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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

Acephate Note to Readers

The Agency is publishing the human health draft risk assessment for acephate, "Acephate. Revised Draft Human Health Risk Assessment (DRA) in Support of Registration Review," for public comment. The ecological draft risk assessment, "Preliminary Ecological Risk Assessment for Registration Review for Acephate," is also available for public comment and can be accessed in the acephate registration review docket, EPA-HQ-OPP-2008-0915, in www.regulations.gov.

Acephate is an organophosphate insecticide registered for use on a variety of agricultural crops, for use in outdoor non-agricultural settings, for indoor treatment of commercial and industrial buildings, and for use in greenhouses.

In the human health risk assessment, EPA used the inhibition of the acetylcholinesterase enzyme as the point of departure for acephate, which was also used for the other organophosphate pesticides. The Agency applied the default uncertainty factors to account for inter- and intra-species variability in the dose-response relationship. It also retained the 10x safety factor (SF), as directed by the Food Quality Protection Act (FQPA), for population subgroups that include infants, children, youth, and women of childbearing age because of the uncertainty in the human dose-response relationship for neurodevelopmental effects.[1] (See Section 4.0 of the human health DRA for the hazard characterization and dose-response assessment.) The Agency is continuing its evaluation of the underlying science which led to the retention of the 10x FQPA SF and will consider all public comments received on this topic.

In the draft assessment, the Agency identified human health risks of concern from current registered uses of acephate in the DRA. The dietary risk assessment shows that there are risk estimates of concern even when looking at exposures to drinking water alone or food only exposures at the acute and steady state duration for all population groups (except adults age 50 and older). In residential settings, the risks from post-application indoor exposure scenarios for children are of concern. The buffers from the edge of the field necessary to protect adults and children from risks from exposures to spray drift-deposited residues are up to 300 feet. A third of the occupational handler scenarios assessed did not pass either with current personal protective equipment (PPE) or with additional PPE and/or engineering controls. In previously treated areas,

[1] For more information about the Agency's use of the 10x FQPA SF, see "Literature Review on Neurodevelopmental Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides. September 15, 2015" available at www.regulations.gov under docket ID EPA-HQ-OPP-2008-0119-0015.

the minimum time needed to reach acceptable levels of risk before workers can re-enter to perform post-application activities is longer than what is currently required in labels. (See Sections 5.0 to 11.0 of the human health DRA for discussions of exposure and risk assessment.)

Risks of concern remain however, even without the 10x FQPA SF.[2] There would still be dietary risks of concern for some population age groups, specifically children age 5 and younger. In residential settings, the majority of the post-application indoor scenarios continue to pose risks of concern for children. Buffers of up to 250 feet would still be needed to protect children from risks from exposures to spray drift-deposited residue. Some occupational handler scenarios continue to be of concern even with additional PPE and/or engineering controls. The minimum time needed to reach acceptable levels of acephate in previously treated areas, although shorter compared to the duration that included the 10x FQPA SF, is still longer than what is currently required in labels.

The Agency will continue to evaluate the available data and pursue approaches to better understand the risk posed to human health by acephate, and the organophosphate pesticides in general. The public is encouraged to submit comments on the risk assessments for acephate during the public comment period. The Agency will consider all comments and information it receives as it moves forward with the registration review of acephate.

[2] Without the 10x FQPA SF, the toxicological endpoints that included it will change by a factor of 10. For example, the population adjusted dose (PAD) for all populations, except adults 50-99 years old, will increase from 0.0003 mg/kg/day to 0.003 mg/kg/day. The level of concern (LOC) for incidental oral and dermal exposures will decrease from 1,000 to 100 while the LOC for inhalation exposure will decrease from 300 to 30. See Table 4.6.5 in the human health DRA for the toxicological endpoints used.

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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

Date: **March 28, 2018**

Subject: Acephate. Revised Draft Human Health Risk Assessment (DRA) in support of Registration Review.

PC Code: 103301
Decision No.: 539010
Petition No.: N/A
Risk Assessment Type: Single Chemical Aggregate
TXR No.: N/A
MRID No.: N/A

DP Barcode: D446177
Registration No.: Multiple Registrations
Regulatory Action: Registration Review
Case No.: 0042
CAS No.: 30560-19-1
40 CFR: 180.108

From: Danette Drew, Chemist/Risk Assessor
Kelly M. Lowe, Environmental Scientist
Risk Assessment Branch V/VII
Health Effects Division (7509P)

Through: Michael Metzger, Branch Chief
Risk Assessment Branch V/VII
Health Effects Division (7509P)

To: Julie Javier, Chemical Review Manager
Risk Management and Implementation Branch 1
Pesticide Re-Evaluation Division (PRD; 7508P)

Table of Contents

1.0 Executive Summary

Acephate is an organophosphate (OP) insecticide registered for use on a variety of agricultural crops; for use in outdoor non-agricultural settings (building foundations/perimeters, non-residential lawns/ornamentals, golf courses, non-crop areas, sod farms, and as ant mound treatment on residential lawns/ornamentals); for indoor treatment of commercial/industrial buildings; and for use in greenhouses.

Exposure Profile

The residues of concern for human health risk assessment are acephate and its degradate methamidophos. Humans may be exposed to acephate and/or methamidophos in food and drinking water since acephate may be applied directly to growing crops and in outdoor settings which may result in residues in foods or residues reaching sources of drinking water. 100% conversion of acephate to its more toxic degradate, methamidophos, is assumed in drinking water. Residential post-application exposures may occur as a result of the outdoor uses in residential settings. Non–occupational exposures may also occur as a result of spray drift from agricultural applications. Residential handler exposure is not expected as the labeled uses do not appear to be intended for homeowner application. Because of the degradation of acephate once applied, residential/non-occupational post-application exposures for adults and children are assumed to be to residues of both acephate and methamidophos. In an occupational setting, workers may be exposed while handling the pesticide prior to application, during application, or when entering previously treated areas. Occupational handlers are anticipated to be exposed to acephate only (i.e., not to the degradate methamidophos), whereas post-application workers may be exposed to residues of both acephate and methamidophos. This risk assessment considers all of the aforementioned exposure pathways.

Hazard Assessment

Acephate is a member of the OP class of pesticides. Like other OPs, the initiating event in the adverse outcome pathway (AOP)/ mode of action (MOA) for acephate involves inhibition of the enzyme acetylcholinesterase (AChE) via phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system.

Acephate is in the oxon form and does not require bioactivation prior to inhibiting AChE; however, the acephate degradate, methamidophos, is a more potent inhibitor of AChE than acephate. Because of this environmental degradate, risk assessment must consider the hazard represented by both acephate and methamidophos. For acephate and methamidophos, acetylcholinesterase inhibition (AChEI) is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. Clinical signs of neurotoxicity can be found throughout the database of toxicity studies at doses much higher than those causing inhibition of AChE.

OPs also exhibit a phenomenon known as steady state AChEI. After repeated dosing at the same level, the degree of inhibition comes into equilibrium with the production of new, uninhibited

enzyme. Therefore, steady state exposure assessments were conducted instead of the traditional chronic scenarios. The toxicology database for acephate is complete for risk assessment.

Across most studies, durations, lifestages, and routes, AChE tends to be more sensitive to acephate inhibition in the brain than red blood cell (RBC). In the gestational comparative cholinesterase assay (CCA) study, the fetus was not more sensitive than the dam. The pregnant female in the gestational CCA was not more sensitive than the non-pregnant female in the subchronic oral toxicity study. Post-natal day (PND) 11 pups are not more sensitive than adults, following acute or repeat exposure.

Acephate is considered to be a possible human carcinogen based on an increased incidence of hepatocellular carcinomas in mice. Quantification of risk using a non-linear approach adequately accounts for all chronic toxicity, including carcinogenicity that could result from exposure to acephate.

Acephate has low acute oral toxicity (Toxicity Category III), and low acute dermal and inhalation toxicity (Toxicity Category IV). It is non-irritating to skin and eyes (Toxicity Category IV) and it is not a skin sensitizer.

Endpoints and Uncertainty Factors for Risk Assessment

The endpoint selected for all exposure scenarios is brain AChEI. A point of departure (POD) was derived from the results of a CCA rat study for the acute dietary, steady state dietary, and incidental oral exposure scenarios. For dermal steady state exposure, a POD was selected based on results from a rat dermal toxicity study. For inhalation steady state exposure, a POD was derived from a 4-week inhalation study in rats.

The 10X Food Quality Protection Act (FQPA) safety factor (SF) has been retained for infants, children, youth, and women of child-bearing age for all exposure scenarios due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see section 4.4). For oral and dermal exposure scenarios, interspecies (10X) and intraspecies (10X) uncertainty factors were applied for a total uncertainty factor of 1000X, except dietary exposures for the adult population subgroup 50-99 years old where the FQPA SF does not apply (total uncertainty factor = 100X for adults 50-99). For the inhalation exposure route, the interspecies extrapolation factor is 3X, with the other factors being the same as above, resulting in a total uncertainty factor of 300X.

Toxicity Adjustment Factors

Both acephate and its metabolite methamidophos inhibit AChE; therefore, this assessment incorporates both residues of concern. Since the acephate point of departure was used in this assessment and methamidophos is a more potent cholinesterase inhibitor, expected methamidophos residues for dietary (food and water) and for post-application (dermal and oral) scenarios were corrected using an acute and steady state toxicity adjustment factor (TAF) derived from benchmark dose modeling.

Residue Chemistry and Tolerance Enforcement

The residue chemistry database for acephate is complete. The residues of concern for tolerance enforcement are acephate (livestock commodities) and acephate and/or methamidophos (plant commodities). U.S. tolerances are established for residues of acephate and/or methamidophos (depending on the commodity) on several plant and livestock commodities to support the registered agricultural uses. There is also a tolerance to support the use of acephate in food handling establishments (FHE) including where food is served.

Dietary (Food and Water) Exposure and Risk

The highly refined probabilistic acute and steady state dietary exposure assessments for acephate were performed using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 3.18 and incorporated U.S. Department of Agriculture's Pesticide Data Program (USDA PDP) food monitoring data, percent crop treated (PCT) estimates, and default or empirical processing and cooking factors. Model-based time-series distribution files for estimated drinking water concentrations (EDWCs) for two acephate use scenarios were included. The dietary (drinking water) assessment was performed on two representative agricultural crop scenarios: a celery scenario which represents all agricultural crops with the low-end maximum application rate and a cotton scenario which represents all agricultural crops with the high-end maximum application rate. The drinking water concentration estimates assume 100% conversion of acephate to the more toxic degradate methamidophos.

The acute dietary (food only) exposure estimates are of concern (exceed 100% the aPAD) for the U.S. population and all population subgroups at the 99.9th percentile, except for the subgroup adults 50-99 years old (at 59% of the aPAD). The risk estimate for the U.S. population is 510% of the aPAD. The risk estimate for children 3-5 years old, the most highly exposed population subgroup, is 810% of the aPAD.

When the cotton drinking water scenario (which represents crops with *high-end* label rate) is used in the acute dietary (water only) assessment, risk estimates are of concern (>100% of the aPAD) for all population subgroups (except adults ages 50 and above) at the 99.9th percentile of exposure (highest exposed subgroup is infants at 2400% of the aPAD). At the 95th percentile of exposure, acute risk estimates for drinking water using the cotton scenario are not of concern for any population subgroup.

When the celery drinking water scenario (which represents crops with *low-end* label rate) is used in the acute dietary (water only) assessment, risk estimates are of concern (>100% of the aPAD) for all population subgroups (except adults ages 50 and above) at the 99.9th percentile of exposure (highest exposed subgroup is infants at 1000% of the aPAD). At the 95th percentile of exposure, acute risk estimates using the celery scenario are not of concern for any population subgroup.

The steady state dietary (food only without Food Handling Establishment (FHE) use) exposure estimates are of concern (exceed 100% the ssPAD) for the U.S. population and all population

subgroups at the 99.9th percentile, except for the subgroup adults 50-99 years old (at 43% of the ssPAD). The risk estimate for the U.S. population is 400% of the ssPAD. The risk estimate for children 3-5 years old, the most highly exposed population subgroup, is 580% of the ssPAD.

The steady state dietary assessment for food only, with FHE uses included, resulted in risk estimates similar to the steady state assessment for food only without FHE uses. The exposures resulting from FHE uses are not significant contributors to the overall food exposure.

When the cotton drinking water scenario (which represents crops with *high-end* label rate) is used in the steady state dietary (water only) assessment, risk estimates are of concern (>100% of the ssPAD) for all population subgroups (except adults ages 50 and above) at the 99.9th percentile of exposure (highest exposed subgroup is infants at 1800% of the ssPAD). At the 95th percentile of exposure, steady state acute risk estimates for drinking water using the cotton scenario are not of concern for any population subgroup except for infants.

When the celery drinking water scenario (which represents crops with *low-end* label rate) is used in the steady state dietary (water only) assessment, risk estimates are of concern (>100% of the ssPAD) for all population subgroups (except adults ages 50 and above) at the 99.9th percentile of exposure (highest exposed subgroup is infants at 700% of the ssPAD). However, at the 95th percentile of exposure, steady state risk estimates using the celery scenario are not of concern for any population subgroup.

Since dietary exposures from food alone were of concern, drinking water exposures were not combined with exposures from food. Combining those exposures would result in even greater risk estimates of concern.

Residential Exposure and Risk

All registered acephate product labels reviewed as part of registration review with residential use sites (e.g., lawns, indoor environments, garden and trees) require that handlers wear specific clothing (e.g., long sleeve shirt/long pants) and/or use personal protective equipment (PPE). Therefore, the Health Effects Division (HED) has made the assumption that these products are not for homeowner use, and has not conducted a quantitative residential handler assessment.

Residential post-application exposure and risk estimates were calculated for the registered uses of acephate on ornamentals, golf courses, and commercial/industrial buildings such as schools, hotels, and hospitals. Residential turf applications are limited to ant mound treatments which are considered perimeter/spot uses. While these types of uses can result in residues on turf, residential exposure is expected to be low, and therefore, a quantitative post-application assessment was not conducted for those uses. The assessments consider both acephate and methamidophos residues. Dermal post-application risk estimates were of concern for all scenarios associated with the use on ornamentals (dermal MOEs of 23 for adults and 40 for children 6 to 11 years; LOC = 1000), and for some scenarios associated with the use in indoor environments (dermal MOEs range from 34 to 1,500 for adults and 40 to 910 for children 1 to <2 years; LOC = 1000). Risks of concern were also identified for incidental oral exposure for

children 1 to <2 years from the indoor uses (incidental oral MOEs range from 0.49 to 22; LOC = 1000). Dermal post-application risk estimates for adults and children (6 to 11 years and 11 to 16 years) exposed to treated turf from golfing are not of concern (dermal MOEs range from 1,500 to 1,700).

Aggregate Exposure and Risk

The acute aggregate risk assessment combines exposures to acephate and methamidophos from food and drinking water. There are acute risk estimates of concern for food only and for water only; therefore, a quantitative acute aggregate risk assessment was not conducted. The steady state aggregate assessment includes the steady state dietary (food and water) and residential exposures. However, because there are risks of concern associated with both dietary and residential exposure, a quantitative steady state aggregate risk assessment was not conducted. Combining those exposures would result in even greater risk estimates of concern.

Non-Occupational Spray Drift Exposure and Risk

A quantitative non-occupational spray drift assessment was conducted for the registered uses of acephate. The assessment considers both acephate residues and residues of methamidophos. Adult dermal and children's (1 to < 2 years old) dermal and incidental oral risk estimates from indirect exposure related to spray drift are of concern (MOEs <1000) at a range of distances from the edge of the field depending on the spray type/nozzle configuration (e.g., 0 to >300 feet). Results indicate that the major spray-drift risk concerns are from aerial applications.

Occupational Exposure and Risk

Occupational handler dermal and inhalation exposure and risk estimates were calculated for the registered uses of acephate. An aggregate risk index (ARI) was used since the LOC values for dermal exposure (1000) and inhalation exposure (300) are different. The target ARI is 1; therefore, ARIs of less than 1 are risk estimates of concern. The occupational handler exposure and risk estimates are of concern to HED (i.e., ARIs < 1) for most scenarios assuming the use of label-required PPE (gloves and, in some cases, use of a PF5 respirator). In all scenarios, inhalation exposure is driving the combined risk estimates, and in some cases, the addition of a respirator (either PF5 or PF10) and/or the use of engineering controls results in an ARI greater than 1. However, there are still some scenarios that do not reach an ARI of greater than 1 even with the highest level of PPE and/or engineering controls.

Occupational post-application dermal exposure and risk estimates were assessed for all registered uses of acephate using submitted chemical-specific dislodgeable foliar residue (DFR) and turf transferable residue (TTR) data. The post-application assessment considers both acephate and methamidophos residues. Based on the current exposure assessment, post-application risk estimates remain of concern in some situations for more than 30 days after application (i.e., MOEs < 1000). Current product-label restricted entry intervals (REIs) are 24 hours.

Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for acephate 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 acephate.

Human Studies Review

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from PHED 1.1, the ORETF, the ARTF, the AHETF database, the Residential SOPs and policies on Seed Treatment, are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[1].

2.0 HED Recommendations

2.1 Data Deficiencies

None

2.2 Tolerance Considerations

Residue chemistry memo: D. Drew, 3/9/2018, D446265.

2.2.1 Enforcement Analytical Method

Adequate enforcement analytical methods are available for analysis of residues of acephate and methamidophos in plants and livestock commodities. For tolerance enforcement, the Pesticide Analytical Manual (PAM) Vol. II lists two Gas Liquid Chromatography (GLC) methods (designated as Methods I and II) with thermionic detection for the determination of acephate (LOD = 0.01 ppm) and methamidophos (LOD = 0.04 ppm) residues in/on plant and livestock commodities. PAM Volume II also lists a Thin Layer Chromatography (TLC) method (designated as Method A) as a confirmatory method. Adequate radiovalidation data for the enforcement method using samples from the plant and livestock metabolism studies have been submitted and evaluated.

The 1/94 Food and Drug Administration (FDA) PESTDATA database (PAM Volume I, Appendix I) indicates that acephate is recovered (>80%) using Multiresidue Methods Section 302 (Luke Method; Protocol D); recovery of methamidophos using the same method is variable.

