaining commodity (lime) assumed 100% crop treated.

9.4.3 Acute Dietary Risk Assessment

HED is concerned when dietary risk exceeds 100% of the aPAD. The DEEM-FCID analyses estimate the dietary exposure and risk of the U.S. population and various population subgroups. The results reported in Table 5.4.6 are for the general U.S. Population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, females 13-49, adults 20-49, and adults 50-99 years. Acute assessments were conducted using water concentrations reflecting the Florida percent crop area (PCA) refinement of 14.2%, together with incorporation depths of 2- and 3-inches. All runs assumed percent crop treated estimates for orange and grapefruit determined assuming production cap limits for aldicarb (100,000 acres per year), as provided by the BEAD.

Risk estimates for the 3-inch incorporation depth scenario are not of concern. Based on Florida PCA refined EDWCs, at the 99.9th percentile of exposure, the general U.S. population occupies 43% of the aPAD. The most highly exposed population subgroup, children 1-2 years old, occupies 95% of the aPAD. Risk estimates for the 2-inch incorporation depth scenario are of concern. Based on Florida PCA refined EDWCs, at the 99.9th percentile of exposure, the general U.S. population occupies 53% of the aPAD. The most highly exposed population subgroup, children 1-2 years old, occupies 103% of the aPAD. HED notes that the most recent proposed label for use of aldicarb in/on orange and grapefruit specify a 3-inch incorporation depth. Previous versions of the label included a range of incorporation depths from 2-3 inches. The 2-inch results are provided in this assessment for risk characterization purposes.

9.4.4 Chronic Dietary Risk Assessment

A chronic dietary assessment was not conducted since the rapid recovery of cholinesterase following acute exposure to aldicarb prevents cumulative toxicity; consequently, the acute dietary assessment is considered protective for any chronic dietary exposures.

9.4.5 Cancer Dietary Risk Assessment

Aldicarb is classified as Category E, Evidence of Non-Carcinogenicity for Humans; therefore, a cancer dietary assessment was not conducted.

9.4.6 Summary Table

Table 5.4.6. Summary of Acute Dietary (Food and Drinking Water) Exposure and Risk for Aldicarb Assuming Surface Water Residues Based on FL PCA Scenario at 99.9th Percentile.

Population Subgroup	2-inch Incorporation Depth		3-inch Incorporation Depth	
	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
General U.S. Population	0.000144	53	0.000117	43
All Infants (<1 year old)	0.000180	67	0.000128	47
Children 1-2 years old*	**0.000278**	**103**	**0.000256**	**95**
Children 3-5 years old	0.000207	77	0.000186	69
Children 6-12 years old	0.000155	58	0.000125	46
Youth 13-19 years old	0.000100	37	0.000071	26
Adults 20-49 years old	0.000118	44	0.000082	30
Adults 50-99 years old	0.000104	39	0.000073	27
Females 13-49 years old	0.000113	42	0.000072	27

* The population with the highest risk estimate is in bold.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are currently no registered or proposed residential uses for aldicarb; therefore, a quantitative residential assessment was not conducted.

7.0 Aggregate Exposure/Risk Characterization

The registered aldicarb uses are not anticipated to result in residential exposure, and thus the acute dietary (food and drinking water) exposure estimates provided in Table 5.4.6 represent the acute aggregate exposure.

8.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Spray drift is a potential source of exposure to those nearby pesticide applications. Where appropriate, the potential for spray drift will be quantitatively evaluated for each pesticide during the Registration Review process which ensures that all uses for that pesticide will be considered concurrently. However, the aldicarb end use product is formulated as a granular and will not result in spray drift because of how it is applied (pre-plant/post-emergent soil incorporation).

9.0 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[6]. The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis[7]. 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 aldicarb.

10.0 Cumulative Exposure/Risk Characterization

The FQPA requires the Agency to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. Aldicarb is a member of the NMC common mechanism group. NMCs like aldicarb share the ability to inhibit AChE through carbamylation 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 NMC common mechanism grouping per OPP's *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999). The 2007 CRA and the subsequent revision used brain AChEI in female rats as the source of dose response data for the relative potency factors and PODs for each NMC, including aldicarb.

Exposure to aldicarb based on the previously active registration on citrus was included in the 2007 *N*-Methyl Carbamate Cumulative Risk Assessment (NMC CRA). Since the proposed use on citrus is similar to the previously registered use, the cumulative exposure to the class of NMC pesticides through food would not be significantly impacted by the proposed citrus use for aldicarb. For the 2007 NMC CRA, food exposure to aldicarb was estimated based on measured pesticide residues in orange, orange juice, and grapefruit[8]. For the most sensitive subpopulation, children 1-2 years old, the food exposure to aldicarb for these citrus foods was minimal for those at high-end of the exposure distribution. Furthermore, assuming a 3" incorporation depth, exposure through drinking water residues resulting from the proposed use would not contribute significantly to the cumulative risk.