2.2.2 Recommended Tolerances

[1] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

The 40 CFR 180.108 contains separate sections with tolerances for parent acephate, *O, S-dimethyl acetyl phosphoramidothioate*, and it metabolite methamidophos, *O, S-dimethyl phosphoramidothioate*. Separate sections were established to eliminate redundancy as methamidophos had pesticidal uses as well (F. Fort, D259662, 10/05/1999). Although U.S. registrations of the insecticide methamidophos were cancelled and the tolerances to support uses of methamidophos (40 CFR 180.315) are expired, it is recommended that the tolerances of acephate and methamidophos included in the 40 CFR 180.108 remain separate to maintain harmonization with Canada and Codex (refer to Section 2.2.3). Separate tolerances for acephate and methamidophos are recommended for cotton gin by products and cotton undelinted seed. Revocation of the regional tolerance for acephate in/on macadamia nuts is recommended because this use is no longer registered. The tolerances for residues of acephate on foods as a result of the use in food handling establishments may be moved from 40 CFR 180.108(a)(2) to the table in 180.108(a)(1); the specific use instructions for food handling establishments should not be included in the tolerance definition and should be removed.

The dry bean commodity definition includes cowpea, which has forage and hay commodities that are considered significant livestock feedstuffs. Crop field trials depicting residues of acephate in/on cowpea forage and hay have not been submitted. In the absence of these data, HED recommends changing the commodity definition of *bean, dry seed* to *bean, dry seed, except cowpea*. If the registrant wishes to support the use on cowpea, residue data depicting residues of acephate in/on cowpea forage and hay should be provided.

Table 2.2.2. Tolerance Summary for Acephate.

Commodity	Established Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments (*correct commodity definition*)
Acephate			
Cotton, gin byproducts		120	
Bean, dry, seed	3.0	3.0	*Bean, dry seed, except cowpea*[2]
Nut, macadamia[1]	0.05	Remove	
Food commodities (other than those covered by a higher tolerance as a result of use on growing crops) in food handling establishments	0.02	0.02	*Remove from 180.108(a)(2) and add to the table in 180.108(a)(1); Remove specific use directions from tolerance definition.*
Methamidophos			
Cotton, gin byproducts		20	
Cotton, undelinted seed		0.20	
Bean, dry, seed	1	1	*Bean, dry seed, except cowpea*[2]

[1] Revocation of the regional tolerance for acephate in/on macadamia nuts is recommended because this use is no longer registered.
[2] If the registrant wishes to support the use on cowpea, residue data depicting residues of acephate in/on cowpea forage and hay should be provided.

2.2.3 International Harmonization

The U.S., Canada, and Codex are harmonized with respect to the residue definition which includes separate sections for acephate and methamidophos.

For acephate, the U.S. tolerance levels are harmonized with the Canadian maximum residue levels (MRLs) for cauliflower and cranberry, and with the Codex MRLs for cranberry and poultry fat.

For methamidophos, the U.S. tolerance levels are harmonized with the Canadian MRLs for cauliflower, head lettuce, and pepper. No U.S. tolerances are currently established for residues of methamidophos in/on cotton seed and livestock commodities; however, Codex lists MRLs of 0.2 ppm for cotton seed; 0.02 ppm for milk; and 0.01 ppm for eggs, mammalian edible offal, poultry edible offal, mammalian (other than marine) meat, and poultry meat. The highest residue of methamidophos in/on cotton seed is 0.05 ppm (F. Fort, D259659, 8/18/1999); therefore, a tolerance of 0.2 ppm for cotton undelinted seed, to harmonize with the Canadian MRL, is supported. The highest anticipated residue estimated for livestock commodities is 0.0068 ppm in cattle kidney which includes residues of acephate and methamidophos. Currently, tolerances for methamidophos on livestock commodities are not established and not necessary as residues of methamidophos are unlikely and no detects have been reported in the PDP data for livestock commodities. As such, establishment of tolerances of methamidophos on livestock commodities is not necessary. The remaining commodities have higher U.S. tolerances than the Canadian and Codex MRLs which precludes harmonization.

2.3 Label Recommendations

2.3.1 Recommendations from Residue Reviews

The following label revisions are recommended based on the residue chemistry reviews:

Remove the livestock feeding and grazing restrictions associated with uses on beans and cotton from the labels. Feeding and grazing restrictions for these crops are not considered practical or enforceable.

Exclude the use of acephate on cowpea from the registered labels. There are no data available depicting expected residues of acephate in/on the livestock feed items cowpea forage and hay.

A plant back interval (PBI) of 30 days for all crops without established tolerances (rotational crops) should be included in the labels registered for crop uses.

2.3.2 Recommendations from Occupational Assessment

There are no label recommendations based on the occupational assessment; however, HED notes that a summary of the risk estimates has been provided, and shows that there are risk estimates of concern for registered uses of acephate based on the use site and label-required personal protective equipment and REIs.

2.3.3 Recommendations from Residential Assessment

HED has not conducted a residential handler assessment for acephate. However, HED notes that there are several registered labels that appear to be marketed for consumer use (one label in particular is named “Acephate 75SP Homeowner”) and include statements regarding the use of

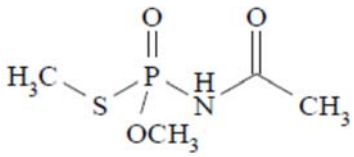
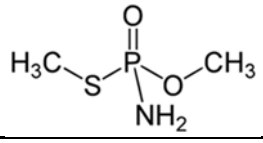
personal protective equipment (PPE) when handling the product (e.g., EPA Reg. # 66330-358, 239-2461, 239-2632, 53883-203 and 71376-1). If these products are meant to be marketed towards consumers/homeowners, HED recommends that label requirements for clothing and/or PPE be reevaluated or a separate consumer-specific label be developed. If it is determined that these products are meant for homeowner use, a residential handler assessment will be required.

3.0 Introduction

3.1 Chemical Identity

Acephate is an OP insecticide registered for use on a variety of agricultural crops, in outdoor settings [building foundations/perimeters, non-residential lawns/ornamentals, ant mound treatment on residential lawns/ornamentals, golf courses, non-crop areas, and sod farms], for indoor treatment of commercial/industrial buildings, and in greenhouses.

The nomenclature of acephate and methamidophos are summarized in Table 3.1.

Table 3.1. Acephate and Methamidophos Nomenclature.	
Compound	Chemical Structure 
Common name	Acephate
IUPAC name	(RS)-N-[methoxy(methylthio)phosphinoyl]acetamide
CAS name	O, S-Dimethyl acetylphosphoramidothioate
CAS #	30560-19-1
Compound	Chemical Structure 
Common name	Methamidophos
IUPAC name	(RS)-(O,S-dimethyl phosphoramidothioate)
CAS name	O,S-dimethyl phosphoramidothioate
CAS #	10265-92-6

3.2 Physical/Chemical Characteristics

Table 3.2.1 Physicochemical Properties of Acephate		
Parameter	**Value**	**Reference**
Acephate		
Molecular weight (g/mole)	183.16	
Melting point/range (°C)	86.9-91.0 °C	MRID 40390601
pKa (20 °C)	8.35	MRID 40390601
Water solubility (mg/L at 25°C)	80.1-83.5 g/100 ml	MRID 40390601

Table 3.2.1 Physicochemical Properties of Acephate		
Parameter	**Value**	**Reference**
Solvent solubility (mg/L at 25°C)	Ethanol:methanol 95:5 v:v (28.0-30.3 g/100 mL), ethyl acetate (4.6-5.1 g/100 mL), toluene (1.0 g/100 mL), and hexane (0.0084-0.0089 g/100 mL)	MRID 40390601
Vapor pressure at 24°C (Pa)	1.7 x 10^{-6} mm Hg	MRID 40390601
Octanol/water partition coefficient Log (K_{OW})	-0.9	MRID 40390601

Table 3.2.2 Physicochemical Properties of Methamidophos.		
Parameter	**Value**	**Reference**
Methamidophos		
Molecular weight (g/mole)	141.2	
Melting point/range (°C)	46.1	Residue Chemistry Chapter of the RED, 10/1/1999, D259664
pKa (20 °C)	Not available	
Water solubility (mg/L at 25°C)	200 g/L	MRID 43661003
Solvent solubility (mg/L at 25°C)	n-octonal (50-100 g/L); toluene (2-5 g/L); n-hexane (<1 gL); acetone, dimethylformamide, dichloromethane, and 2propanol (>200 g/L)	
Vapor pressure at 24°C (Pa)	1.7 x 10^{-6} mm Hg	MRID 43661003
Octanol/water partition coefficient Log (K_{OW})	Not available	

3.3 Pesticide Use Pattern

There are numerous registered end-use products containing acephate as the active ingredient (ai). Registered use sites include agricultural crops, Christmas tree plantations, seed treatment for cotton and peanuts, indoor treatment of commercial/industrial buildings, outdoor building foundations/perimeters, golf courses, non-crop areas, ornamental lawns/turf, ornamental plants (including those grown for cut flower production), residential lawns/ornamentals (ant mound treatment only), and sod farms. The registered formulations include mostly dry flowable or water soluble packet formulations, but there are also liquid and granular products, as well as total release foggers (greenhouse applications), and aerosol products (indoor crack and crevice applications). Most registered products are intended for foliar applications, applied via aerial, groundboom, or airblast equipment. Chemigation is only allowed for applications to cranberries. There are some tree injection, soil-directed, seed treatment, and ant mound treatment (via handheld equipment) applications. Indoor applications are limited to spot and crack and crevice applications, and labels specifically state "not for indoor residential use." Turf applications on residential sites are limited to ant mound treatments only. Use of low pressure handwand equipment is prohibited except for use on ornamental trees, shrubs and floral plants grown for non-agricultural or non-commercial use. See Appendix B for the use summary table.

3.4 Anticipated Exposure Pathways

Humans may be exposed to acephate, and its degradate methamidophos, in food and drinking water, since acephate may be applied directly to growing crops and in outdoor settings which may result in residues in foods or residues reaching sources of drinking water. Residential non-occupational post-application exposures may occur as a result of the outdoor uses in residential settings. Non–occupational exposures may also occur as a result of spray drift from agricultural applications. Residential handler exposure is not expected based on the registered labels. Due to the degradation of acephate once applied, residential non-occupational post-application exposures for adults and children were assumed to be to both residues of acephate and methamidophos.

In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. Occupational handlers are anticipated to be exposed to acephate only (i.e., not to the degradate methamidophos). Occupational post-application exposures may occur when workers enter previously treated areas. Post-application workers may be exposed to residues of both acephate and methamidophos. This risk assessment considers all of the aforementioned exposure pathways based on the existing acephate uses.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.epa.gov/laws-regulations/summary-executive-order-12898-federal-actions-address-environmental-justice). 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 USDA under the National Health and Nutrition 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. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

Acephate is a member of the OP class of pesticides. Like other OPs, the initiating event in the AOP/MOA, for acephate involves inhibition of the enzyme acetylcholinesterase via phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral

nervous system (see Figure 1). Acephate is in the oxon form and does not require bioactivation prior to inhibiting AChE; however, the acephate degradate methamidophos is a more potent inhibitor of AChE than acephate. Because of this environmental degradate, risk assessment must consider the hazard represented by both acephate and methamidophos. For acephate and methamidophos, AChEI is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. AChEI 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.

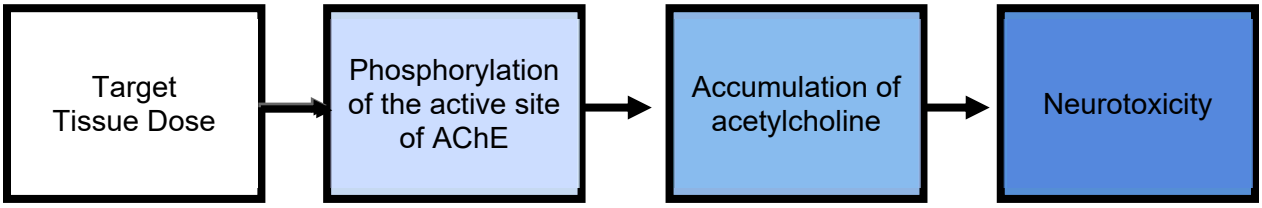


Figure 1. Adverse outcome pathway for OPs

4.1 Toxicology Studies Available for Analysis

The toxicology database for acephate is extensive and adequate for risk assessment. Studies are available for all routes of exposure. Toxicology data requirements and confirmation that acephate meets these requirements are presented in Appendix A.1. There are no data gaps for acephate. The toxicology database includes the following toxicity studies:

- Subchronic oral toxicity studies in rats, mice, and dogs
- Chronic oral toxicity studies in rats, mice, and dogs
- Carcinogenicity studies in rats and mice
- Mutagenicity study battery
- Developmental studies in rats and rabbits
- Reproduction studies in rats
- Acute neurotoxicity studies in rats
- Acute delayed neurotoxicity studies in hens
- Subchronic neurotoxicity studies in hens and rats
- Developmental neurotoxicity studies in rats
- Comparative cholinesterase assay (CCA, acute and multiple doses; gestational)
- Dermal toxicity studies in rats and rabbits
- Dermal absorption study in rats
- Inhalation toxicity studies in rats
- Metabolism study in rats
- Immunotoxicity study in rats
- Studies with cholinesterase measurements submitted under the endocrine disruptor screening program (Hershberger, pubertal and uterotrophic assays)

High quality dose response data for all routes of exposure are also available for the degradate methamidophos, which is the index chemical (used to establish relative potency factors) for the OP cumulative risk assessment.

- Subchronic oral toxicity studies in rats and dogs
- Chronic oral toxicity studies in rats, mice, and dogs
- Carcinogenicity studies in rats and mice
- Mutagenicity study battery
- Developmental studies in rats and rabbits
- Reproduction studies in rats
- Acute neurotoxicity studies in rats
- Acute delayed neurotoxicity studies in hens
- Subchronic neurotoxicity studies in hens and rats
- Developmental neurotoxicity studies in rats
- Comparative cholinesterase assay (CCA, acute and multiple doses; gestational)
- Dermal toxicity studies in rabbits and rats
- Inhalation toxicity studies in rats
- Metabolism study in rats

4.2 Absorption, Distribution, Metabolism, and Excretion (ADME)

Generally, absorption and distribution of OPs are rapid, with extensive metabolism and no accumulation in the tissues. This is the case with acephate. Metabolism studies in rats indicate that acephate is rapidly and completely absorbed from the stomach and quickly excreted in urine. There is no evidence of bioaccumulation and no difference in metabolism between the sexes.

An acephate metabolism study was performed in rats. Total recoveries of radioactivity ranged from 97-106% of the administered dose (AD) following an oral dose of 25 or 100 mg/kg, with no differences in the excretory profile observed between sexes and dose levels. Radioactive residues from both sexes at either dose were isolated in the urine (83-89% AD), feces (1.8-3.0% AD), and expired carbon dioxide (4.6-9.7% AD). At both dose levels, cage wash, tissues, GI tract and carcass each account for <3.3% AD.

In both sexes, the time point of maximum plasma concentration (T_{max}) was observed 0.5 hours after dosing at 25 or 100 mg/kg, and maximum plasma concentrations (C_{max}) were 21.9-24.9 µg/g at 25 mg/kg dose and 84-98 µg/g at 100 mg/kg dose (concentrations being proportional to dose). Both doses and sexes had elimination rate constant values of 0.012-0.014 h^{-1}. Approximately 93% of the administered doses were eliminated within 24 hours, and terminal phase half-lives were 49-58 hours.

The major radioactive component in urine from rats was unmetabolized acephate (77-80% AD). The only significant metabolism of acephate is the formation of $^{14}CO_2$ (9-10% of dose). Small quantities of methamidophos (4% of dose) and 3 other compounds (representing <4% of dose) were found in the urine. These components were des-acetamidoacephate (DMPT), O-desmethyl acephate (SMPT), and O-desmethyl methamidophos (SMPAA). However, metabolic origins of methamidophos and these 3 metabolites are uncertain, because they were present as contaminants in the dosing solutions at about the same percentage.

4.2.1 Dermal Absorption

In a male rat *in vivo* dermal absorption study, the dermal absorption factor (DAF) was found to be 3.6% after 8 hours exposure at 5 mg/cm^2. This study indicated that the dermis was a very effective barrier against acephate with 0.1% or less of the administered dose found in the blood at any time (2, 8, or 24 hours) in all animals tested at both doses. A dermal toxicity study was used for dermal exposure assessments; therefore, the DAF was not used for quantitative risk assessment of dermal exposures.

4.3 Toxicological Effects

Acephate has quality dose response data across multiple lifestages, durations, and routes of exposure for both RBC and brain AChE inhibition. Many of these studies have been evaluated using benchmark dose (BMD) modeling techniques. Acephate inhibits AChE activity in various species including hens, rats, mice, rabbits, and dogs. Based on the available data, acephate causes dose-related inhibition in red blood cell (RBC) and brain AChE activity, with AChEI being greatest in the brain. Inhibition of RBC and brain AChE activity always precedes clinical signs of AChEI and systemic toxicity.

Clinical signs of neurotoxicity can be found throughout the database for acephate. The clinical signs that acephate produces are associated with AChEI, such as tremors, salivation, chromodacryorrhea, and dyspnea.

Data from the hen studies indicate that acephate produces adverse signs characteristic of AChEI, but no delayed neurotoxicity or histological changes in brain, spinal cord, or peripheral nerves. In the rangefinder, acute, and subchronic neurotoxicity studies, signs of neurotoxicity included findings such as lacrimation, altered gait, constricted pupils, whole body tremors, decreased rotarod performance, and/or increased rearing. These signs were observed at doses 6 to 147-fold higher than those which caused 10% AChEI in brain. In a developmental neurotoxicity study in rats, no treatment-related effects were observed in dams or pups, except AChEI. AChE activity assessments were not conducted in the dams, but dose-related inhibition of brain AChE activity was observed in male and female pups on Day 21 at ≥0.5 mg/kg/day.

At the same doses where clinical signs of neurotoxicity were seen, systemic toxicity was often observed (at least 6-fold higher than that which caused 10% AChEI in brain). The most consistent systemic toxicological findings following chronic acephate exposure were decreased body weights and/or body weight gain in rodents and, in dogs, decreases in hematological parameters, increased thromboplastin time, increased absolute liver weight, and histological changes in the liver.

There were no sensitive sub-populations identified in the developmental, reproduction, or CCA studies. The developmental toxicity studies in rats and rabbits, as well as the reproductive toxicity study in rats, did not demonstrate any increased sensitivity of the fetus or offspring of rats or rabbits after pre-natal and/or postnatal exposure to acephate. The most important finding was an increase in abortions in the rabbit; however, this finding was noted at a dose 37-fold higher than the regulatory POD (based on brain AChEI) used for risk assessment. Therefore, the

POD is protective for all effects observed in these studies. There was no conclusive evidence of sex-sensitivity within the toxicological database.

Acephate is a possible human carcinogen based on an increased incidence of hepatocellular carcinomas in mice; however, it was concluded that quantification of cancer risk using a non-linear approach adequately accounts for all chronic toxicity, including carcinogenicity that could result from exposure to acephate.

Acephate has low acute oral toxicity (Category III), and low acute dermal and inhalation toxicity (Category IV). It is non-irritating to skin and eyes (Category IV) and it is not a skin sensitizer.

Methamidophos, a degradate of acephate, also has high-quality dose-response data across multiple lifestages, durations, and routes of exposure for AChE inhibition and shares a common mode of action with acephate. Methamidophos is a more potent inhibitor of AChE, and the TAF is reported in Section 4.6.2. Methamidophos is classified as Not Likely to be Carcinogenic to Humans.

Many of these studies have been evaluated using BMD modeling techniques. More detail concerning the characterization and quantification of the toxic effects of acephate is provided in Appendix A.2. OPP's ChE policy and use of BMD modeling is also described. A table of the BMD modeling results is provided in Appendix A.2 (Tables A.2.1 through A.2.5). A toxicity profile table, which had been provided in a previous risk assessment (Fort, 1999, D259663) and a supplementary table including more recent studies, can be found in Appendix A.2 (Tables A.2.6.1 and A.2.6.2). It is noted that the toxicity profile table has not been updated to include BMD results since these can be found in the previous tables (A.2.1 through A.2.5).

4.3.1 Critical Durations of Exposure

One of the key elements in risk assessment is the appropriate integration of temporality between the exposure and hazard assessments. One advantage of an AOP understanding is that human health risk assessments can be refined, focused on the most relevant durations of exposure. Table 4.3.1.1 provides a summary of the selected results from experimental toxicology studies in which AChEI of adult rat brain was selected to highlight the effect of duration. Data from the adult rat brain AChEI are presented, because AChE in the brain was more sensitive to the effects of acephate than in the RBC. Only the BMD_{10} results are shown, because the central estimate is used for purposes of comparison according to the BMD guidance.

Table 4.3.1.1. Comparison of Acephate BMD_{10} Results (mg/kg/day) for Brain AChEI over Time in Adult Rats.			
Days of dosing	**Males**	**Females**	**MRID#, Test**
1	0.5 [a]	0.5 [a]	46151801, Acute CCA
16	---	0.436 (dam)	46151805, Gestational CCA
91	0.295	0.354	44203304, 13-Week SNT
91	0.470	0.433	40504819, 13-Week Oral Tox
819	0.332	0.494	00084017, 104-Week Chronic Tox/Carc

[a] The BMD_{10} for adults were not accurately identified in the acute CCA based on empirical evidence; however, 13% inhibition of brain AChE was observed at the lowest dose tested (0.5 mg/kg/day) in both sexes.
--- = Not measured in the test
CCA = Comparative cholinesterase assay
SNT = Subchronic neurotoxicity
Tox = Toxicity; Carc = Carcinogenicity

In adults, OPs exhibit a phenomenon known as steady-state AChEI. After repeated dosing at the same dose level, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. At this point, the amount of AChEI at a given dose remains relatively consistent across duration. In general, OPs reach steady-state within 2-3 weeks, but this can vary among OPs. For acephate, the results in Table 4.3.1.1 indicate that steady-state occurs almost immediately; AChEI remained consistent across all durations from a single dose exposure up to 819 daily doses. For example, the dose giving 10% inhibition acutely (approximately 0.5 mg/kg/day) is comparable to the BMD_{10} for females through 819 days (0.494 mg/kg/day). Although there was some variation, this can be expected from using different studies, due to differences in dose selection leading to differences in the quality of modeling. Considering this, there is both consistency across durations and across multiple studies. Given the results in Table 4.3.1.1, for acephate, single day and steady state durations are appropriate for human health risk assessment. As such, the endpoint selection focuses on acute single day effects and steady-state effects (21 days and longer).

Although the durations of the toxicity and exposure assessments may differ among the OPs, an exact match is not necessary and would suggest a level of precision that the toxicity data do not support. Given this, the 21-day and longer exposure assessment is scientifically supportable and also provides consistency with the OP cumulative risk assessment (OP Cumulative Risk Assessment (CRA); 2002, 2006) and across the single chemical risk assessment for the OPs. As such, the single chemical OP assessment will evaluate steady-state instead of the typical chronic duration dietary assessment. The steady-state point of departure is protective of any longer exposure duration, including chronic exposure, since cholinesterase inhibition does not increase after reaching maximum inhibition or steady-state.

4.4 Literature Review on Neurodevelopment Effects

For the OPs, historically the Agency has used inhibition of AChE as the POD for human health risk assessment; at present time, this policy continues. This science policy is based on decades of work which shows that AChE inhibition is the initial event in the pathway to acute cholinergic neurotoxicity. The use of AChE inhibition data for deriving PODs was supported by the FIFRA SAP (2008, 2012) for chlorpyrifos as the most robust source of dose-response data for

extrapolating risk and is the source of data for PODs for acephate. A detailed review of the epidemiological studies used in this review can be found either in the 2014 chlorpyrifos revised draft human health risk assessment (D424485, D. Drew et al., 12/29/2014) or in the 2015 literature review for other organophosphates (OPP/USEPA; D331251; 9/15/15).

Newer lines of research on OPs in the areas of potential AOPs, *in vivo* animal studies, and notably epidemiological studies in mothers and children, have raised some uncertainty about the agency's risk assessment approach with regard to the potential for neurodevelopmental effects in fetuses and children. Many of these studies have been the subject of review by the agency over the last several years as part of efforts to develop a risk assessment for chlorpyrifos (D424485, D. Drew et al., 12/29/2014). Initially, the agency focused on studies from three US cohorts: 1) The Mothers and Newborn Study of North Manhattan and South Bronx performed by the Columbia Children's Center for Environmental Health (CCCEH) at Columbia University; 2) the Mt. Sinai Inner-City Toxicants, Child Growth and Development Study or the "Mt. Sinai Child Growth and Development Study;" and 3) the Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by researchers at University of California Berkeley. The agency has evaluated these studies and sought external peer review (FIFRA SAP reviews in 2008 and 2012; federal panel, 2013[2]) and concludes they are of high quality. In the three US epidemiology cohort studies, mother-infant pairs were recruited for the purpose of studying the potential health effects of environmental exposures during pregnancy on subsequent child development. Each of these cohorts evaluated the association between prenatal chlorpyrifos and/or OP exposure (with adverse neurodevelopmental outcomes in children through age 7 years). For the 2014 chlorpyrifos revised human health risk assessment (D424485, D. Drew et al., 12/29/2014), EPA included epidemiologic research results from these three US prospective birth cohort studies, but primarily focused on the results of CCCEH since this cohort has published studies on the association between cord blood levels of chlorpyrifos and neurodevelopmental outcomes. The agency retained the FQPA 10X Safety Factor (SF) in the 2014 chlorpyrifos revised risk assessment, in large part, based on the findings of these studies.

In the 2015 updated literature review (OPP/USEPA; D331251; 9/15/15), the agency conducted a systematic review expanding the scope of the 2012/2014 review focused on US cohort studies with particular emphasis on chlorpyrifos. The expanded 2015 review includes consideration of the epidemiological data on any OP pesticide, study designs beyond prospective cohort studies, and non-U.S. based studies. The updated literature review identified seven studies which were relevant (Bouchard et al., 2010; Fortenberry et al., 2014; Furlong et al., 2014; Guodong et al., 2012; Oulhote and Bouchard, 2013; Zhang et al., 2014; Shelton et al., 2014). These seven studies have been evaluated in context with studies from the 2012/2014 review (D424485, D. Drew et al., 12/29/2014). Only a brief summary is provided below.

The OP exposure being assessed in many of these studies used concentrations of urinary dialkyl phosphate metabolites (DAPs) as the urinary biomarker. Total DAPs is a non-specific measure of OP exposure and is the sum of six separate molecules - three dimethyl alkylphosphate (DMAP) molecules of DMP, DMTP, DMDTP, and three diethyl alkylphosphate (DEAP) molecules of DEP, DETP, and DEDTP. Each metabolite is a breakdown product from multiple

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

OPs (Table 4.4.-1; CDC, 2008)[3]. Specifically, DMP, DMTP, and DMDTP are associated with 18, 13, and 5 OPs, whereas DEP, DETP, and DEDTP are associated with 10, 10, and 4 OPs, respectively. Thus, using urinary DAPs alone as an exposure measure, it is not possible to separate the exposure and associated effects for single, specific OPs.

Table 4.4.1.CDC Table of organophosphate pesticides and their dialkyl phosphate metabolites (2008).

Pesticide	DMP	DMTP	DMDTP	DEP	DETP	DEDTP
Azinphos methyl	X	X	X			
Chlorethoxyphos				X	X	
Chlorpyrifos				X	X	
Chlorpyrifos methyl	X	X				
Coumaphos				X	X	
Dichlorvos (DDVP)	X					
Diazinon				X	X	
Dicrotophos	X					
Dimethoate	X	X	X			
Disulfoton				X	X	X
Ethion				X	X	X
Fenitrothion	X	X				
Fenthion	X	X				
Isazaphos-methyl	X	X				
Malathion	X	X	X			
Methidathion	X	X	X			
Methyl parathion	X	X				
Naled	X					
Oxydemeton-methyl	X	X				
Parathion				X	X	
Phorate				X	X	X
Phosmet	X	X	X			
Pirimiphos-methyl	X	X				
Sulfotepp				X	X	
Temephos	X	X				
Terbufos				X	X	X
Tetrachlorvinphos	X					
Trichlorfon	X					

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

For studies which measured urinary 3,5,6-trichloro-2-pyridinol (TCPy) (e.g., Fortenberry et al., 2014; Eskenazi et al., 2007; Whyatt et al., 2009), this metabolite can be derived from chlorpyrifos, chlorpyrifos-methyl, and the herbicide triclopyr. TCPy is also the primary environmental degradate of chlorpyrifos, chlorpyrifos-methyl, and triclopyr; thus exposure can be found directly on food treated with these pesticides. CCCEH studies have largely used chlorpyrifos measured in cord blood as the specific biomarker (e.g., Lovasi et al., 2010; Whyatt et al., 2004; Rauh et al., 2011). The CHARGE study (Shelton et al., 2015) did not measure

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

biomarkers, but instead used geospatial analysis to focus on the residential proximity to OP exposure using data from the California Department of Pesticide Regulation, with five OPs accounting for a total of 73% of the pesticide applied near residential settings (chlorpyrifos, acephate, diazinon, bensulide, and dimethoate).

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

With respect to neurological effects near birth, the CHAMACOS and Mt. Sinai cohorts measured neurological effects at birth, and observed a putative association with total DEAP, total DMAP, and total DAP exposure (Engel et al., 2007; Young et al., 2005). Similarly, a Chinese study (Zhang et al., 2014) reported statistically significant associations for total DEAPs, total DMAPs, and total DAPs from prenatal OP pesticide exposure and neonatal neurodevelopment assessed 3 days after birth. However, another cross-sectional Chinese study, Guodong et al. (2012), observed no association with urinary DAPs and a developmental quotient score for 23-25 month old children.

The 3 US cohorts (CCCEH, Mt. Sinai, CHAMACOS) each reported evidence of impaired mental and psychomotor development, albeit not consistent by age at time of testing (ranging from 6 months to 36 months across the three cohorts). Attentional problems and Attention Deficit Hyperactivity Disorder (ADHD) were reported by three prospective cohorts [Rauh et al., 2006; Eskenazi et al., 2007; Marks et al., 2010; and Fortenberry et al. (2014)] with additional support from a case control study, Bouchard et al. (2010). The exposure metric varied among these studies. Specifically, Fortenberry et al. (2014) found suggestive evidence of an association with TCPy and ADHD in boys, whereas statistically significant associations were observed by Rauh et al. (2006) with chlorpyrifos exposure and ADHD. Eskenazi et al. (2007) reported associations with total DMAPs and total DAPs and ADHD; Marks et al. (2010) reported associations with total DEAP, DMAP, and total DAP exposure and ADHD. In a national cross-sectional study of Canadian children, using 2007-2009 data for children age 6-11 years (Oulhote and Bouchard, 2013), there were no overall statistically significant associations observed between child urinary DEAP, DMAP, or total DAP metabolite levels and parentally reported behavioral problems. In contrast, Bouchard et al. (2010), looking at U.S. children age 8-15 years in the 2000-2004 National Health and Nutrition Examination Survey (NHANES), observed a positive association between attention and behavior problems and total DAPs and DMAPs, but not DEAPs. As part of their analysis, Oulhote and Bouchard (2013) noted that their outcome assessment for behavioral problems may not have been as sensitive as Bouchard et al. (2010), which may in part account for the difference in the observed results from these studies.

In addition, the three US cohorts and the CHARGE study have reported suggestive or positive associations between OP exposure and autism spectrum disorders (Rauh *et al*., 2006; Shelton et

al., 2014; Eskenazi et al., 2007; Furlong et al., 2014). Specifically, Furlong et al. (2014) documented suggestive evidence of an association between total DEAP exposure and reciprocal social responsiveness among blacks and boys. Eskenazi et al. (2007) reported a statistically significant association between pervasive developmental disorder (PDD) and total DAP exposure, whereas Eskenazi et al. (2010) reported non-significant, but suggestive, increased odds of PDD of 2.0 (0.8 to 5.1; p=0.14). Rauh et al. (2006) documented a significant association between PDD and specifically chlorpyrifos exposure. Both PDD and reciprocal social responsiveness are related to the autism spectrum disorder. Using a different exposure assessment method (geospatial analysis and residential proximity to total OP exposure), Shelton et al. (2014) also showed statistically significant associations between total OP exposure and ASD. While these studies vary in the magnitude of the overall strength of association, they have consistently observed a positive association between OP exposure and ASD. Finally, CCCEH, Mt. Sinai, CHAMACOS have reported an inverse relation between the respective prenatal measures of chlorpyrifos and intelligence measures at age 7 years (Rauh et al., 2011; Engel *et al.,* 2011; Bouchard et al., 2011).

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

A review of the scientific literature on potential modes of action/adverse outcome pathways (MOA/AOP)[4] leading to effects on the developing brain was conducted for the 2012 FIFRA SAP meeting (USEPA, 2012) and updated for the December 2014 chlorpyrifos revised risk assessment (D424485, D. Drew et al., 12/29/2014). In short, multiple biologically plausible hypotheses and pathways are being pursued by researchers that include targets other than AChE inhibition, including cholinergic and non-cholinergic systems, signaling pathways, proteins, and others. However, no one pathway has sufficient data to be considered more credible than the others. The fact that there are, however, sparse AOP data to support the *in vitro* to *in vivo* extrapolation, or the extrapolation from biological perturbation to adverse consequence significantly limits their quantitative use in risk assessment. The SAP concurred with the agency in 2008 and 2012 about the lack of definable key events in a MOA/AOP leading to

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

developmental neurobehavioral effects. However, since the 2014 literature review, there are no substantive changes in the ability to define and quantitate steps in an MOA/AOP leading from exposure to effects on the developing brain. Published and submitted guideline DNT laboratory animal studies have been reviewed for OPs as part of the 2012/2014 review (D424485, D. Drew et al., 12/29/2014) and the updated 2015 review (OPP/USEPA; D331251; 9/15/15). Neurobehavioral alterations in laboratory animals were often reported, albeit at AChE inhibiting doses, but there was generally a lack of consistency in terms of pattern, timing, or dose-response for these effects, and a number of studies were of lower quality. However, this information does provide evidence of long-lasting neurodevelopmental disorders in rats and mice following gestational exposure.

At this time, a MOA(s)/AOP(s) has/have not been established for neurodevelopmental outcomes. This growing body of literature does demonstrate, however, that OPs are biologically active on a number of processes that affect the developing brain. Moreover, there is a large body of *in vivo* laboratory studies which show long-term behavioral effects from early life exposure, albeit at doses which cause AChE inhibition. EPA considers the results of the toxicological studies relevant to the human population, as qualitatively supported by the results of epidemiology studies. The agency acknowledges the lack of established MOA/AOP pathway and uncertainties associated with the lack of ability to make strong causal linkages and unknown window(s) of susceptibility. These uncertainties do not undermine or reduce the confidence in the findings of the epidemiology studies. The epidemiology studies reviewed in the 2012/2014 and 2015 literature reviews represent different investigators, locations, points in time, exposure assessment procedures, and outcome measurements. Despite all these differences in study design, with the exception of two negative studies in the 2015 literature review (Guodong et al., 2012; Oulhote and Bouchard, 2013), authors have identified associations with neurodevelopmental outcomes associated with OP exposure across four cohorts and twelve study citations. Specifically, there is evidence of delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children who were exposed to OPs during gestation. Investigators reported strong measures of statistical association across several of these evaluations (odds ratios 2-4 fold increased in some instances), and observed evidence of exposures-response trends in some instances, *e.g.*, intelligence measures.

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

are associated with neurodevelopmental outcomes prior to a revised human health risk assessment.