11.0 Occupational Exposure/Risk Characterization

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

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a

[6] http://www regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037

[7] http://www regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219

[8] USDA's PDP collects thousands of food samples annually and analyzes these samples for residues of hundreds of pesticides. Residue data from PDP was used to estimate food exposure for the NMC CRA. PDP found a number of detectable residues of aldicarb or its metabolites in grapefruit, orange, and orange juice. More specifically, the number of detectable residues (and years sampled) were 4 out of 1462 grapefruit samples with concentrations <= 0.063 ppm (2005-2006); 13 out of 4864 orange sample with concentration <= 0.025 ppm (1994-1996, 2000-2001, & 2004-2005); and 46 out of 2879 orange juice samples with concentrations <= 0.035 ppm (1997-1998 & 2004-2006).

manner specific to each application event. Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the proposed uses.

Occupational Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed below on an individual basis.

Application Rate: The maximum single application rate (4.95 lb ai/A) was used in the exposure calculations as noted in Table 3.3.

Unit Exposures: It is the policy of HED to use the best available data to assess handler exposure. In the case of aldicarb, a chemical-specific study (MRID 43852501[9]) is available that has been determined acceptable for risk assessment and is representative of the specific "low dust" granular formulation of the aldicarb product. A summary of the study data as collected is included in Appendix D. For scenarios representing open loading and open cab applications, unit exposure data from the chemical-specific study were used. It should be noted that the study was conducted with handlers wearing a single layer of clothing (short-sleeved shirt, short pants and coveralls) and gloves. While workers did wear dust masks in the study, the inhalation unit exposures from the study represent potential exposure without a respirator. Since the currently registered label requires mixer/loaders wear a respirator, the mixer/loader inhalation unit exposures were adjusted to account for current label PPE (i.e., filtering facepiece respirator).

In addition, for the closed loading/closed cab scenarios, HED relied on available Occupational Pesticide Handler Exposure Data as surrogate data. For closed loading and closed cab application of granulars, these data include the PHED 1.1 database. Some of these data are proprietary, and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[10]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[11].

Area Treated or Amount Handled: The area treated, or amount handled for this assessment was based on HED ExpoSAC Policy 9.1.

Exposure Duration: HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. Exposure duration is determined by many things, including the exposed population, the use site, the pest pressure triggering the use of the pesticide, and the cultural practices surrounding that use site. For most agricultural uses, it is

[9] D221446, J. Carleton, 02/28/1996. EPA MRID 43852501: Rosenheck, L., Schuster, L. (1995) Worker Loader and Applicator Exposure to Temik 15G. Study number 94388, Unpublished study prepared by ABC Laboratories, Pan-Ag Division; Rhone-Poulenc Ag Company.

[10] Available: https://www.epa.gov/sites/production/files/2020-03/documents/opp-hed-pesticide-handler-surrogate-unit-exposure-table-march-2020.pdf

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

reasonable to believe that occupational handlers will not apply the same chemical every day for more than a one-month time frame; however, there may be a large agribusiness and/or commercial applicators who may apply a product over a period of weeks (e.g., completing multiple applications for multiple clients within a region). Since toxicity doesn't increase with increasing duration of exposure for aldicarb, risks estimated using the acute POD are protective for all exposure durations.

Personal Protective Equipment: Estimates of dermal and inhalation exposure were calculated for various levels of PPE. Results are presented for mixers/loaders and applicators based on the personal protective equipment represented by the unit exposures:

- Baseline (i.e., a single layer of clothing), chemical-resistant gloves and either no respirator (for applicators) or with a PF10 respiratory protection device (for mixer/loaders) and
- Engineering controls (closed loading system or closed cab).

Combining Exposures/Risk Estimates:
Dermal and inhalation risk estimates were combined in this assessment, since the toxicological effects for these exposure routes were similar. Dermal and inhalation risk estimates were combined using the following formula:

Total MOE = Point of Departure (mg/kg/day) ÷ Combined dermal + inhalation dose (mg/kg/day)

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates
Occupational handler risk estimates are presented using both HED's standard occupational exposure methodology and the available chemical-/formulation-specific handler data, where available.