4.5 Safety Factor for Infants and Children (FQPA SF)

As noted above, the lack of an established MOA/AOP makes quantitative use of the epidemiology studies in risk assessment challenging, particularly with respect to determining dose-response, critical duration of exposure, and window(s) of susceptibility. However, epidemiology studies consistently identified associations with neurodevelopmental outcomes associated with OP exposure, such as delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children, but at exposure levels that are probably low enough that are unlikely to result in AChE inhibition. Therefore, there is a need to protect children from exposures that may cause neurodevelopmental effects; this need prevents the agency from reducing or removing the statutory FQPA Safety Factor[5]. This rationale applies to both acephate and methamidophos. **Thus, the FQPA 10X Safety Factor will be retained for acephate for the population subgroups that include infants, children, youth, and women of childbearing age for all exposure scenarios.**

4.5.1 Completeness of the Toxicology Database

The database of toxicology studies for acephate and methamidophos are complete and considered adequate for risk assessment. Developmental toxicity studies in rats and rabbits, a reproductive toxicity study in rats, and a CCA study (acute, repeated dose, and gestational) are available for both acephate and methamidophos.

4.5.2 Evidence of Neurotoxicity

Acephate and methamidophos are OPs with a neurotoxic AOP; neurotoxicity is the most sensitive effect in all species, routes, and lifestages and is being used to derive PODs for risk assessment. Therefore, the risk assessment is protective of potential neurotoxicity for every life stage and route of exposure.

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

There was no evidence to indicate increased sensitivity of the PND 11 pups or fetuses compared to adults for acephate or methamidophos. For risk assessment, the PODs and endpoints selected were protective of all lifestages. For the oral route, acephate endpoints based on AChEI in pups were used, and the TAFs for methamidophos were also based on pups. For the dermal and inhalation routes, route-specific studies were used and data shown in Appendix A.6 indicate that the TAF for adults will be protective for pups. Based on the use pattern and the environmental conditions required for acephate degradation, inhalation exposure is expected for only acephate (not methamidophos).

[5] OPP's standard approaches are consistent with EPA's children's environmental health policy. https://www.epa.gov/children/epas-policy-evaluating-risk-children

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

4.5.4 Residual Uncertainty in the Exposure Database

There is no residual uncertainty in the exposure database. Dietary risk estimates were based on refined estimates of residues in foods and estimates of the percentage of the crop that may be treated. In addition, for drinking water, upper-bound water concentration estimates based on modeling were assumed. Residential exposures were based on the 2012 Residential SOPs and chemical-specific dislodgeable foliar residue (DFR) and turf transferable residue (TTR) data. Potential residues of the acephate degradate methamidophos have been accounted for. The dietary and residential exposure estimates are not underestimated.

4.6 Toxicity Endpoint and Point of Departure Selections

4.6.1 Dose-Response Assessment

Table 4.6.7.1 summarizes the acephate toxicity endpoints and PODs selected from an evaluation of the database. This endpoint selection was based on a weight of the evidence evaluation using the following considerations:

- *Relative sensitivity of the brain and RBC compartments*: Across most studies, durations, lifestages, and routes, AChE tends to be more sensitive to acephate and methamidophos inhibition in the brain than the RBC. As such, OPP has emphasized the use of brain AChE data in POD derivation.
- *Potentially susceptible populations (fetuses, juveniles, or pregnant women*): The available AChE data across multiple lifestages (adults, pregnant adults, fetuses, juveniles) show no quantitative lifestage sensitivity for acephate. Pups were 1.58-fold more sensitive to methamidophos than adults.
- *Route of exposure*: It is preferred to match, to the degree possible, the route of exposure in the toxicity study with that of the exposure scenario(s) of interest. In the case of acephate and methamidophos, there are oral, dermal, and inhalation studies, which include AChE data.
- *Duration of exposure*: It is preferred to match, to the degree possible, the duration of toxicity study with that of the exposure duration of interest. In the case of acephate and methamidophos, there are single dose and repeated dose oral studies, but only repeated dose dermal and inhalation studies.
- *Consistency across studies*: In cases where multiple datasets are available for a single duration, it is important to evaluate the extent to which data are consistent (or not) across studies. The acephate and methamidophos databases are consistent across studies which allows for PODs to be derived from multiple critical studies, thereby increasing the confidence in such values.

Descriptions of the primary toxicity studies used for selecting toxicity endpoints and points of departure for various exposure scenarios are presented in Appendix A of this document. Summary tables of BMD analyses can be found in Appendix A.2, and the technical details of the analysis can be found in the BMD memo (Bever, 2014, TXR # 0056995).

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} values and $BMDL_{10}$ values (see Appendix A.2. for summary of OPP's ChE policy). The BMD_{10} is the estimated dose where ChE is inhibited by 10% compared to background. The $BMDL_{10}$ is the lower confidence bound on the BMD_{10}. As a matter of science policy, the agency uses the BMDL, not the BMD, for use as the POD (USEPA, 2012). BMD/BMDL modeling for all individual datasets was completed using BenchMark Dose Software 2.4; an exponential or Hill model was used to fit the data, with and/or without the assumption of constant variance across each dataset.

Acute Dietary Endpoint (All Populations)

A POD for the acute dietary (all populations) exposure scenario was derived from the response observed in an acute CCA rat study (MRID 46151801). A $BMDL_{10}$ of 0.272 mg/kg was selected and was associated with brain ChE inhibition in male pups (PND 11). The corresponding BMD_{10} was 0.513 mg/kg. Brain cholinesterase inhibition was selected as the endpoint for the POD, since BMD_{10} values were much lower than those for RBC cholinesterase inhibition. Data from the PND 11 pups 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 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA SF due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)) is applied to the $BMDL_{10}$ to obtain an aPAD of 0.0003 mg/kg/day for exposure scenarios with infants, children, youth, and women of childbearing age. The only population subgroup for which the FQPA SF is not retained is adults 50-99; therefore, the aPAD for this population subgroup is 0.003 mg/kg/day.

Steady-State Dietary Endpoint (All Populations)

A POD for the steady-state dietary exposure scenarios was derived from the response observed in an acute CCA rat study (MRID 46151801). As shown in Section 4.3.1, the maximal inhibition of acephate is reached after a single dose. The acute CCA study was chosen because it provided the lowest POD from the best modeled data sets. A $BMDL_{10}$ of 0.272 mg/kg/day was selected and was associated with brain ChE inhibition in male pups (PND 11). The corresponding BMD_{10} was 0.513 mg/kg/day. Brain cholinesterase inhibition was selected as the endpoint for the POD, since BMD_{10} values were much lower than those for RBC cholinesterase inhibition. There were two repeat dose oral toxicity studies which resulted in $BMDL_{10}$s that were lower than 0.272 mg/kg/day: male adult brain at 819 days in a 104 week chronic toxicity/carcinogenicity study in rats (0.255 mg/kg/day) and male adult cortex at 91 days in a 13 week subchronic neurotoxicity study (0.199 mg/kg/day). These two studies did not allow the same level of confidence as the acute study, because they did not pass the statistical tests of appropriate model

fit nor did the model fit appear as good upon visual inspection. Several other studies also provided a $BMDL_{10}$ of approximately 0.3 mg/kg/day as follows: 0.358 and 0.340 mg/kg/day from brain in female and male, respectively, in a 13 week subchronic oral toxicity study; 0.317 mg/kg/day from dam brain in a gestational CCA study; 0.298 mg/kg/day in female cortex at 91 days in a 13 week subchronic neurotoxicity study; and 0.315 mg/kg/day in male pup brain in the repeated dose CCA. The first two data sets (0.358 and 0.340 mg/kg/day) did not pass all statistical tests for goodness of model fit, but confidence was high in these results due to visual inspection of the model and comparison of the predicted results to the empirical data. The next two data sets (0.317 and 0.298 mg/kg/day) passed all statistical tests for goodness of fit, but confidence was less than the first two studies due to poor dose selection.

A $BMDL_{10}$ of 0.196 mg/kg/day was derived from the chronic oral toxicity study in dog for the adult female brain at 53 weeks. However, when allometric scaling (3/4 bodyweight scaling) is used to adjust to a human equivalent dosage, the doses become 0.0653 mg/kg/day from the rat acute CCA study and 0.123 mg/kg/day from the dog chronic oral toxicity study. Furthermore, when comparing the chronic oral toxicity study in the dog to the acute CCA study in rat, the dog uses fewer animals per group and has a higher dose group variance compared to the rat, allowing more confidence in the results from the rat study. As a result, the selected endpoint derived from the acute CCA study is considered protective of the inhibition observed in the chronic dog study.

The endpoint and POD are protective of other effects observed in the database. An uncertainty factor of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA SF due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)) is applied to the $BMDL_{10}$ to obtain a ssPAD of 0.0003 mg/kg/day for all exposure scenarios, except adults 50-99. Reducing the FQPA SF for adults 50-99 results in the ssPAD of 0.003 mg/kg/day.

Steady-State Incidental Oral Endpoint

A POD of 0.272 mg/kg/day was selected due to the same rationale provided above for steady state dietary exposures. A total uncertainty factor of 1000X is appropriate for incidental oral exposures (10X for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA SF due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)); therefore, the Level of Concern (LOC) for incidental oral exposures is 1000.

Steady-State Dermal Endpoints

A 21-day dermal rat toxicity study (MRID 44541101) was performed. Results from the BMD analysis of this study were not used due to large variance among dose groups and poor dose selection. Therefore, the no observed adverse effect level (NOAEL) approach was considered more appropriate to establish a POD for this study, although the NOAEL approach is limited to the doses tested. The lowest observed adverse effect level (LOAEL) was 300 mg/kg/day based on 14% inhibition of AChE in female brain, and the NOAEL occurred at 60 mg/kg/day. As demonstrated by the similarity of cholinesterase inhibition at a common high dose of 300 mg/kg/day in both the pilot and main dermal toxicity studies, there is no difference in brain cholinesterase inhibition after 5 doses or 15 doses. Therefore, to further refine the NOAEL, the

5-day pilot study (Appendix M on page 340 of MRID 44541101) was also considered. In the pilot test at the highest dose tested (300 mg/kg/day), brain AChEI was noted in females (↓14%) and males (↓10%). At 150 mg/kg/day, brain AChEI was noted in males (↓12%), but not in females. Although greater than 10% inhibition was noted in the 150 mg/kg/day males, there was large variation in the control group. The relationship between brain cholinesterase inhibition in the males in the pilot study and dose was unclear (i.e. lack of dose-response).

The data from the dermal toxicity study are adequate to demonstrate that using the dermal absorption factor of 3.6% with the oral endpoint of 0.272 mg/kg/day will significantly exaggerate actual hazard. The pharmacokinetics of the absorption through the skin is much slower than through the gastro-intestinal tract, resulting in lower blood concentrations to illicit an adverse response. Therefore, using the data from the route-specific dermal toxicity studies is considered more appropriate. Furthermore, as detailed at the beginning of the Section (4.6.1), there is no sensitivity in fetuses, juveniles, or pregnant women for acephate. Dermal exposure to methamidophos may occur, and the toxicity adjustment factor is used to insure that the risk assessment is protective.

Based on all this information, the LOAEL is 300 mg/kg/day due to brain cholinesterase inhibition observed in both sexes in the pilot and full dermal toxicity studies. The NOAEL of 150 mg/kg/day from the pilot dermal toxicity study was used as the POD. For additional information, please consult Appendix A.7.

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

Inhalation Endpoints/ Steady-State

Based on the use pattern and the environmental conditions necessary for acephate degradation, inhalation exposure is expected for only acephate (not methamidophos). An acceptable, guideline 4-week inhalation toxicity study in rats (MRID 40504818) was submitted that provided mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) data for the particle distribution of the aerosol. The lowest dose group (1 mg/m^3) approximated the $BMDL_{10}$ for this study of 1.205 mg/m^3; therefore, the MMAD and GSD data from this dose group was used. A POD for the steady-state inhalation exposure scenarios was derived from this study. The $BMDL_{10}$ of 1.205 mg/m^3 was associated with brain ChE inhibition in female adults. The corresponding BMD_{10} was 1.581 mg/m^3. Brain cholinesterase inhibition was selected as the endpoint for the POD, since BMD_{10} values were significantly lower than those for RBC cholinesterase inhibition. The modeling of this data set was very good. All statistical tests for fit were passed. Visual inspection of the modeling also lent confidence. The prediction of the BMD also approximated empirical evidence. The human equivalent dose was calculated for various exposure scenarios using the regional deposited dose ratio (RDDR) program and resulted in doses of 0.05-0.20 mg/kg and human equivalent concentrations (HECs) of 0.001-0.003 mg/L (see Table 4.6.7.3). For steady-state inhalation exposures, a total uncertainty factor of 300X is appropriate (3X for interspecies extrapolation, 10X for intraspecies variation, and 10X database

uncertainty factor incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)). The interspecies factor was reduced from 10X to 3X, due to the HEC calculation accounting for pharmacokinetic interspecies differences. For details regarding the calculation of the HECs and human equivalent doses and values for specific exposure scenarios and ventilation rates, please consult Appendix A.8.

4.6.2 Degradate (Methamidophos) Toxicity Adjustment Factor

Microbes in the soil, stomach, and intestine can degrade acephate to methamidophos. Photolysis in soil also occurs, and acephate is degraded in plants. Acephate is very water soluble, but does not break down readily by photolysis in water.

Methamidophos has sufficient data for cholinesterase inhibition to support modeling of a BMD_{10} by the oral route of exposure and adequate information to determine a comparative effect level (CEL) by the dermal and inhalation routes. The CEL is the experimental dose causing a maximum of 15% brain cholinesterase inhibition. The high quality dose-response data for methamidophos permits reliable estimates of PODs for all routes without resorting to the use of the less precise NOAELs. Methamidophos was chosen as the index chemical in the Organophosphorus Cumulative Risk Assessment – 2006 Update (CRA, refer to this document for more information). A primary reason for this selection was the confidence in the POD values, because accuracy in the index chemical would impact the overall uncertainty in the entire risk assessment. For methamidophos, the BMD_{10}s and the $BMDL_{10}$s were very similar suggesting good dose-response data with little variability and a very good fit of the data to the model. There was no increased sensitivity in the pups or offspring, and the BMD_{10}s were similar between sexes. The methamidophos data were not re-evaluated due primarily to the unusually high quality of the data sets but also due to the following reasons: (1) the sophistication of the statistical analysis used in the CRA, (2) confirmation of conclusions in the CRA by the Scientific Advisory Panel, (3) additional analyses performed in 2011 (D382498, 1/25/2011), and (4) the vast majority of the toxicity data were reviewed as part of the CRA; exceptions include a developmental neurotoxicity study (TXR # 0054510) reviewed on 6/7/2007 and gestational and repeated dose comparative cholinesterase studies (TXR # 0054242) reviewed on 8/26/2010 which would not change the conclusions regarding an appropriate TAF.

Methamidophos has been found to be a more potent AChE inhibitor than acephate. To account for the increased potency of methamidophos in risk estimates, BMD modeling was used to evaluate relative potency for acephate and methamidophos and to estimate the TAFs for acute and steady-state exposure durations. As described in the guidance document for CRA (USEPA, 2002), comparisons of toxic potency should be made using a uniform basis of comparison, by using to the extent possible a common response derived from a comparable measurement methodology, species, and sex for all the exposure routes of interest. Dose-response modeling is preferred over the use of NOAELs/LOAELs for determining relative toxic potency. NOAELs and LOAELs do not necessarily reflect the relationship between dose and response for a given chemical, nor do they reflect a uniform response across different chemicals.

The toxicity of methamidophos was compared to acephate using the BMD_{10} when data sets allowed quality BMD modeling. Otherwise, a CEL was calculated. Multiplying the measured

methamidophos residues by the relative potency factor provides a measure of acephate toxicity-equivalents. The TAFs are provided in the following two tables.

Route of Administration	Methamidophos BMD_{10} (mg/kg/day)	Acephate BMD_{10} (mg/kg/day)	Toxicity Adjustment Factor [a]
Oral (pups)	0.186 [b]	0.513 [c]	2.76

[a] Values were obtained by dividing the acephate BMD_{10} by the methamidophos BMD_{10}. Multiplying the measured methamidophos residues by the toxicity adjustment factor provides a measure of acephate toxicity-equivalents.
[b] Value was obtained from D382498, 1/25/2011.
[c] Acephate BMD_{10} value in the current study is 0.513 mg/kg/day and is presented in Appendix 2. Toxicity Profile (Table A.2.1). Although 0.51 mg/kg/day is reported in D382498, 1/25/2011, this value has actually just been rounded, because the TAF is reported as 2.76.

Route of Administration	Methamidophos CEL (mg/kg/day; % inh.)	Acephate CEL (mg/kg/day; % inh.)	Toxicity Adjustment Factor [a]
Inhalation	0.310 (↓11) [b]	1.492 (↓13) [b]	4.81
Dermal	0.75 (↓5) [c]	300 (↓14) [c]	400

[a] Values were obtained by dividing the acephate CEL by the methamidophos CEL. Multiplying the measured methamidophos residues by the toxicity adjustment factor provides a measure of acephate-equivalents.
[b] Values were obtained from the Organophosphorus Cumulative Risk Assessment, 2006, Table I.B-2.
[c] Values were obtained from the Organophosphorus Cumulative Risk Assessment, 2006, Table I.B-3.
Inh. = Brain cholinesterase inhibition
CEL = Comparative effect level, which was used in the cumulative risk assessment as an alternative to BMD_{10}s, because the dermal and inhalation studies with cholinesterase measurements are limited. The CEL was defined as the experimental dose causing a maximum of 15% brain cholinesterase inhibition.

The POD selected for all oral exposure scenarios was derived from pup brain AChEI; consequently, the TAF will be 2.76. Results for the calculation of the TAF from data presented in the OP Cumulative Risk Assessment are compared to these results in Appendix A.6.

The available data demonstrating AChEI, as a result of dermal or inhalation exposure to acephate or methamidophos, did not allow TAFs based on BMD_{10} estimations. Consequently, a TAF was established in the OP Cumulative Risk Assessment based on CELs. These values were selected as the highest experimental dose which caused a maximum of 15% brain AChEI. Thus, the dermal TAF is considered to be 400. An inhalation TAF of 4.81 was calculated; however, based on the exposure pattern, an inhalation TAF is not needed.

4.6.3 Recommendation for Combining Routes of Exposures for Risk Assessment

When there are potential occupational and residential exposures to a pesticide, the risk assessment must address exposures from three major sources (oral, dermal, and inhalation) and determine whether the individual exposures can be combined if they have the same toxicological effects. PODs for the incidental oral, dermal, and inhalation routes are all derived from brain AChE inhibition. As a result, exposure from all routes can be combined.

4.6.4 Cancer Classification and Risk Assessment Recommendation

Acephate has been classified by the Health Effects Division-Carcinogenicity Peer Review Committee (CPRC) as a "Group C", possible human carcinogen. This classification was also supported by the FIFRA Scientific Advisory Panel (SAP) based on statistically significant increase in hepatocellular carcinomas in mice. This classification is based on adequate carcinogenicity studies in rat and mouse. However, it was concluded that no quantitative risk assessment (using a linear approach, Q1*) is needed based on the occurrence of hepatocellular carcinomas in only one sex (female) of one species (mouse) and only at the highest dose; and the lack of mutagenicity seen in *in vivo* mutagenicity studies. Quantification of cancer risk using a non-linear approach adequately accounts for all chronic toxicity, including carcinogenicity that could result from exposure to acephate.

Methamidophos is classified as Not Likely to be Carcinogenic to Humans.

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

Table 4.6.5.1 Summary of Toxicological Doses and Endpoints and Points of Departure for Acephate in Dietary and Non-Occupational Human Health Risk Assessments [a]

Exposure Scenario	Point of Departure (mg/kg/day)	Uncertainty/FQPA Factors	RFD, PAD, & LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations Except Adults 50-99 Years)	$BMDL_{10}$ = 0.272 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 10x	aRfD = 0.003 mg/kg/day aPAD = 0.0003 mg/kg/day	Acute CCA Study (MRID 46151801) in the rat BMD_{10} = 0.5128 mg/kg/day Inhibition of brain AChE in male pups on PND 11.
Acute Dietary (Adults 50-99 Years)	$BMDL_{10}$ = 0.272 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 1x	Acute RfD = aPAD = 0.003 mg/kg/day	Acute CCA Study (MRID 46151801) in the rat BMD_{10} = 0.5128 mg/kg/day Inhibition of brain AChE in male pups on PND 11.
Steady-State Dietary (All Populations Except Adults 50-99 Years)	$BMDL_{10}$ = 0.272 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 10x	ssRfD = 0.003 mg/kg/day ssPAD = 0.0003 mg/kg/day	Acute CCA Study (MRID 46151801) in the rat BMD_{10} = 0.5128 mg/kg/day Inhibition of brain AChE in male pups on PND 11.
Steady-State Dietary (Adults 50-99 Years)	$BMDL_{10}$ = 0.272 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 1x	ssRfD = ssPAD = 0.003 mg/kg/day	Acute CCA Study (MRID 46151801) in the rat BMD_{10} = 0.5128 mg/kg/day Inhibition of brain AChE in male pups on PND 11.

Table 4.6.5.1 Summary of Toxicological Doses and Endpoints and Points of Departure for Acephate in Dietary and Non-Occupational Human Health Risk Assessments [a]

Exposure Scenario	Point of Departure (mg/kg/day)	Uncertainty/FQPA Factors	RFD, PAD, & LOC for Risk Assessment	Study and Toxicological Effects
Incidental Oral Steady-State	$BMDL_{10}$ = 0.272 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 10x	Residential LOC for MOE < 1000	Acute CCA Study (MRID 46151801) in the rat BMD_{10} = 0.5128 mg/kg/day Inhibition of brain AChE in male pups on PND 11.
Dermal Steady-State	NOAEL = 150 mg/kg/day (pilot study)	UF_A = 10x UF_H = 10x FQPA SF = 10x	Residential LOC for MOE < 1000	21-Day dermal toxicity and pilot studies (MRID 44541101) in the rat LOAEL = 300 mg/kg/day (main/pilot study) Inhibition of brain AChE in both sexes.
Inhalation Steady-State	$BMDL_{10}$ = 1.205 mg/m^3	UF_A = 3x UF_H = 10x FQPA SF = 10x	Residential LOC for MOE < 300	4-Week inhalation toxicity study (MRID 40504818) in the rat BMD_{10} = 1.581 mg/m^3 [b] Inhibition of brain AChE in female adults on Day 29.
Cancer (oral, dermal, inhalation)	Classification: Group C chemical – possible human carcinogen			

[a] 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. BMDL = lower limit of the bench mark dose. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). SF = Safety Factor. PAD = population adjusted dose (a = acute, ss = steady-state or maximal AChE inhibition which typically occurs around 2-3 weeks for OPs and is a specific exposure assessment conducted for OPs instead of the traditional short, intermediate, or chronic assessments. The SS assessment is protective of longer durations of exposure, including chronic.). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. Toxicity Adjustment Factor to convert methamidophos to acephate equivalents is 2.76 (oral), 400 (dermal), and 4.81 (inhalation).

[b] Specific human equivalent doses and human equivalent concentrations (HECs), as related to exposure scenario and ventilation rate, are reported in Appendix A.8. Cholinesterase Inhibition from Acephate in Inhalation Studies.

Table 4.6.5.2 Summary of Toxicological Doses and Endpoints for Acephate for Use in Occupational Human Health Risk Assessments [a]				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Factors**	**LOC for Risk Assessment**	**Study and Toxicological Effects**
Dermal Steady-State	NOAEL = 150 mg/kg/day (pilot study)	UF_A = 10x UF_H = 10x UF_{DB} = 10x	Occupational LOC for MOE < 1000	21-Day dermal toxicity and pilot studies (MRID 44541101) in the rat LOAEL = 300 mg/kg/day (main/pilot study) Inhibition of brain AChE in both sexes.
Inhalation Steady-State	$BMDL_{10}$ = 1.205 mg/m^3	UF_A = 3x UF_H = 10x UF_{DB} = 10x	Occupational LOC for MOE < 300	4-Week inhalation toxicity study (MRID 40504818) in the rat BMD_{10} = 1.581 mg/m^3 [b] Inhibition of brain AChE in female adults on Day 29.
Cancer (oral, dermal, inhalation)	Classification: Group C chemical – possible human carcinogen			

[a] 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. BMDL = lower limit of the bench mark dose. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_{DB} = database uncertainty factor. LOC = level of concern. Toxicity Adjustment Factor to convert methamidophos to acephate equivalents is 2.76 (oral), 400 (dermal), and 4.81 (inhalation).

[b] Specific human equivalent doses and human equivalent concentrations (HECs), as related to exposure scenario and ventilation rate, are reported in Appendix A.8. Cholinesterase Inhibition from Acephate in Inhalation Studies.

Steady State= steady state or maximal AChE inhibition which occurs around 2-3 weeks for OPs and is a specific exposure assessment conducted for OPs instead of the traditional short, intermediate, or chronic assessments. The steady state assessment is protective of longer durations including chronic.

Table 4.6.5.3 Summary of Human Equivalent Concentrations (HECs) and Doses Values for Acephate						
Population	**Scenario**	**Tox Duration Adjustment**		**HEC**		**Human Equivalent Dose**
		hr/day	**day/wk**	**mg/L**	**mg/m^3**	**mg/kg-day**
Occupational	Handler	0.75	1	0.002	2.132	0.20
Residential	Handler			0.003	2.842	0.07
	Outdoor post-application			0.003	2.842	0.08
	Indoor post-application		0.714	0.002	2.030	0.05
	Bystander	0.25	0.714	0.001	0.508	NA

HEC = human-equivalent concentration; HED = human-equivalent dose.
HEC = rat POD × daily duration adjustment × weekly daily duration adjustment × RDDR.
Human Equivalent Dose = HEC × human-specific conversion factor × daily duration.

4.7 Endocrine Disruption

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic, and chronic durations and assess carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental, and reproductive effects in different taxonomic groups. As part of its reregistration decision for acephate, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), acephate is subject to the endocrine screening part of the EDSP.

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP, where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[6] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

Acephate is on List 1 for which EPA has received all of the required Tier 1 assay data. The Agency has reviewed all of the assay data received for the appropriate List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets (see Docket # EPA-HQ-OPP-2008-0915) for acephate. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, and the test guidelines and the Tier 1 screening battery, please visit our website[7].

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

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

5.0 Dietary Exposure and Risk Assessment

Dietary memo: D. Drew, 3/20/2018, D446264.

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

Residue chemistry memo: F. Fort, 4/10/1997, D225794.

The nature of the residue in plants (bean, lettuce, cotton) and livestock (ruminants and poultry) has been adequately delineated. Acephate was the primary compound found in the metabolism studies, followed by methamidophos. Methamidophos levels were much lower than acephate in the edible plant portions and in livestock commodities. For risk assessment, the residues of concern in plant and livestock commodities are acephate and its cholinesterase- inhibiting metabolite, methamidophos

5.1.2 Summary of Environmental Degradation

Drinking water memo: R. David Jones, 1/15/2016, D421707.

Acephate is not persistent under aerobic conditions, and is not expected to be persistent in anaerobic aquatic environments where it will be associated with the aqueous phase due to its short anaerobic half-life.

Aerobic soil metabolism is the main degradation process for acephate. Observed half-lives are less than two days under the nominal or expected use conditions, producing the intermediate degradate methamidophos, which is also an insecticidal compound. Acephate hydrolyzes slowly except at high pH (half-life at pH 9 of 18 days) and does not rapidly photodegrade. Acephate is not persistent in anaerobic clay sediment: creek water systems in the laboratory, with a half-life of 6.6 days. The major degradates under anaerobic conditions were carbon dioxide and methane, comprising > 60% of the applied acephate after 20 days of anaerobic incubation. No other anaerobic degradates were present at > 10% during the incubation. There are no acceptable data for the aerobic aquatic metabolism of acephate; supplemental information indicates that acephate degrades more rapidly in aquatic systems when sediment is present.

Surface water runoff and spray drift are expected to be major sources of exposure for acephate. Acephate is very soluble (801-835 g·L-1) and very mobile (Koc = 2.7) in the laboratory. Based on the vapor pressure of acephate (pure active: 1.7 x 10-6 torr (MRID 40390601) and its calculated Henry's Law constant (5.1 x 10-13 atm·mole·m-3), it is not expected that acephate will volatilize from either soil or water in significant quantities.

Methamidophos is not persistent in aerobic environments, but may be more persistent in anaerobic aquatic environments where it will be associated with the aqueous phase.

Aerobic soil metabolism is the main degradation process for methamidophos. Methamidophos degraded with a calculated half-life of 14 hours in a sandy loam soil at an application rate (6.5 ppm) greater than the currently registered application rate (0.5 ppm from the maximum label single application rate of 1 lb a.i.·A^{-1}), producing the intermediate degradate S-methyl phosphoramidothioate, which also is rapidly metabolized by soil microorganisms to carbon dioxide and microbial biomass (half-life of < 5 days). Supplemental information also identifies O, S-dimethyl phosphorothioate (DMPT) as a major degradate which is also rapidly degraded in

soil (half-life < 4 days). In sterile aqueous solutions, methamidophos photodegrades slowly (dark control-corrected half-life > 200 days) and there is no evidence of hydrolysis at acid pHs. Hydrolysis degradates at neutral and alkaline pHs include: O-*des*-methyl, DMPT, and the volatile degradate dimethyl disulfide.

Laboratory studies showed that bioaccumulation of methamidophos in largemouth bass was insignificant; the maximum bioconcentration factor of 0.09 in whole fish occurred on day 28 and decreased to <0.014 ppm in the fish (quantification limit) after one day depuration.

Potential transport mechanisms include pesticide surface water runoff, and spray drift. Methamidophos is very soluble (>200 grams per liter ($g \cdot L^{-1}$) and very mobile (K_{OC} = 0.9). Volatilization from soil or water is not expected to be a major route of dissipation for methamidophos because of its rapid metabolism in soil and its calculated Henry's law constant (1.6×10^{-11} atm-$m^3 \cdot mole^{-1}$).

5.1.3 Comparison of Metabolite Pathways

In plants, acephate is enzymatically hydrolyzed to methamidophos, S-methyl N-acetylphosphoramidothioate (SMPT), O,S-dimethyl phosphorothioate (DMPT), and O-methyl N-acetylphosphoramidate (OMAPAA), and hydrolysis products, including methyl mercaptan and acetate, then enter the plant carbon pool. DMPT may also be formed via deaminolysis of methamidophos.

In livestock, acephate undergoes enzyme hydrolysis, oxidation, and incorporation of intermediates into the biosynthetic carbon pools. Hydrolysis of the P-N or C-N bond would form acetamide and DMPT or methamidophos and an enzyme-acetyl complex. The acetamide could then be deaminated for incorporation into naturally occurring acetamide, amino acids and proteins, and fatty acids and lipids. The S-methyl label may be preferentially incorporated into amino acids and proteins. This could occur via formation of OMPT, or via hydrolysis of the P-S bond to form OMAPAA. In addition, hydrolysis of the P-O bond yields SMPT which can be further degraded to S-methyl phosphoramidothioate (SMPAA) and an acetyl group.

In rats, acephate is rapidly absorbed and excreted (Section 4.2). The major radioactive component in urine from rats was unmetabolized acephate (77-80% AD). The only significant metabolism of acephate is the formation of $^{14}CO_2$ (9-10% of dose). Small quantities of methamidophos (4% of dose) and 3 other compounds (representing <4% of dose) were found in the urine. These components were des-acetamidoacephate (DMPT), Odesmethyl acephate (SMPT), and Odesmethyl methamidophos (SMPAA). However, metabolic origins of methamidophos and these 3 metabolites are uncertain, because they were present as contaminants in the dosing solutions at about the same percentage.

The metabolism of acephate is similar across plants, ruminants, poultry, and rats.

5.1.4 Residues of Concern Summary

Table 5.1.4. 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	Acephate and methamidophos	Acephate or methamidophos[1]
	Rotational Crop	Acephate and methamidophos	Acephate and methamidophos
Livestock	Ruminant	Acephate and methamidophos	Acephate
	Poultry	Acephate and methamidophos	Acephate
Drinking Water		Acephate and methamidophos	NA

[1] The following plant commodities have separate tolerances for residues of acephate and methamidophos: dry beans, succulent beans, Brussels sprouts, cauliflower, celery, cranberry, head lettuce, pepper, peppermint tops, spearmint tops. The following plant commodities have tolerances for acephate only (excludes methamidophos): cotton and peanut. The Food Handling Establishments (FHEs) tolerance for all foods (other than those already covered by higher crop tolerance) is for acephate only.

5.2 Residue Chemistry and Food Residue Profile

Residue chemistry memo: D. Drew, 3/9/2018, D446265.

Residue Chemistry

This section provides the status of residue chemistry requirements for acephate and includes residue data submitted and reviewed since the 2001 Interim Reregistration Eligibility Decision (IRED).

The 2001 IRED for acephate determined that adequate field trial data were available to reassess the established tolerances for acephate on the following commodities: beans (succulent and dry form), Brussels sprouts, cauliflower, celery, cottonseed, cranberries, lettuce (head), peanuts, peppers, soybean, and macadamia nuts. In addition, sufficient data were available to reassess established tolerances resulting from the use of acephate as spot and crack and crevice treatment in food handling establishments. The tolerance for mint and cottonseed were modified and several tolerances for feedstuffs were revoked. Data deficiencies identified in the IRED included the need for some additional information from the original primary crop (cotton, bean and lettuce) and poultry metabolism studies which were considered upgradable. The registrant provided additional information (MRID 45931901) and the requirements for the metabolism studies in cotton, lettuce, bean and poultry are considered fulfilled.

In addition to the metabolism information, the 2001 IRED identified the need for a magnitude of the residue study in cotton gin byproducts and a confined rotational crop study. These studies were received and reviewed. The submitted field trial data for acephate on cotton gin byproducts (MRID 45256201) is acceptable and suitable for recommending a tolerance for cotton gin byproducts. The location and distribution of the cotton gin byproduct field trials are adequate. An acceptable method was used for residue quantitation, and adequate storage stability data are available to support sample storage durations and conditions for all analytes. The use pattern followed in the magnitude of residue study is in accord with the label use pattern. The dietary burden to livestock was recalculated to consider residues in cotton gin byproducts and to use the most current version of Table 1 (OPPTS Test Guidelines 860.1000; June 2008) and it is determined that the potential residues on livestock commodities are covered by the tolerances currently established in the 40 CFR 180.108.

At the time of the IRED, preliminary data had been submitted pertaining to confined rotational crops. A confined rotational crop study (860.1850) has since been submitted (MRID 40874101). The submitted confined rotational study was found to be scientifically unacceptable for several reasons (i.e., low specific activity, lack of raw data, lack of storage stability data, incomplete characterization, and no confirmatory analytical technique). Although the confined rotational study is considered unacceptable and the total radioactive residues (TRR) were not identified in the plant (lettuce and wheat) matrices, HED has determined that the residues of concern in rotated crops are the same as in primary crops, acephate and methamidophos. No other cholinesterase-inhibiting metabolites, or other metabolites of toxicological concern, have been found across multiple metabolism studies in plants and animals. In addition, acephate and methamidophos both have very rapid soil metabolism and the major intermediate degradates in soil and plants are identical (S-methyl N-acetylphosphoramidothioate (SMPT) and O,S-dimethyl phosphorothioate (DMPT)) and are not of toxicological concern. SMPT and DMPT also degrade quickly into compounds (i.e., carbon dioxide, methyl mercaptan, acetate) that may then be incorporated into the natural plant or soil constituents. An additional confined rotational crop study (860.1850) is not being requested at this time.

A field accumulation in rotated crop study (860.1900) in order to determine if tolerances for acephate are required on rotated crops, or if plant back intervals (PBIs) are required on the labels has not been submitted. Acephate degrades rapidly in the environment by microbial metabolism with a mean aerobic soil metabolism half-life of 1.5 days and somewhat more slowly in a single anaerobic aquatic metabolism study ($t_{1/2}$= 6.6 d) (D. Jones et. al., D418159, 2/11/16). Acephate predominantly degrades to methamidophos in aerobic soils with a calculated half-life of 14 hours in a sandy loam soil. Acephate is not persistent in anaerobic clay sediment: creek water systems in the laboratory, with a half-life of 6.6 days. Methamidophos degraded in anaerobic sandy loam sediment with a DT_{50} (degradation time in which 50% degrades) of 41 days. In addition, in the confined rotational study, where the entire maximum seasonal rate was applied at once (6 lb a.i./A), low TRRs were reported in mature lettuce and wheat matrices from the 30 day and 120 day PBIs (< 0.22 ppm and < 0.06 ppm, respectively), and no detectable (<0.01 ppm) levels of acephate or methamidophos were present in any of the crop samples at 30 day and 120 day PBIs. Based on the rapid degradation of acephate and methamidophos and the results of the confined rotational study, HED has concluded that detectable residues of acephate or methamidophos are not likely in rotated crops with a 30 day PBI. A field accumulation in rotated crop study is not being requested at this time. HED recommends that a PBI of 30 days for crops without established tolerances is included in the labels.