Table 11.1.1 shows loader and applicator risk estimates assuming open loading/open cab scenarios using the available chemical-specific handler data. Table 11.1.2 shows loader and applicator risk estimates assuming closed loading/closed cab scenarios based on the PHED surrogate unit exposure data.

Exposure and risk estimates for handlers using closed systems may be considered overestimates as the PHED surrogate unit exposures are not representative of the low dust aldicarb formulations. Furthermore, where risk concerns exist, the combined risk estimates are driven by dermal exposure. It should be noted that an assumption of 100% dermal absorption was used in the dermal exposure/risk calculations since an acceptable dermal absorption study was not submitted. Given that the registered product is a granular formulation, it is unlikely that 100% absorption would occur.

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Aldicarb - Open Pour/Open Cab Application Using Chemical-Specific Data.

Crop or Target	Dermal Unit Exposure (µg/lb ai)[1] [Level of PPE]	Inhalation Unit Exposure (µg/lb ai)[1] [Level of PPE]	Maximum Application Rate (lb ai/A)[2]	Area Treated Daily (Acres)[3]	Dermal		Inhalation		Total
					Dose (mg/kg/day)[4]	MOE (LOC = 10)[5]	Dose (mg/kg/day)[6]	MOE (LOC = 10)[7]	MOE (LOC = 10)[8]
Mixer/Loader (Load Granules – tractor drawn spreader)									
Citrus and Grapefruit	0.22 [SL/G]	0.007 [PF10]	4.95	80	0.0011	12	0.000035	380	12
Applicator (granules – tractor-drawn spreader)									
Citrus and Grapefruit	0.089 [SL/G]	0.013 [No-R]	4.95	80	0.00044	30	0.000064	200	26

1 SL/G = single layer with gloves. No-R = no respirator. PF10 = use of a PF10 respirator. Based on MRID 43852501. The study inhalation unit exposure for mixer/loaders (0.07 ug/lb ai) is representative of baseline protection (i.e. no respirator) and was adjusted to represent use of a PF10 respirator.
2 Based on proposed supplemental labeling for EPA Reg. No. 87895-4.
3 Exposure Science Advisory Council Policy #9.1.
4 Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre) × Area Treated (A/day) × DAF (100%) ÷ BW (80 kg).
5 Dermal MOE = Dermal $BMDL_{10}$ (0.013 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
6 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre) × Area Treated (A/day) ÷ BW (80 kg).
7 Inhalation MOE = Inhalation $BMDL_{10}$ (0.013 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
8 Total MOE = $BMDL_{10}$ (0.013 mg/kg/day) ÷ [Dermal Dose + Inhalation Dose]

Table 11.1.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for Aldicarb - Engineering Controls (Based on the PHED Surrogate Data).

Crop or Target	Dermal Unit Exposure (µg/lb ai)[1] [Level of PPE]	Inhalation Unit Exposure (µg/lb ai)[1] [Level of PPE]	Maximum Application Rate (lb ai/A)[2]	Area Treated Daily (Acres)[3]	Dermal		Inhalation		Total
					Dose (mg/kg/day)[4]	MOE (LOC = 10)[5]	Dose (mg/kg/day)[6]	MOE (LOC = 10)[7]	MOE (LOC = 10)[8]
Loader (Load Granules – tractor drawn spreader)									
Citrus and Grapefruit	8.6 [EC]	0.083 [EC]	4.95	80	0.043	**0.31**	0.00041	32	**0.31**
Applicator									
Citrus and Grapefruit	2.0 [EC]	0.109 [EC]	4.95	80	0.0099	**1.3**	0.00054	24	**1.2**

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (March 2020) as noted; Level of mitigation: EC= Eng. Controls.
2 Based on proposed supplemental labeling for EPA Reg. No. 87895-4.
3 Exposure Science Advisory Council Policy #9.1.
4 Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre) × Area Treated (A/day) × DAF (100%) ÷ BW (80 kg).

5 Dermal MOE = Dermal $BMDL_{10}$ (0.013 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
6 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre) × Area Treated (A/day) ÷ BW (80 kg).
7 Inhalation MOE = Inhalation $BMDL_{10}$ (0.013 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
8 Total MOE = $BMDL_{10}$ (0.013 mg/kg/day) ÷ [Dermal Dose + Inhalation Dose].

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

11.2.1 Dermal Post-Application Exposure and Risk Estimates

A quantitative post-application assessment has not been conducted for aldicarb because aldicarb is soil incorporated and there is limited potential for worker dermal exposure to soil incorporated pesticides.

Restricted Entry Interval (REI)
The REI specified on the label for the proposed uses [48 hours] is based on the acute toxicity of aldicarb. Aldicarb is classified as Toxicity Category I via the dermal, oral, and inhalation routes of exposure. Due to severe effects (death) following corneal and dermal dosing, dermal and eye irritation studies were waived in the acute toxicity database. Because of the limited worker exposure profile (soil-incorporation), the REI on the labels is adequate to protect for worker exposure. Therefore, the [156 subpart K] Worker Protection Statement interim REI of 48 hours is adequate to protect agricultural workers from post-application exposures to aldicarb.

11.2.2 Inhalation Post-Application Exposures and Risk Estimates

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. 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 aldicarb.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments.

12.0 References

Habiba, U. (03/01/2016). **Aldicarb**: Summary of the Hazard and Science Policy Council (HASPOC): Recommendations on the Need for an Acute Inhalation Toxicity Study.

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

Sette, W.F. (09/15/1998). **Aldicarb** – Report of the Hazard Identification Assessment Review Committee.

Appendix A. Toxicology Profile

A.1 Toxicology Data Requirements

The toxicology data requirements (40 CFR 158.340) for the food uses of aldicarb are in Table A.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1. Aldicarb Toxicology Data Requirements

Study		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	no[A]
870.2500	Primary Dermal Irritation	yes	no[A]
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes[B]
870.3150	Oral Subchronic (non-rodent)	yes	yes
870.3200	21-Day Dermal	yes	no[C]
870.3250	90-Day Dermal	no	-
870.3465	90-Day Inhalation	yes	no[C]
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (non-rodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (non-rodent)	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
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5450	Mutagenicity—Dominant Lethal Test	yes	yes
870.5500	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotoxicity (hen)	yes	yes
870.6100b	90-Day Neurotoxicity (hen)	CR	yes
870.6200a	Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b	90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300	Develop. Neurotoxicity	yes	yes
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	-
870.7800	Immunotoxicity	yes	yes

[A] Eye and dermal irritation studies are not required due to lethality from these exposure routes.
[B] Chronic toxicity study satisfies this requirement.
[C] Not required due to severe irritation.
CR conditionally required.

A.2 Toxicity Profiles

Table A.2.1. Aldicarb Acute Toxicity Profile				
Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute Oral	00057333	LD_{50} = 0.8 mg/kg/day	I
870.1200	Acute Dermal	00091241 00069916	LD_{50} = 20 mg/kg, water LD_{50} = 5 mg/kg, propylene glycol	I
870.1300	Acute Inhalation	00069916 00057333	LC_{50} < 0.007 mg/L	I
870.2400	Primary Eye Irritation	00069916	No corneal irritation at lethal dose	N/A
870.2500	Primary Skin Irritation	00069916	None at fatal levels	N/A
870.2600	Dermal Sensitization	N/A	N/A	N/A

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile of Aldicarb Technical		
Study Type [GLN No.]	**MRID No./Classification**	**Results[1]**
Sub-chronic oral toxicity (Beagle dog) [870.3150]	41919901 (1991) Acceptable/Non-guideline 0, 0.01, 0.02, or 0.06 mg/kg/day (diet) 14 weeks Cholinesterase samples 2-hours post dose	NOAEL=0.02 mg/kg/day LOAEL=0.06 mg/kg/day based on plasma and RBC AChEI in males and females
21-day dermal toxicity (CD® Sprague-Dawley rats) [870.3200]	44636101 (1998) Non-guideline/Unacceptable 0, 100, 250, or 500 mg/kg/day, 6 hours/day, 5 days/week for 3 weeks	Unacceptable due to inconsistent findings in body weight and cholinesterase inhibition; concerns for several aspects of the study (adequacy of skin contact with test material; wetting of test material; amount of skin exposed; limited data on active ingredient)
Developmental toxicity rodent (Sprague-Dawley Crl:CD BR rats) [870.3700a]	41004501 (1988) Acceptable/Guideline 0, 0.125, 0.25, or 0.5 mg/kg/day GD 6-16 (gavage)	<u>Maternal</u>: NOAEL=0.125 mg/kg/day LOAEL=0.25 mg/kg/day Based on decreased body weight gain and food consumption. At 0.50 mg/kg/day (HDT), 3 dams died on Day 7. Significant increases in signs of AChEI (hypoactivity, ataxia, tremors, lacrimation, unkempt appearance, urine stains, loose stools, cold extremities, nasal and ocular crusting, audible respiration) were observed <u>Developmental</u>: NOAEL=0.125 mg/kg/day LOAEL=0.25 mg/kg/day based on ecchymosis of the trunk