Food Residue Profile

The residues of concern for risk assessment for plant and livestock commodities are acephate and methamidophos. The residues of concern for tolerance enforcement depends on the likelihood of finding the metabolite methamidophos in a particular commodity. The 40 CFR §180.108 contains separate sections for acephate and for methamidophos (from acephate application) which were established to differentiate methamidophos tolerances from acephate applications from methamidophos tolerances from the now-cancelled methamidophos pesticidal uses (F. Fort, D259662, 10/05/1999). The following plant commodities have separate tolerances in 40 CFR §180.108 for residues of acephate and residues of methamidophos: dry beans, Brussels sprouts,

cauliflower, celery, cranberry, head lettuce, pepper, peppermint tops, spearmint tops. The following commodities have tolerances for acephate only as significant methamidophos residues are not expected to occur: cotton, peanut, and livestock commodities. Similarly, the FHEs tolerance for all foods (other than those already covered by higher crop tolerance) is for acephate only

USDA PDP 2006-2014 food monitoring detected residues of acephate and methamidophos in several crop commodities. Commodities with detectable residues include cauliflower (1.3% detects), celery (25% detects), cranberry (2.5% detects), head lettuce (1.9%) bell peppers (16%) and non-bell peppers (13%). Acephate residues are found at much higher levels than methamidophos residues. Commodities with no detectable residues include canned dry beans, soybean grain, and peanut butter.

5.3 Water Residue Profile

Drinking water memo: R. David Jones, 3/21/2017, D421707.

The drinking water concentrations estimated from acephate uses were provided by the Environmental Fate and Effects Division (EFED) in the following memorandum: "Preliminary Drinking Water Assessment for Registration Review of Acephate" (D421707, R.D. Jones, 3/21//2017) and incorporated directly into this dietary assessment. Water residues were incorporated in the DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources."

The recommended EDWCs from surface and ground water sources are in Table 5.3. Surface water EDWCs were modeled using the Surface Water Concentration Calculator (SWCC) and ground water EDWCs were modeled using Pesticide Root Zone Model-Ground Water (PRZM-GW). All EDWCs assumed 100% conversion of acephate to the more toxic degradate methamidophos. The surface water EDWCS were selected for use in the dietary exposure assessments since those values were higher than those for ground water.

Based on the EFED recommendations, HED has selected the scenarios in Table 5.3 as appropriate for inclusion in the steady state and acute dietary risk assessments. While there are many crops with acephate uses, the dietary (drinking water) assessment was performed on just two representative agricultural crop scenarios: 1) a celery scenario which represents all crops with the *low-en*d maximum application rate (~2 lb a.i./A maximum seasonal rate), and 2) a cotton scenario which represents all crops with the *high-end* maximum application rate (~4 lb a.i./A maximum seasonal rate).

A quantitative dietary (drinking water) assessment was not performed for the non-agricultural (non-food) uses of acephate. The non-agricultural uses have, in general, higher single application rates than those for the food uses which are mostly 1 lb a.i./acre or less. Overall application rates for non-agricultural uses are estimated at up to 162 lb a.i./A (non-residential building perimeter). Because many of the labels did not specify a maximum seasonal rate or the total number of applications that could be made, the calculated application rates and resulting EDWCs for the non-agricultural uses may be overestimated. While a quantitative dietary (drinking water) assessment was not performed for the non-agricultural uses, these uses would result in greater EDWCs and greater resulting dietary risk estimates than those based on the agricultural uses.

For the selected drinking water scenarios, a distribution of surface water residues was used probabilistically in the dietary model. EFED provided daily time-series outputs that simulate 29 years (1962-1990) of residues of acephate in surface drinking water for the celery (CARowCropRLF_V2) and the cotton (MSCottonSTD) scenarios. All of the time-series data were adjusted to reflect 100% conversion of acephate to methamidophos by adjustment for molecular weight and by multiplying the residues by the acute and steady state TAF of 2.76. No further adjustments were made to the acute distribution files, but since the steady state average dietary assessments use 21-day forward rolling averages for drinking water, the steady state distributions were further adjusted to be 21-day forward rolling averages. In the 21-day rolling average distributions, the first data point is the average of days 1-21, the second data point is the average of days 2-22, the third data point is the average of days 3-23, etc. The 21-day rolling average continues until the last 20 days of residues of the final distribution year.

Table 5.3. EDWCs for Acephate (as Methamidophos[1])

CROP SCENARIO	Peak ($\mu g \cdot L^{-1}$)	Annual Mean ($\mu g \cdot L^{-1}$)	Overall Mean EDWC ($\mu g \cdot L^{-1}$)
Cotton (MSCottonSTD)	71.3	1.02	0.450
Celery (CARowCropRLF_V2)	11.0	0.379	0.284

[1] EDWCs are adjusted for methamidophos by molecular weight conversion. These values do not include the TAF of 2.76. The TAF is incorporated into the DEEM analysis EDWC distribution files.

Monitoring Data

There is very little useful water monitoring data for acephate, due to its non-persistent nature. There were no data for acephate or methamidophos in the California surface water database or in the United States Geological Survey National Water Quality Assessment (USGS NAWQA) surface water monitoring program. The 6 OP Drinking Water Monitoring Study (MRID 45526201) analyzed for acephate and methamidophos, but cross-contamination of samples during the analysis and changes in the analytical protocol during the study rendered the data from these two compounds unusable.

5.4 Dietary Risk Assessment

Dietary Assessment memo: D. Drew, 3/20/2018, D446264.

5.4.1 Description of Residue Data Used in Dietary Assessment

Acute and steady state dietary (food and water) exposure and risk assessments for acephate were conducted using DEEM-FCID version 3.18. This model uses 2003-2008 food consumption data from USDA's NHANES/WWEIA. The highly refined (for food only) probabilistic acute and steady state dietary exposure assessments for acephate incorporated USDA PDP food monitoring data, PCT estimates from the Biological and Economic Analysis Division (BEAD), and default or empirical processing and cooking factors. The EFED provided EDWCs as daily time-series outputs from modeling. The dietary (drinking water) assessment was performed on two representative agricultural crop scenarios: a celery scenario which represents all agricultural crops with the low-end maximum application rate and a cotton scenario which represents all

agricultural crops with the high-end maximum application rate. The drinking water concentration estimates assume 100% conversion of acephate to the more toxic degradate methamidophos. The EFED provided EDWCs as daily time-series outputs from modeling.

Since the acephate POD was used in the dietary exposure assessment, but methamidophos is a more potent cholinesterase inhibitor, methamidophos residues (in food and water) were corrected using an acute and steady state TAF of 2.76 prior to adding to any residues of acephate.

5.4.2 Percent Crop Treated (PCT) Used in Dietary Assessment

A Screening Level Usage Analysis (SLUA) pesticide use profile for acephate was provided by the BEAD (04/09/2014). The following maximum percent crop treated estimates from the SLUA were used in the acute and steady state dietary risk assessments for the following crops: dry beans and soybeans, 2.5%; cauliflower, 20%; celery, 70%; cotton, 35%; lettuce, 40%; peanuts, 10%; and peppers, 45%. 100% CT was assumed for all other crops including Brussels sprouts, mint, and cranberry as estimates were not available for these.

For the FHE use, an estimated maximum 5% (rounded from 4.65%) of establishments treated is used in the steady state assessment (BEAD, 10/7/2014, D413125, *Upper Bound Estimate of the Likelihood of Insecticide Residues on Food Resulting from Treatment in Food Handling Establishments*).

5.4.3 Acute Dietary Risk Assessment

The acute dietary (food only) exposure estimates are of concern (exceed 100% the aPAD) for the U.S. population and all population subgroups at the 99.9th percentile, except for the subgroup adults 50-99 years old (at 59% of the aPAD). The risk estimate for the U.S. population is 510% of the aPAD. The risk estimate for children 3-5 years old, the most highly exposed population subgroup, is 810% of the aPAD.

When the cotton drinking water scenario (which represents crops with *high-end* label rate) is used in the acute dietary (water only) assessment, risk estimates are of concern (>100% of the aPAD) for all population subgroups (except adults ages 50 and above) at the 99.9th percentile of exposure. The highest exposed subgroup is infants at 2400% of the aPAD. At the 95th percentile of exposure, acute risk estimates for drinking water using the cotton scenario are not of concern for any population subgroup.

When the celery drinking water scenario (which represents crops with *low-end* label rate) is used in the acute dietary (water only) assessment, risk estimates are of concern (>100% of the aPAD) for all population subgroups (except adults ages 50 and above) at the 99.9th percentile of exposure. The highest exposed subgroup is infants at 1000% of the aPAD. At the 95th percentile of exposure, acute risk estimates using the celery scenario are not of concern for any population subgroup.

A stepwise approach is used to calculate aggregate dietary (food and water) exposure and risk to a pesticide. If a risk of concern is identified for any population subgroup in any of the steps, the exposure and risk estimates for the "next step" of the assessment are not calculated since they

would also result in risks of concern. For acephate and methamidophos, the acute food and water exposures were not combined as this would result in even greater risk estimates of concern.

The results of the acute dietary assessments are presented in Tables 5.4.3.1 through 5.4.3.3.

Table 5.4.3.1. Results of Acute Dietary (Food Only) **Exposure and Risk Analysis.**

Population Subgroup	aPAD [1] (mg/kg/day)	95th Percentile		99th Percentile		99.9th Percentile	
		Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
General U.S. Population	0.0003	0.000072	24	0.000190	63	0.001520	510
All Infants (<1 year old)		0.000082	27	0.000147	49	0.000434	140
Children 1-2 years old		0.000147	49	0.000255	85	0.001210	400
Children 3-5 years old		0.000110	37	0.000246	82	0.002432	**810**
Children 6-12 years old		0.000072	24	0.000166	55	0.000843	280
Youth 13-19 years old		0.000052	17	0.000140	46	0.000897	300
Adults 20-49 years old		0.000058	19	0.000191	64	0.001526	510
Adults 50-99 years old		0.000050	1.7	0.000194	6.5	0.001781	59
Females 13-49 years old		0.000054	18	0.000169	56	0.001208	400

[1]Includes 10X FQPA SF for all population subgroups except adults 50-99 years old. The aPAD for adults 50-99 years old is 0.003 mg/kg/day

Table 5.4.3.2. Results of Acute Dietary (Drinking Water Only-Cotton Use) **Exposure and Risk Analysis.**

Population Subgroup	aPAD [1] (mg/kg/day)	95th Percentile		99th Percentile		99.9th Percentile	
		Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
General U.S. Population	0.0003	0.000104	34	0.000508	170	0.002596	860
All Infants (<1 year old)		0.000193	64	0.001437	480	**0.007359**	**2400**
Children 1-2 years old		0.000143	48	0.000746	250	0.003787	1300
Children 3-5 years old		0.000124	41	0.000619	210	0.003195	1100
Children 6-12 years old		0.000086	29	0.000455	150	0.002315	770
Youth 13-19 years old		0.000069	23	0.000382	130	0.001949	650
Adults 20-49 years old		0.000106	35	0.000509	170	0.002583	860
Adults 50-99 years old		0.000111	3.7	0.000490	16	0.002448	82
Females 13-49 years old		0.000104	34	0.000511	170	0.002584	860

[1]Includes 10X FQPA SF for all population subgroups except adults 50-99 years old. The aPAD for adults 50-99 years old is 0.003 mg/kg/day

Table 5.4.3.3. Results of Acute Dietary (Drinking Water Only- Celery Use) **Exposure and Risk Analysis.**

Population Subgroup	aPAD [1] (mg/kg/day)	95th Percentile		99th Percentile		99.9th Percentile	
		Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
General U.S. Population	0.0003	0.000081	27	0.000395	130	0.001053	350
All Infants (<1 year old)		0.000135	45	0.001245	410	**0.003090**	**1000**
Children 1-2 years old		0.000112	37	0.000574	190	0.001596	530
Children 3-5 years old		0.000099	33	0.000492	160	0.001278	430
Children 6-12 years old		0.000068	23	0.000354	120	0.000982	330

Table 5.4.3.3. Results of Acute Dietary (Drinking Water Only- Celery Use) **Exposure and Risk Analysis.**							
Population Subgroup	**aPAD [1] (mg/kg/day)**	**95th Percentile**		**99th Percentile**		**99.9th Percentile**	
		Exposure (mg/kg/day)	**% aPAD**	**Exposure (mg/kg/day)**	**% aPAD**	**Exposure (mg/kg/day)**	**% aPAD**
Youth 13-19 years old		0.000054	18	0.000299	100	0.000866	290
Adults 20-49 years old		0.000083	28	0.000399	130	0.000992	330
Adults 50-99 years old		0.000090	3.0	0.000381	13	0.000902	30
Females 13-49 years old		0.000081	27	0.000402	130	0.001006	340

[1]Includes 10X FQPA SF for all population subgroups except adults 50-99 years old. The aPAD for adults 50-99 years old is 0.003 mg/kg/day

5.4.4 Steady State Dietary Risk Assessment

The DEEM acute two-day module was used to conduct highly refined steady state assessments using the steady state endpoint and 21-day forward-rolling water averages. These steady state (two-day average) assessments estimate 21-day ("steady-state") average daily food and drinking water exposures.

The steady state dietary (food only without Food Handling Establishment (FHE) use) exposure estimates are of concern (exceed 100% the ssPAD) for the U.S. population and all population subgroups at the 99.9th percentile, except for the subgroup adults 50-99 years old (at 43% of the ssPAD). The risk estimate for the U.S. population is 400% of the ssPAD. The risk estimate for children 3-5 years old, the most highly exposed population subgroup, is 580% of the ssPAD.

The steady state dietary assessment for food only with FHE uses included resulted in risk estimates similar to the steady state assessment for food only without the FHE uses. The risk estimate for children 3-5 years old, the most highly exposed population subgroup, is 580% of the ssPAD at the 99.9th percentile of exposure for both food including the FHE uses (exposure = 0.001754 mg/kg/day) and food without FHE uses (exposure = 0.001739 mg/kg/day). The exposures resulting from FHE uses do not contribute significantly to the overall food exposure.

When the cotton drinking water scenario (which represents crops with *high-end* label rate) is used in the steady state dietary (water only) assessment, risk estimates are of concern (>100% of the ssPAD) for all population subgroups (except adults ages 50 and above) at the 99.9th percentile of exposure. The highest exposed subgroup is infants at 1800% of the ssPAD. At the 95th percentile of exposure, steady state acute risk estimates for drinking water using the cotton scenario are not of concern for any population subgroup except for infants at 110% of the ssPAD.

When the celery drinking water scenario (which represents crops with *low-end* label rate) is used in the steady state dietary (water only) assessment, risk estimates are of concern (>100% of the ssPAD) for all population subgroups (except adults ages 50 and above) at the 99.9th percentile of exposure. The highest exposed subgroup is infants at 700% of the ssPAD. However, at the 95th percentile of exposure, steady state risk estimates using the celery scenario are not of concern for any population subgroup.

Since dietary exposures from food alone were of concern, drinking water exposures were not combined with exposures from food. Combining those exposures would result in even greater risk estimates of concern.

The results of the steady state dietary assessments are presented in Tables 5.4.4.1 through 5.4.4.4.