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile of Aldicarb Technical		
Study Type [GLN No.]	**MRID No./Classification**	**Results[1]**
Developmental toxicity in non-rodent (Dutch Belted rabbit) [870.3700b]	0132668 (1983) Acceptable/Guideline 0, 0.1, 0.25, or 0.5 mg/kg/day GD 7-27 (gavage)	Maternal: NOAEL=0.1 mg/kg/day LOAEL=0.25 mg/kg/day based on decreased body weight, pale kidneys and hydroceles on the oviducts Developmental: NOAEL=>0.5 mg/kg/day
Reproduction and fertility effects (Sprague-Dawley Crl:CD BR rats) [870.3800]	42148401 (1991) Acceptable/Guideline males: 0, 0.1, 0.4, 0.7, or 1.4 mg/kg/day females: 0, 0.2, 0.4, 0.9, or 1.7 mg/kg/day	Parental/Systemic: NOAEL=0.4 mg/kg/day LOAEL=0.7-0.9 mg/kg/day based on decreased body weight gains and RBC and plasma AChEI Reproductive: NOAEL=0.7-0.9 mg/kg/day LOAEL=1.4-1.7 mg/kg/day based on decreased viability and body weights, and signs of debilitation
Chronic oral toxicity in rodents (Sprague-Dawley Crl:CD BR rats) [870.4100a]	43045401 (1993) Acceptable/Guideline males: 0, 0.047, 0.47, or 1.44 mg/kg/day females: 0, 0.06, 0.59, or 1.87 mg/kg/day	NOAEL=0.047 mg/kg/day LOAEL=0.47 mg/kg/day based on plasma and RBC AChEI
Chronic oral toxicity dogs (Beagle) [870.4100b]	40695401, 42191501 (1988) Acceptable/Guideline 0, 1, 2, 5, 10 ppm (0, 0.028, 0.056, 0.13, or 0.25 mg/kg/day)	NOAEL<0.028 mg/kg/day LOAEL=0.028 mg/kg/day based on plasma AChEI
Carcinogenicity in rats (Sprague-Dawley Crl:CD BR rats) [870.4200]	43045401 (1993) Acceptable/Guideline males: 0, 0.047, 0.47, or 1.44 mg/kg/day females: 0, 0.06, 0.59, or 1.87 mg/kg/day	NOAEL=0.047 mg/kg/day LOAEL=0.47 mg/kg/day based on plasma/RBC AChEI No evidence of carcinogenicity
Carcinogenicity in mice (CD-1) [870.4300]	00044732; 00044733; 00044734 (1972) Acceptable/Guideline 0, 0.1, 0.2, 0.4, or 0.7 mg/kg/day (diet)	NOAEL=0.2 mg/kg/day LOAEL=0.4 mg/kg/day based on increased mortality No evidence of carcinogenicity

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile of Aldicarb Technical		
Study Type [GLN No.]	**MRID No./Classification**	**Results[1]**
Gene Mutation Chinese hamster ovary (CHO) cell HGPRT forward gene mutation assay [870.5300]	00148168 (1985) Acceptable/Guideline 1000-5000 µg/ml	Negative with and without activation at a marginally cytotoxic dose
Cytogenetics: Mammalian bone marrow chromosome aberration test ICR mouse [870.5385]	41661301; 41663102 (1990) Acceptable/Guideline 0.1-0.4 mg/kg	No chromosomal aberrations in mouse bone marrow cells
Unscheduled DNA Synthesis [870.5500]	00141673 (1984) Acceptable/Guideline 33-10,000 µg/well	No effects
Dominant Lethal Study (Sprague-Dawley rat)	43575101 (1995) Acceptable/Guideline	Systemic LOAEL=2.28 mg/kg based on body weight reductions, tremors, and plasma, RBC and brain AChEI No evidence of a dominant lethal effect
Acute neurotoxicity screening battery (Sprague-Dawley Crl:CD BR rats) [870.6200a]	43442301 (1994) Acceptable/Guideline 0, 0.05, 0.1, 0.5 mg/kg (gavage)	NOAEL<0.05 mg/kg/day LOAEL=0.05 mg/kg/day, based on plasma and RBC AChEI NOAEL = 0.05 mg/kg LOAEL = 0.1 mg/kg, based on brain AChEI
Subchronic neurotoxicity screening battery (Sprague-Dawley Crl:CD BR rats) [870.6200b]	43829602 (1995) Acceptable/Guideline 0, 0.5, 0.20, 0.40 mg/kg/day (gavage) for 13 weeks	NOAEL<0.05 mg/kg/day LOAEL=0.05 mg/kg/day based on pinpoint pupils and blood and brain AChEI
Developmental neurotoxicity (Sprague-Dawley Crl:CD7 BR VAF/Plus 7 rats) [870.6300]	43829601 (1995) Acceptable/Guideline 0, 0.05, 0.10, or 0.30 mg/kg/day GD 6-LD 10 (gavage)	<u>Maternal</u>: NOAEL=0.05 mg/kg/day LOAEL=0.1 mg/kg/day based on plasma AChEI RBC AChEI at 0.1 mg/kg/day 16% (LD 7); 11% (LD 11) not statistically significant; at 0.3 mg/kg/day, GD 7/LD 7 AChEI 27% <u>Offspring</u>: NOAEL=0.05 mg/kg/day LOAEL=0.1 mg/kg/day based on reduced body weights and decreased motor activity
Metabolism and pharmacokinetics [870.7485]	00102022 (1966) 00102023 (1967) Acceptable/Guideline	85% of an acute oral dose to rats was excreted in 24 hours. The metabolism of aldicarb was primarily to the sulfoxide (40%), with a smaller amount then slowly converted to the sulfone