Table 5.4.4.1. Results of Steady State Dietary (Food Only with FHE) **Exposure and Risk Analysis.**

Population Subgroup	ssPAD [1] (mg/kg/day)	95th Percentile		99th Percentile		99.9th Percentile	
		Exposure (mg/kg/day)	% ssPAD	Exposure (mg/kg/day)	% ssPAD	Exposure (mg/kg/day)	% ssPAD
General U.S. Population	0.0003	0.000086	29	0.000207	70	0.001215	400
All Infants (<1 year old)		0.000108	36	0.000172	57	0.000393	130
Children 1-2 years old		0.000163	54	0.000258	86	0.001246	420
Children 3-5 years old		0.000128	42	0.000275	92	0.001754	**580**
Children 6-12 years old		0.000084	28	0.000167	56	0.000754	250
Youth 13-19 years old		0.000056	19	0.000137	46	0.000725	240
Adults 20-49 years old		0.000062	21	0.000206	68	0.001234	410
Adults 50-99 years old		0.000056	1.9	0.000218	7.3	0.001304	43
Females 13-49 years old		0.000059	20	0.000175	58	0.000932	310

[1]Includes 10X FQPA SF for all population subgroups except adults 50-99 years old. The ssPAD for adults 50-99 years old is 0.003 mg/kg/day

Table 5.4.4.2. Results of Steady Dietary (Food Only- No FHE) **Exposure and Risk Analysis.**

Population Subgroup	ssPAD [1] (mg/kg/day)	95th Percentile		99th Percentile		99.9th Percentile	
		Exposure (mg/kg/day)	% ssPAD	Exposure (mg/kg/day)	% ssPAD	Exposure (mg/kg/day)	% ssPAD
General U.S. Population	0.0003	0.000070	23	0.000194	65	0.001206	400
All Infants (<1 year old)		0.000086	28	0.000154	51	0.000373	120
Children 1-2 years old		0.000139	46	0.000230	77	0.001219	410
Children 3-5 years old		0.000106	35	0.000250	83	0.001739	**580**
Children 6-12 years old		0.000069	23	0.000153	51	0.000744	250
Youth 13-19 years old		0.000049	16	0.000131	44	0.000720	240
Adults 20-49 years old		0.000056	19	0.000200	67	0.001298	430
Adults 50-99 years old		0.000050	1.6	0.000212	7.1	0.001298	43
Females 13-49 years old		0.000052	17	0.000169	56	0.000925	310

[1]Includes 10X FQPA SF for all population subgroups except adults 50-99 years old. The ssPAD for adults 50-99 years old is 0.003 mg/kg/day

Table 5.4.4.3. Results of Steady State Dietary (Drinking Water Only- Cotton Use) **Exposure and Risk Analysis.**

Population Subgroup	ssPAD [1] (mg/kg/day)	95th Percentile		99th Percentile		99.9th Percentile	
		Exposure (mg/kg/day)	% ssPAD	Exposure (mg/kg/day)	% ssPAD	Exposure (mg/kg/day)	% ssPAD
General U.S. Population	0.0003	0.000134	45	0.000511	170	0.001688	560
All Infants (<1 year old)		0.000324	110	0.001420	470	**0.005401**	**1800**
Children 1-2 years old		0.000189	63	0.000743	250	0.002569	860
Children 3-5 years old		0.000166	55	0.000615	200	0.002026	680

Table 5.4.4.3. Results of Steady State Dietary (Drinking Water Only- Cotton Use) Exposure and Risk Analysis.							
Population Subgroup	ssPAD [1] (mg/kg/day)	95th Percentile		99th Percentile		99.9th Percentile	
		Exposure (mg/kg/day)	% ssPAD	Exposure (mg/kg/day)	% ssPAD	Exposure (mg/kg/day)	% ssPAD
Children 6-12 years old		0.000116	39	0.000449	150	0.001483	490
Youth 13-19 years old		0.000094	31	0.000377	120	0.001343	450
Adults 20-49 years old		0.000137	45	0.000508	170	0.001663	550
Adults 50-99 years old		0.000137	4.5	0.000498	17	0.001548	52
Females 13-49 years old		0.000135	45	0.000506	170	0.001705	570

[1]Includes 10X FQPA SF for all population subgroups except adults 50-99 years old. The ssPAD for adults 50-99 years old is 0.003 mg/kg/day

Table 5.4.4.4. Results of Steady State Dietary (Drinking Water Only- Celery Use) Exposure and Risk Analysis.							
Population Subgroup	ssPAD [1] (mg/kg/day)	95th Percentile		99th Percentile		99.9th Percentile	
		Exposure (mg/kg/day)	% ssPAD	Exposure (mg/kg/day)	% ssPAD	Exposure (mg/kg/day)	% ssPAD
General U.S. Population	0.0003	0.000109	36	0.000320	110	0.000725	240
All Infants (<1 year old)		0.000236	79	0.001024	340	**0.002118**	**700**
Children 1-2 years old		0.000153	51	0.000480	160	0.001076	360
Children 3-5 years old		0.000134	45	0.000389	130	0.000846	280
Children 6-12 years old		0.000094	31	0.000285	95	0.000653	220
Youth 13-19 years old		0.000075	25	0.000248	83	0.000555	190
Adults 20-49 years old		0.000111	37	0.000322	110	0.000666	220
Adults 50-99 years old		0.000114	3.8	0.000303	10	0.000624	21
Females 13-49 years old		0.000108	36	0.000328	110	0.000668	220

[1]Includes 10X FQPA SF for all population subgroups except adults 50-99 years old. The ssPAD for adults 50-99 years old is 0.003 mg/kg/day

5.4.5 Characterization of Dietary Risk

HED has conducted highly refined acute and steady state dietary (food only) exposure and risk assessments for acephate and methamidophos using DEEM version 3.18. These assessments are considered to be highly refined since they incorporate PDP monitoring data, estimated percent crop treated data, and default or empirical processing or cooking factors. The main contributor of exposures in the food only assessments is Brussels sprouts and bell peppers. Bell peppers had a significant number of detectable residues in PDP (16%). For Brussels sprouts, the use of field trial data with detectable residues and assuming100 PCT (as a PCT was not reported in the BEAD SLUA) results in an upper-bound risk estimate. Monitoring data for residues of acephate and methamidophos on Brussels sprouts, along with an estimated PCT would refine the anticipated residue on Brussels sprouts.

A quantitative dietary (drinking water) assessment was not performed for the non-agricultural uses of acephate. Application rates for non-agricultural uses range from 0.25 lb a.i./A (wasteland) to 162 lb a.i./A (non-residential building perimeter). Because many of the labels did not specify a maximum seasonal rate or the total number of applications that could be made, the calculated application rates and resulting EDWCs are likely overestimated. While it may be possible that some non-agricultural uses may result in drinking water exposures that are not of

concern, many of the non-agricultural uses would be expected to result in risk estimates of concern based on the calculated label rates.

6.0 Residential Exposure and Risk Estimates

ORE memo: K. Lowe, 3/28/18, D446403.

6.1 Residential Handler Exposure/Risk Estimates

All registered acephate product labels reviewed as part of Registration Review with residential use sites (e.g., lawns, indoor environments, garden and trees) require that handlers wear specific clothing (e.g., long sleeve shirt/long pants) and/or use personal protective equipment (PPE). Therefore, HED has made the assumption that these products are not for homeowner use, and has not conducted a quantitative residential handler assessment. It should be noted that HED has included these labels/uses in the occupational assessment, assuming the use of the required clothing and/or PPE on the labels.

6.2 Residential Post-application Exposure/Risk Estimates

There is the potential for post-application exposure for individuals exposed as a result of being in an environment that has been previously treated with acephate. Acephate can be used in areas frequented by the general population including residential ornamentals, golf courses, and indoor premises such as schools, hotels and hospitals. It can be used on residential lawns, but is limited to ant mound treatments only, which are considered perimeter/spot uses. While these types of uses can result in residues on turf, residential exposure is expected to be low; therefore, a quantitative residential post-application assessment was not conducted for these uses.

The quantitative exposure and risk assessment for residential post-application exposures is based on the following scenarios from the registered uses:

- Adult post-application dermal exposure from treated ornamentals,
- Children (6<11 years old) post-application dermal exposure from treated ornamentals,
- Adult post-application dermal exposure from contact with treated golf course turf,
- Children (6<11 and 11<16 years old) post-application dermal exposure from contact with treated golf course turf,
- Adult and children (1<2 years old) post-application inhalation exposure to vapors from treated indoor premises,
- Adults and children (1<2 years old) post-application dermal exposure from treated indoor premises, and
- Children (1<2 years old) post-application incidental oral exposure from treated indoor premises.

The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs[8]. While not the only lifestage potentially exposed for

[8] Available: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

these post-application scenarios, the lifestage that is included in the quantitative assessment is health protective for the exposures and risk estimates for any other potentially exposed lifestage.

DFR/TTR Data: A total of four chemical-specific DFR data sets have been submitted for acephate on the following crops/use sites: succulent beans (MRID 44763902), cauliflower (MRID 44763904), greenhouse roses (MRID 44763903), and tobacco (MRID 44763901). In addition, one TTR study has also been submitted (MRID 44806401). All five studies have been reviewed by HED and found to be acceptable for risk assessment. All of the studies measured both acephate and its degradate, methamidophos.

In order to assess residential post-application exposure to golf course turf, residue data from the TTR study were used. In order to assess residential post-application exposure to treated ornamentals, DFR data from the study on greenhouse roses were used. It should be noted that the predicted greenhouse rose DFR data (assuming a log linear regression) underestimated the measured residue value for the first few days of sampling (up until Day 3). Other analyses were conducted (non-linear regression and biphasic regression), but neither provided a better fit of the data. Therefore, in order to be protective of residential dermal post-application exposure right after application, HED conducted the exposure and risk calculations using the measured values.

For the indoor scenarios, where there are no available chemical-specific residue data, an assumption was made that 5% of the acephate residues would degrade to methamidophos. This assumption is based on a review of available TTR and DFR data for the OPs where both the parent and metabolite were measured in residue samples. Five percent was found to be the high-end value for the percent of parent that metabolized during the course of the residue studies. It should be noted that there is a level of uncertainty in using the assumption of 5% since it reflects the percentage of degradate formed outdoors.

Body Weight: For adults, when an endpoint is not sex-specific (i.e., the endpoints are not based on developmental or fetal effects) a body weight of 80 kg is typically used in risk assessment; however, in this case, a female-specific body weight of 69 kg was used. While the endpoint of concern, brain AChE inhibition, is not sex-specific, the female-specific body weight was used to protect for pregnant women due to uncertainty in the human dose-response relationship for neurodevelopmental effects[9]. Body weights of 57, 32, and 11 kg were used to assess exposure to children (11 to <16 years old), children (6 to <11 years old) and children (1 to <2 years old), respectively.

<u>Summary of Residential Post-application Non-Cancer Exposure and Risk Estimates</u>
Dermal post-application risk estimates were of concern for all scenarios associated with the use on ornamentals (dermal MOEs of 23 for adults and 40 for children 6 to 11 years; LOC = 1000) and for some scenarios associated with the use in indoor environments (dermal MOEs range from 34 to 1,500 for adults and 40 to 910 for children 1 to <2 years; LOC = 1000). Risks of concern were also identified for incidental oral exposure for children 1 to <2 years from the uses indoors (incidental oral MOEs range from 9.0 to 460; LOC = 1000). Dermal post-application risk estimates for adults and children (6 to 11 years and 11 to 16 years) exposed to treated turf from golfing are not of concern (MOEs range from 1,500 to 1,700). The risk estimates are

presented below in Table 6.2.1. Table 6.2.2 presents a total aggregate risk index (ARI) for the combined (across different routes) indoor scenarios for adults and children. The target ARI is 1; therefore, ARIs of less than 1 are risk estimates of concern.

Table 6.2.1. Residential Post-application Non-cancer Exposure and Risk Estimates for Acephate and Methamidophos.						
Lifestage	**Post-application Exposure Scenario**		**Application Rate[1]**	**Adjusted Residue Value or Mass Applied[2]**	**Combined (acephate + methamidophos) Dose (mg/kg/day)[3]**	**MOEs[4]**
	Use Site	**Route of Exposure (LOC)**				
Adult	Gardens (ornamentals)	Dermal (1000)	1 lb ai/A	Acephate: 0.81 ug/cm^2 Methamidophos: 0.028 ug/cm^2	6.41	**23**
Child 6< 11 years old					3.78	**40**
Adult	Golf Course Turf	Dermal (1000)	4.77 lb ai/A	Acephate: 0.12 ug/cm^2 Methamidophos: 0.00041 ug/cm^2	0.087	1,700
Child 11<16 years old					0.087	1,700
Child 6< 11 years old					0.10	1,500
Adult	Indoor Premises	Inhalation (300)	0.085 lb ai/gal and 0.5 gallons/day	Acephate: 19,295 mg Methamidophos: 964.75 mg	0.00016	310
Children 1 < 2 years old					0.00027	**190**
Adult	Indoor Premises (perimeter/spot coarse) CARPET	Dermal (1000)		Acephate: 4.5 ug/cm^2 Methamidophos: 0.225 ug/cm^2	4.5	**34**
Children 1< 2 years old		Hand-to-Mouth (1000)			3.7	**40**
		Object-to-Mouth (1000)			0.030	**9.0**
Adult	Indoor Premises (perimeter/spot coarse) HARD SURFACES	Dermal (1000)			0.013	**20**
Children 1< 2 years old		Hand-to-Mouth (1000)			1.5	**100**
		Object-to-Mouth (1000)			2.5	**61**
Adult	Indoor Premises (perimeter/spot pin stream) CARPET	Dermal (1000)		Acephate: 1.1 ug/cm^2 Methamidophos: 0.055 ug/cm^2	0.010	**27**
Children 1< 2 years old		Hand-to-Mouth (1000)			0.0088	**31**
		Object-to-Mouth (1000)			1.1	**140**
Adult	Indoor Premises (perimeter/spot pin stream) HARD SURFACES	Dermal (1000)			0.91	**170**
Children 1< 2 years old		Hand-to-Mouth (1000)			0.0074	**37**
		Object-to-Mouth (1000)			0.0032	**84**
Adult	Indoor Premises (crack/crevice) CARPET	Dermal (1000)		Acephate: 0.3 ug/cm^2 Methamidophos: 0.015 ug/cm^2	0.36	**410**
Children 1< 2 years old		Hand-to-Mouth (1000)			0.6	**250**
		Object-to-Mouth (1000)			0.0025	**110**
					0.0022	**130**
Adult					0.3	**500**
Children 1< 2 years old					0.25	**610**
					0.0020	**140**

Table 6.2.1. Residential Post-application Non-cancer Exposure and Risk Estimates for Acephate and Methamidophos.						
Lifestage	**Post-application Exposure Scenario**		**Application Rate[1]**	**Adjusted Residue Value or Mass Applied[2]**	**Combined (acephate + methamidophos) Dose (mg/kg/day)[3]**	**MOEs[4]**
	Use Site	**Route of Exposure (LOC)**				
		Object-to-Mouth (1000)			0.00088	**310**
Adult	Indoor Premises (crack/crevice) HARD SURFACES	Dermal (1000)			0.099	1,500
Children 1< 2 years old					0.16	**910**
		Hand-to-Mouth (1000)			0.00067	**410**
		Object-to-Mouth (1000)			0.00059	**460**

1 Based on registered labels (Appendix B).

2 Residue value from DFR or TTR study adjusted for differences in application rate for acephate and methamidophos between the studies and registered rates. For ornamentals, the predicted Day 0 DFR value representing an application rate of 2.15 lb ai/A from MRID 44763903 was used. For turf, the predicted Day 0 TTR value representing an application rate of 5 lb ai/A was used. For dermal and HTM exposure from indoor premises, default residue values of 4.5, 1.1, and 0.3 ug/cm^2 were used to represent perimeter/spot/bedbug (coarse), perimeter/spot/bedbug (pin stream), and crack and crevice applications, respectively. These residue values were not adjusted for percent active ingredient. For inhalation exposure to vapors, the total mass of acephate applied was calculated based on the residential handler inputs for indoor applications (i.e., application rate and amount handled).

3 Doses (mg/kg/day) for acephate and methamidophos were calculated separately using the equations provided in the 2012 Residential SOPs. The methamidophos dose was adjusted by the TAF of 400, 4.81, or 2.76 for dermal, inhalation or oral routes. The acephate and adjusted methamidophos doses were then summed together to estimate a combined dose.

4 MOE = POD (mg/kg/day) ÷ Dose (mg/kg/day) ; where the dermal POD = 150 mg/kg/day, inhalation POD = 0.05 mg/kg/day and oral POD = 0.272 mg/kg/day

Table 6.2.2. Combined (across routes) Post-application Risk Estimates for Acephate and Methamidophos.								
Lifestage / Scenarios		Inhalation MOE	Inhalation LOC	Dermal MOE	Dermal LOC	Incidental oral MOE	Incidental oral LOC	ARI[1]
Perimeter/ Spot Coarse - Carpet	Adults	310	300	**34**	1000	NA	NA	**0.03**
	Children 1 to <2 years old	**190**	300	**40**	1000	**9**	1000	**0.01**
Perimeter/ Spot Coarse - Hard Surface	Adults	310	300	**100**	1000	**NA**	NA	**0.09**
	Children 1 to <2 years old	**190**	300	**61**	1000	**27**	1000	**0.02**
Perimeter/ Spot Pin Stream - Carpet	Adults	310	300	**140**	1000	**NA**	NA	**0.12**
	Children 1 to <2 years old	**190**	300	**170**	1000	**37**	1000	**0.03**
Perimeter/ Spot Pin Stream – Hard surface	Adults	310	300	**410**	1000	**NA**	NA	**0.29**
	Children 1 to <2 years old	**190**	300	**250**	1000	**110**	1000	**0.07**
Crack and Crevice - Carpet	Adults	310	300	**500**	1000	**NA**	NA	**0.34**
	Children 1 to <2 years old	**190**	300	**610**	1000	**140**	1000	**0.10**
	Adults	310	300	1,500	1000	**NA**	NA	**0.61**

Table 6.2.2. Combined (across routes) Post-application Risk Estimates for Acephate and Methamidophos.								
Lifestage / Scenarios		Inhalation MOE	Inhalation LOC	Dermal MOE	Dermal LOC	Incidental oral MOE	Incidental oral LOC	ARI[1]
Crack and Crevice – Hard surface	Children 1 to <2 years old	**190**	300	**910**	1000	**410**	1000	**0.20**

[1] ARI = Aggregate Risk Index = 1÷ [(Inhalation LOC ÷ Inhalation MOE) + (Dermal LOC ÷ Dermal MOE) + (Incidental oral LOC ÷ Incidental oral MOE)].

6.3 Residential Risk Estimates for Use in Aggregate Assessment

Table 6.3.1 reflects the residential risk estimates that are recommended for use in the aggregate assessment. It should be noted that there are post-application exposures following outdoor and indoor applications that present risks of concern, and would not be applicable for aggregate risk assessment until risks are mitigated. For acephate, none of the scenarios for children 1 to <2 years old result in acceptable MOEs, therefore, a recommendation for that age group has not been made.

- The recommended residential exposure for use in the adult aggregate assessment reflects post-application dermal exposure from golfing on treated turf (dermal MOE = 1,700).
- The recommended residential exposure for use in the child 11<16 years old aggregate assessment reflects post-application dermal exposure from golfing on treated turf (dermal MOE = 1,700).
- The recommended residential exposure for use in the child 6<11 years old aggregate assessment reflects post-application dermal exposure from golfing on treated turf (dermal MOE = 1,500).

Table 6.3.1. Recommendations for the Residential Exposures for the Acephate Aggregate Assessment.

Lifestage	Exposure Scenario	Dose (mg/kg/day)[1]				MOE[2]			
		Dermal	Inhalation	Oral	Total	Dermal	Inhalation	Oral	Total
Adult	Post-application from golfing	0.087	--	N/A	0.087	1,700	--	N/A	1,700
Children 11<16 years old		0.087	--	N/A	0.087	1,700	--	N/A	1,700
Children 6<11 years old		0.10	--	N/A	0.10	1,500	--	N/A	1,500

1 Dose = the highest dose for each applicable lifestage of all residential scenarios assessed. Total = dermal + inhalation + incidental oral (where applicable).

2 MOE = the MOEs associated with the highest residential doses. Total = 1 ÷ (1/Dermal MOE) + (1/Inhalation MOE) + (1/Incidental Oral MOE), where applicable.

7.0 Non-Occupational Spray Drift Exposure and Risk Estimates

ORE memo: K. Lowe, 3/28/18, D446403.