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile of Aldicarb Technical		
Study Type [GLN No.]	**MRID No./Classification**	**Results[1]**
Immunotoxicity Study (Swiss Webster or B6C3F1 mice) [870.7800]	00410546 (1989) Acceptable/Guideline (published paper)	Aldicarb had no significant effect on numbers and percentages of splenic total T-lymphocytes, T-helper cells, T-suppressor/cytotoxic cells, or B-cells when administered to female B6C3F1 mice at 1, 10, or 100 ppb in drinking water for 34 days. Additionally, there was no significant effect on either splenic natural killer cell function or cytotoxic T-cell function
Comparative cholinesterase (Sprague-Dawley Crl:CD BR rats)	47994302-47994303 (2009) 47994304-47994305 (2010) Acceptable/Non-guideline Adults: 0, 0.03, 0.05, 0.065, 0.08, 0.15, or 0.3 mg/kg PND 11 pups: 0, 0.005, 0.01, 0.02, 0.04, or 0.08 mg/kg	PND 11 pups showed sensitivity for both RBC and brain cholinesterase inhibition See Table A.2.3 below for benchmark dose analyses.
Special neurotoxicity studies: Moser VC (Long-Evans rats)	45068601 (1999) TAP 157 94-106	NOAEL<0.05 mg/kg LOAEL=0.05 mg/kg (pups) Effects in pups: Blood (both sexes), brain AChEI (males). Note: PND 17-day pups exhibited twice the level of brain AChEI as adults
Acute oral study (human)	42373001 (1992) 46131001 (supplementary report) Acceptable/Non-guideline Males: 0, 0.01, 0.025, 0.06, 0.06, or 0.075 mg/kg Females: 0, 0.025, or 0.05 mg/kg	NOAEL = not determined for females LOAEL = 0.025 mg/kg, based on RBC cholinesterase inhibition NOAEL = 0.01 mg/kg LOAEL = 0.025 mg/kg, based on clinical signs and RBC cholinesterase inhibition in males

[1]NOAEL = No observed adverse effects level; LOAEL = Lowest observed adverse effects level; AChE = Cholinesterase; AChEI = Cholinesterase inhibition; RBC = red blood cell.

Table A.2.3 Summary of Benchmark Dose (BMD) Analyses for RBC and Brain AChEI from Acute CCA Studies					
Results of BMD Modeling (mg/kg) for Brain and RBC Cholinesterase, Acute Oral Dosing Studies in Rats					
Study	**Age/Sex**	**Brain BMD_{10}**	**Brain $BMDL_{10}$**	**RBC BMD_{10}**	**RBC $BMDL_{10}$**
MRID 47994302-05 Acute CCA[A]	PND 11 Male	0.0143 mg/kg	0.0112 mg/kg	0.00477 mg/kg	0.00387 mg/kg
MRID 47994302-05 Acute CCA[A]	PND 11 Female	0.0136 mg/kg	0.0103 mg/kg	0.00731 mg/kg	0.00387 mg/kg
MRID 47994302-05 Acute CCA[A]	Adult Male	0.0535 mg/kg	0.0484 mg/kg	0.0228 mg/kg	0.0153 mg/kg
MRID 47994302-05 Acute CCA[A]	Adult Female	0.0615 mg/kg	0.0498 mg/kg	0.0242 mg/kg	0.0144 mg/kg

MRID 47994302 - 47994305; samples taken at peak effect times: 40 minutes (adults)/60 minutes (PND 11 pups).

Appendix B. Physical/Chemical Properties

Table B.1. Physicochemical Properties of Technical Grade Aldicarb		
Parameter	**Value**	**Reference**
Molecular Weight	190.3 g/mol	D392450, S. Mathur, 12/12/2011 [MRID 485225-04]
Physical State	Solid	
Melting range	96 - 97 °C	
pH	6.0	
Density	0.565 g/mL	
Water solubility	5191 mg/L at 20 °C	
Vapor pressure	0.9 mPa (25 °C)	
Octanol/water partition coefficient, Log (K_{OW})	1.06	
UV/visible absorption spectrum	UV absorption was conducted under acidic (λ = 772, 779, 757 nm), neutral (λ = 488. 757, 765 nm) and basic (λ = 765, 779, 757 nm) conditions.	

Appendix C. Review of Human Research

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 include studies from the Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1), the Agricultural Handler Exposure Task Force (AHETF) database. These data are subject to ethics review pursuant to 40 CFR 26, have received that review, and are compliant with applicable ethics requirements. For certain studies that 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 http://www.epa.gov/pesticides/science/handler-exposure-data.html and http://www.epa.gov/pesticides/science/post-app-exposure-data.html.

The Human Studies Review Board reviewed the aldicarb human study and concluded that the study is scientifically valid and the data are reliable and that the use of the human study endpoint was appropriate for human health risk assessment. The final report of the HSRB is available on the Agency website[14].

[14] HSRB Report: http://archive.epa.gov/hsrb/web/pdf/april2006mtgfinalreport62606-2.pdf

Appendix D. Summary of Available Occupational Handler Exposure Data

One chemical-specific study was submitted in support of the reregistration of aldicarb and was judged to be appropriate for use in occupational exposure/risk assessments (D221446, J. Carleton, 02/28/1996). These data have not been integrated with PHED for this assessment because the granules used are a vinyl coated formulation (i.e., a "low dust formulation") which is likely to lead to differences in exposure. The study can be identified by the following information:

EPA MRID 43852501: Rosenheck, L., Schuster, L. (1995) Worker Loader and Applicator Exposure to Temik 15G. Study number 94388, Unpublished study prepared by ABC Laboratories, Pan-Ag Division; Rhone-Poulenc Ag Company.

This study quantified exposure to aldicarb for workers loading and applying Temik 15G (EPA Reg. No. 264-330) at the maximum rate of 6 lb ai/acre in pecan groves using shank injection. Dermal and inhalation exposure levels to aldicarb and its two principal by-products, aldicarb sulfoxide and aldicarb sulfone, were measured. Five replicates of the loading and application of Temik 15G were monitored at each of the three locations for a total of 15 loading and 15 application replicates (mixer/loaders were monitored separately from the applicators). The study was conducted in three locations; Raymond, Mississippi; Brownwood, Texas; and Albany, Georgia.

The use of a modified Tye seeder in the three different locations was consistent with commercial agricultural practice (i.e., recommended equipment for aldicarb applications). The test subjects also wore protective clothing that met U.S. EPA Worker Protection Standards, consisting of nitrile rubber gloves, rubber boots, goggles, hard hat, a dust mask and a chemical resistant apron (loader only) over short-sleeved shirt, short pants and coveralls. The duration of each loading replicate was approximately 4 hours, and during this time the modified seeder was loaded and emptied twice (once at the start and again after about 2 hours). The application replicates were monitored using open cab tractors over a period of approximately 4 hours. The loaders handled a range of 900 lb to 1485 lb of Temik 15G (135 lb to 223 lb ai) per replicate. The maximum application rate was approximately 40 lb product per acre (6 lb ai/A, the maximum rate). Aldicarb was packaged in 45 pound bags and open cab tractors were used.

Dermal exposures were monitored using whole-body dosimetry (long underwear, later sectioned into arms, chest, back, and lower body), handwashes and facial and neck swipes. The long underwear (100% cotton) was worn under short pants and a short-sleeved shirt. Hand exposure was monitored by having each test subject remove gloves and wash both hands twice in detergent solution (0.01% v/v Aerosol OT 75). Face and neck exposures were monitored by wiping the face and neck with 10 percent cotton gauze pads wet with the detergent solution. Inhalation exposures were monitored using a XAD2 resin tube, polyurethane foam, and glass fiber filter to collect both vapor and particulate matter. The tubes were attached to a personal air pump with a flow rate of approximately 1.5 liters/minute. The limits of quantification (LOQs) for each matrix are presented in Table 1.

Table 1: Limits of Quantification and Detection in Study

Area	LOQ (µg/ml)	<LOQ:Replicates		LOD (µg/ml)	Non-detects:Replicates	
		Loader	Applicator		Loader	Applicator
Dermal:						
Arm, chest, back	1.00	21:45	25:45	0.40	6:45	6:45
Lower Body	2.00	0:15	3:15	0.67	0:15	2:15
Handwash	1.00	1:15	2:15	0.30	0:15	2:15
Facial Wipe	0.10	4:15	2:15	0.01	0:15	0:15
Inhalation:						
OVS Tube	0.05	1:15	6:15	0.020	0:15	1:15

a LOD = Minimum Standard Concentration Tested (0.01µg/ml) * Dilution Factor.
Arm, chest, back Dilution Factor = 40
Lower Body Dilution Factor = 67
Handwash Dilution Factor = 30
Facial Wipe Dilution Factor = 1
OVS Tube Dilution Factor = 1

Note: For **Loaders**: Aldicarb 38 of 90 samples were <LOQ, 11 of 90 samples were <LOD, Aldicarb sulfone 79 of 90 samples were < LOQ, 47 of 90 samples were <LOD and aldicarb sulfoxide 56 of 90 samples were < LOQ, 20 of 90 samples were <LOD.

For Applicators: Aldicarb 56 of 90 samples were <LOQ, 15 of 90 samples were <LOD, Aldicarb sulfone 83 of 90 samples were < LOQ, 55 of 90 samples were <LOD and aldicarb sulfoxide 79 of 90 samples were < LOQ, 27 of 90 samples were <LOD.

For detected peaks whose values fell below the LOQ but above the limit of detection (LOD), results were reported as 50 percent of the LOQ. This is within current Agency guidelines. However, when the results fell below the LOD (i.e. "no peak detected"), the study reported the result as only 10 percent of the LOQ. The study did not mention the LOD value used for this interpretation. In place of the 10 percent LOQ value given non-detects, 50 percent LOD was used in the exposure calculations. The LOD for each matrix was calculated based on the lowest quantifiable level in the calibration curve as presented in the analytical methods section of the study.

The study was conducted in accordance with most of 875 Guidelines Group A, Applicator Monitoring Exposure Test Guidelines. Field recovery for aldicarb, aldicarb sulfoxide, and aldicarb sulfone are presented in Table 2.

Table 2: Field Fortification Recoveries.

Matrix	Field Percent Recovery (CV %)*			N
	Aldicarb	Aldicarb Sulfoxide	Aldicarb Sulfone	
Inhalation Tube	77 (4)	NA	NA	8
Handwash	78 (13)	75 (5)	90 (11)	8
Facial Swab	84 (7)	92 (5)	92 (4)	8
Body Dosimeter	83 (7)	81 (5)	91 (3)	8

* CV = standard deviation ÷ mean

Laboratory recovery for aldicarb, aldicarb sulfoxide and aldicarb sulfone is presented in Table 3. Storage stability data were acceptable. Control samples had residues less than the LOQ and the recoveries were within the EPA acceptable range of 70-120%.

Table 3: Laboratory Recoveries.			
Matrix	Laboratory Percent Recovery (CV %, n)		
	Aldicarb	Aldicarb Sulfoxide	Aldicarb Sulfone
Inhalation Tube	81 (16, n=24)	84 (12, n=24)	83 (10, n=24)
Handwash	93 (7.6, n=17)	83 (9.7, n=17)	98 (7.7, n=17)
Facial Swab	90 (13, n=13)	90 (9.7, n=13)	92 (11, n=13)
Body Dosimeter	83 (16, n= 21)	89 (12, n=21)	96 (10, n=21)

The values used in risk assessment were adjusted for field recovery (results below 90 percent increased to 100 percent) and normalized to mg (µg for inhalation) of aldicarb exposure per lb of aldicarb handled (incorporating the 50 percent LOD value for non-detects and 50 percent LOQ for values below the LOQ). The values calculated are presented in Table 4.

Table 4: Results from Aldicarb Pecan Loader and Applicator Study.						
Task	Dermal (mg ai exposure/ lb ai handled)			Inhalation (µg ai exposure/ lb ai handled)		
	Arithmetic Mean*	Geometric Mean	Median	Arithmetic Mean*	Geometric Mean	Median
Loader	0.00022	0.00019	0.00017	0.070	0.025	0.022
Applicator	0.000089	0.000081	0.000078	0.013	0.0044	0.0044

* Used as the unit exposure for occupational risk estimation