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

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to

prevent them.[10] Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

In order to evaluate the drift potential and associated risks, an approach based on drift modeling coupled with techniques used to evaluate residential uses of pesticides was utilized. Essentially, a residential turf assessment based on exposure to deposited residues has been completed to address drift from the agricultural applications of acephate. In the spray drift scenario, the deposited residue value was determined based on the amount of spray drift that may occur at varying distances from the edge of the treated field using the AgDrift (v2.1.1) model and the *Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift Policy*. Once the deposited residue values were determined, the remainder of the spray drift assessment was based on the algorithms and input values specified in the recently revised (2012) *Standard Operating Procedures For Residential Risk Assessment (SOPs)*.

For acephate, chemical-specific TTR data are available, therefore, the estimated TTR are based on a chemical specific transferable residue as discussed in Section 5.0. Exposures to acephate and its degradate, methamidophos, were calculated separately. Once the estimated methamidophos exposures were calculated, the resulting values were adjusted by the TAF value of 400, and then added to the acephate exposures in order to calculate the risk estimates.

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

Combined Risk Estimates from Lawn Deposition Adjacent to Applications

[10] This approach is consistent with the requirements of the EPA's Worker Protection Standard.
[11] http://www.agdrift.com/

The spray drift risk estimates are based on an estimated deposited residue concentration as a result of the screening level agricultural application scenarios. Acephate is registered on various agricultural crops, Christmas tree plantations, non-crop areas, and sod farms. The calculations were conducted using the highest registered application rate for each use site. Most of the registered products are applied either via aerial, groundboom, airblast or with handheld equipment. The recommended drift scenario screening level options are listed below:

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

In addition to the screening level spray drift scenarios described above, additional results are provided which represent viable drift reduction technologies (DRTs) that represent potential risk management options. In particular, different spray qualities have been considered as well as the impact of other application conditions (e.g., boom height, use of a helicopter instead of fixed wing aircraft, crop canopy conditions).

Dermal risk estimates were calculated for adults. Dermal and incidental oral risk estimates for children (1 to <2 years old) were combined because the toxicity endpoint for each route of exposure is the inhibition of brain cholinesterase (ChE). The total applicable LOC is 1000, so MOEs < 1000 represent risk estimates of concern.

Adult dermal and children's (1 to < 2 year old) dermal and incidental oral risk estimates related to spray drift are of concern, and result in a range of buffers depending on the spray drift scenario. These are summarized in Table 7.0.1 (full results can be found in the ORE memo D446403). Results indicate that the major risk concern is from aerial applications. Appropriate drift reduction technologies such as changing the spray type/nozzle configuration to coarser spray applications may result in less drift and reduced risk concerns (i.e., higher MOEs) from aerial applications. Similarly, using coarser sprays and lowering boom height for groundboom sprayers reduces risk concerns.

Table 7.0.1. Summary of Spray Drift Buffers for Acephate.

Crop	Application rate (lb ai/A)	Adult Buffer Summary			Children 1 < 2 years Buffer Summary (Dermal + Incidental Oral)		
		Buffers Necessary to reach MOE of 1000			Buffers Necessary to reach MOE of 1000		
		Aerial	Groundboom	Airblast	Aerial	Groundboom	Airblast
Sod Farms	4.77	NA	0 - 10	NA	NA	50 - >300	NA
Non-bearing Citrus (airblast) Sod Farms (groundboom)	3.99	NA	0 - 10	0	NA	50 - 300	0-100

Table 7.0.1. Summary of Spray Drift Buffers for Acephate.							
Crop	Application rate (lb ai/A)	Adult Buffer Summary			Children 1 < 2 years Buffer Summary (Dermal + Incidental Oral)		
		Buffers Necessary to reach MOE of 1000			Buffers Necessary to reach MOE of 1000		
		Aerial	Groundboom	Airblast	Aerial	Groundboom	Airblast
Southern pine orchards	2.99	0 - 100	NA	NA	200 - >300	NA	NA
Tobacco	1.125	0	0	NA	75 - >300	10 - 75	NA
Typical and High Acreage Crops	1	0	0	0	75 - >300	10 - 75	0 - 50

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

ORE memo: K. Lowe, 3/28/18, D446403.

There are two available ambient air monitoring studies that specifically looked for acephate and methamidophos in ambient air. One was conducted by the California Department of Pesticide Regulation (DPR) and the other by the California Air Resources Board (CARB). DPR implemented a multi-year statewide air monitoring network to measure pesticides in various agricultural communities[12]. Results from the 2014 monitoring year contained information on acephate; however, out of 157 samples, no detections were reported for acephate. CARB conducted air monitoring in Fresno County in 2002[13], and detectable air concentrations were reported for acephate and methamidophos. The Agency has developed a preliminary bystander volatilization inhalation exposure assessment for acephate, and its degradate, methamidophos, using the currently available inhalation toxicity data and the CARB air monitoring data.

Ambient air monitoring typically is focused on characterizing the airborne pesticide levels within a localized airshed or community structure of some definition (e.g., city, township, or municipality). This type of monitoring effort also can be focused on capturing chronic background levels or other temporal characteristics of interest such as focusing on seasonal pesticide use patterns. Typically, samples are taken for 24 consecutive hours and collected at the same site over an extended period of time (e.g., several weeks or months). In contrast to application site air monitoring, information on the precise timing and location of pesticide applications are rarely collected in ambient air monitoring studies. However, this does not mean that an application did not occur near an ambient sampler during the monitoring period.

The CARB study monitored for the pesticides acephate and methamidophos in Fresno County from July 8 through August 23, 2002. Five sampling sites were selected in relatively high-population areas or in areas frequented by people (e.g., schools or school district offices, fire stations, or other public buildings). At each site, 28 discrete 24-hour samples were collected

[12] http://www.cdpr.ca.gov/docs/emon/airinit/amn_2014_report_final.pdf
[13] http://www.cdpr.ca.gov/docs/emon/pubs/tac/tacpdfs/acph_mtham02.pdf

during a 7-week sampling period. Collocated (replicate) samples were collected for seven dates at each sampling location.

Of the 168 ambient samples collected, one contained a concentration of acephate above the reported estimated quantitation limit (EQL) of 10 ng/m^3, and 10 contained concentrations of methamidophos above the reported EQL of 3.5 ng/m^3. Table 8.0.1 provides a summary of the combined acephate and methamidophos volatilization risk estimates for each site. The comparison of the mean air concentration values against the steady-state HEC is a reasonable match of the toxicological effect and exposure profile. This arithmetic mean comparison was completed to represent the potential for a seasonal exposure profile. In addition, with the conservative use of the steady-state endpoint to evaluate peak exposures from the ambient monitoring, none of the air sample concentrations resulted in risk estimates of concern.

Table 8.0.1. Residential Bystander: Preliminary Volatilization Risk Analysis for Acephate from Ambient Air Monitoring Data.

Study	# Sampling Sites	Number of samples[a]	Duration of samples	Duration of sampling period	Maximum Combined Air Concentration (mg/m^3)[b]	Arithmetic Mean Combined Air Concentration (mg/m^3)[b]	Single-Day MOEs[c] (LOC = 300)	Steady-state MOEs[d] (LOC = 300)
Ambient Air Monitoring								
Ambient Air Monitoring in Fresno County 2002	Five sampling sites	168	24-hour	7 weeks	7.70E-05	2.98E-05	6,600	17,000

a. For acephate, only one sample was above the estimated quantitation limit (EQL) of 10 ng/m^3. For methamidophos, 10 contained concentrations above the reported EQL of 3.5 ng/m^3.
b. Combined air concentration = acephate air concentration + (methamidophos air concentration * TAF of 4.81)
c. Single Day MOE = Steady-state HEC (0.508 mg/m^3) / Study maximum air concentration (mg/m^3). LOC = 300.
d. Steady-state MOE = Steady-state HEC (0.508 mg/m^3) / Study arithmetic mean air concentration (mg/m^3). LOC = 300.

9.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, when there are food uses of a chemical, aggregate risk assessments must be conducted that consider exposures from three major routes: oral, dermal, and inhalation. The main pathways of exposure for acephate include: dietary (food and water) and residential. In an aggregate assessment, exposures from relevant routes and pathways are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

9.1 Acute Aggregate Risk

The acute aggregate risk assessment combines exposures from food and drinking water. For acephate (and methamidophos), there are acute risk estimates of concern for food only and for water only. As a result, the food and water exposures are not combined (aggregated) as combining these exposures would result in even higher risk estimates of concern (see Section 5.4.3 Acute Dietary Risk Assessment).

9.2 Steady State Aggregate Risk

The steady state aggregate assessment combines dietary (food and water) exposures and residential exposures. There are steady state risk estimates of concern for food only and for water only (see Section 5.4.4 Steady State Dietary Risk Assessment). There are also residential risk estimates of concern for several residential uses (see Section 6.0 Residential Exposure and Risk Estimates). Combining the dietary exposures with residential exposures would result in even higher risk estimates of concern. Because of the risk concerns for both dietary and residential exposures, a quantitative steady state aggregate assessment was not conducted.

9.3 Cancer Aggregate Risk

Acephate is considered to be a possible human carcinogen. The quantification of risk using a non-linear approach (i.e., RfD) will adequately account for all chronic toxicity, including carcinogenicity, that could result from exposure to acephate.

10.0 Cumulative Exposure/Risk Characterization

OPs, like acephate, share the ability to inhibit AChE through phosphorylation of the serine residue on the enzyme leading to accumulation of acetylcholine and ultimately cholinergic neurotoxicity. This shared MOA/AOP is the basis for the OP common mechanism grouping per OPP's Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999). The 2002 and 2006 CRAs used brain AChE inhibition in female rats as the source of dose response data for the relative potency factors and PoDs for each OP, including acephate. Prior to the completion of Registration Review, OPP will update the OP CRA on AChE inhibition to incorporate new toxicity and exposure information available since 2006.

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

11.0 Occupational Exposure and Risk Estimates

ORE memo: K. Lowe, 3/28/18, D446403.

11.1 Occupational Handler Exposure/Risk Estimates

The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios which cover all the registered uses of acephate:

- Mixing/loading dry flowables (DF) to support aerial, groundboom, chemigation, and airblast applications;
- Mixing/loading DF pellets to support aerial, groundboom, chemigation, and airblast applications;
- Mixing/loading DF prills[14] to support aerial, groundboom, chemigation, and airblast applications;
- Mixing/loading water soluble packets (WSP) to support aerial, groundboom, chemigation, and airblast applications;
- Mixing/loading granulars to support aerial and tractor-drawn spreader applications,
- Mixing/loading liquids for tree injections;
- Applying sprays with aerial, groundboom, and airblast equipment;
- Applying granulars with tractor-drawn spreader;
- Applying ready-to-use (RTU) liquids via aerosol can;
- Flagging to support aerial spray applications;
- Mixing/loading/applying liquids, WSP and dry flowables via backpack;
- Mixing/loading/applying liquids, WSP and dry flowables via mechanically-pressurized handgun;
- Mixing/loading/applying liquids, WSP and dry flowables via manually-pressurized handwand;
- Loading/applying granulars via belly grinder, cup, rotary spreader, and spoon;
- Loading/applying paint slurry via paintbrush; and
- Commercial and on-farm seed treatment for cotton and peanuts.

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 in the occupational and residential exposure memo (D446403).

Body Weight: For adults, when an endpoint is not sex-specific (i.e., the endpoints are not based on developmental or fetal effects) a body weight of 80 kg is typically used in risk assessment; however, in this case, a female-specific body weight of 69 kg was used. While the endpoint of concern, brain AChE inhibition, is not sex-specific, the female-specific body weight was used to protect for pregnant women due to uncertainty in the human dose-response relationship for neurodevelopmental effects.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

[14] Prills are extruded pellets.

A total aggregated risk index (ARI) was used since the LOC values for dermal exposure (1000) and inhalation exposure (300) are different. The target ARI is 1; therefore, ARIs of less than 1 are risk estimates of concern. The aggregate risk index (ARI) was calculated as follows.

Aggregate Risk Index (ARI) = 1÷ [(Dermal LOC ÷ Dermal MOE) + (Inhalation LOC ÷ Inhalation MOE)]

Occupational handler dermal and inhalation exposure and risk estimates were calculated for the registered uses of acephate. The occupational handler exposure and risk estimates indicate that the dermal and inhalation risk estimates are of concern to HED (i.e., ARIs ≤ 1) for most scenarios assuming the use of label-required PPE (gloves and, in some cases, use of a PF5 respirator). A summary of occupational handler risk estimates is provided in Appendix C.

The following scenarios are of concern (i.e., ARIs <1) assuming the label-required PPE is worn:

- Aerial mixer/loaders
  - DF formulation: all scenarios
  - DF (pellets) formulation: all scenarios with application rates >1 lb ai/A and high acreage field crops
  - DF (prills) formulation: all scenarios except for nurseries and non-crop areas
  - Granulars: all scenarios
  - WSP: all scenarios except for nurseries, non-crop areas, non-bell pepper, and Christmas tree farms
- Airblast mixer/loaders:
  - DF formulation: all scenarios
  - DF (prills): all scenarios with application rates >1 lb ai/A
- Chemigation mixer/loaders:
  - DF formulation: all scenarios
  - DF (prill) formulation: all scenarios
  - WSP: all scenarios
- Groundboom mixer/loaders:
  - DF: all scenarios
  - DF (pellets): sod farm scenario at 4.77 lb ai/A
  - DF (prills): sod farms, golf courses, and high acreage field crops
  - WSP: sod farm scenario at 3.99 lb ai/A and high acreage field crops
- Tractor-drawn spreader mixer/loaders: all scenarios except golf course (tees and greens only)
- Applying via airblast: all scenarios
- Applying via groundboom: golf courses, sod, non-bearing citrus, and high acreage field crops
- Applying granulars via aerial: all scenarios
- Applying via tractor-drawn spreader: all scenarios except for golf courses (tees/greens)
- Applying via RTU aerosol cans: all scenarios
- Flagging for aerial applications: all scenarios, except for applications to nurseries
- Mixing/loading/applying via backpack: all scenarios except Christmas tree farms
- Mixing/loading/applying via manually-pressurized handwand (assuming PF5 respirator): indoor applications (food handling establishments, warehouses, childcare centers/school)

using either DF or WSP formulations
- Mixing/loading/applying via mechanically-pressurized handgun: all scenarios
- Loading/applying via belly grinder: all scenarios
- Loading/applying via rotary spreader: all scenarios
- Loading/applying via spoon: greenhouse and nursery stock applications
- Loading/applying via paintbrush: all scenarios
- Seed treatment: all activities except cotton seed planters

In all scenarios, inhalation exposure is driving the combined risk estimates, and in some cases, the addition of a respirator (either PF5 or PF10) and/or the use of engineering controls results in an ARI greater than 1. However, there are still some scenarios that do not reach an ARI of greater than 1 even with the highest level of PPE and/or engineering controls.

HED has no data to assess exposures to pilots using open cockpits. The only data available is for exposure to pilots in enclosed cockpits. Therefore, risks to pilots are assessed using the engineering control (enclosed cockpits) and baseline attire (long-sleeve shirt, long pants, shoes, and socks); per the Agency's Worker Protection Standard stipulations for engineering controls, pilots are not required to wear protective gloves for the duration of the application. With this level of protection, there are no risk estimates of concern for applicators.

The Agency matches quantitative occupational exposure assessment with appropriate characterization of exposure potential. While HED presents quantitative risk estimates for human flaggers where appropriate, agricultural aviation has changed dramatically over the past two decades. According the 2012 National Agricultural Aviation Association (NAAA) survey of their membership, the use of GPS for swath guidance in agricultural aviation has grown steadily from the mid 1990's. Over the same time period, the use of human flaggers for aerial pesticide applications has decreased steadily from ~15% in the late 1990's to only 1% in the most recent (2012) NAAA survey. The Agency will continue to monitor all available information sources to best assess and characterize the exposure potential for human flaggers in agricultural aerial applications.

11.2 Occupational Post-application Exposure/Risk Estimates

11.2.1 Occupational Post-application Inhalation Exposure/Risk Estimates

Agricultural/Foliar Uses: 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 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration

Review, the agency will utilize this analysis to determine if data (i.e., flux studies) or further analysis is required for acephate.

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.

Commercial Indoor Uses: Commercial applicators do not typically return to the treated areas after an indoor commercial pesticide application (sites such as warehouses, food handling establishments, and hotels, etc.) and thus an occupational post-application inhalation exposure assessment was not performed for commercial applicators.

Seed Treatment Uses: A post-application inhalation exposure assessment is not required for the seed treatment uses as exposure is expected to be negligible. Seed treatment assessments provide quantitative inhalation exposure assessments for seed treaters and secondary handlers (i.e., planters). It is expected that these exposure estimates would be protective of any potential low-level post-application inhalation exposure that could result from these types of applications.

11.2.2 Occupational Post-application Dermal Exposure/Risk Estimates

Occupational Post-application Dermal Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational post-application risk assessments. Each assumption and factor is detailed in the occupational and residential exposure memo (D446403).

A total of four chemical-specific DFR data sets have been submitted for acephate on the following crops/use sites: succulent beans (MRID 44763902), cauliflower (MRID 44763904), greenhouse roses (MRID 44763903), and tobacco (MRID 44763901). In addition, one TTR study has also been submitted (MRID 44806401). All five studies have been reviewed by HED and found to be acceptable for risk assessment. All of the studies measured both acephate and its degradate, methamidophos.

A summary of how the DFR data were used is summarized in Table 11.2.2.1.

Table 11.2.2.1. Summary of DFR Data Use in Occupational Post-application Assessment for Acephate.

Crop for which DFR data available	Location included in study	Crops for which DFR data used as surrogate
Tobacco (44763901)	North Carolina	Tobacco
Cauliflower (44763904)	California	Cauliflower, Brussels sprouts, Citrus
Succulent Beans (44763902)	Oregon	Beans, Celery, Cranberry, Lettuce, Mint, Peanut, Pepper, Soybean
Greenhouses Roses (44763903)	California	Cut flowers, Nursery crop, Greenhouse crop
Turf (44806401)	Florida	Golf courses, Sod

Occupational Post-application Non-Cancer Dermal Risk Estimates

The post-application exposure scenarios associated with the registered uses of acephate are summarized in Tables 11.2.2.2 through 11.2.2.6.

For the turf use sites, using the TTR data, there are risks of concern only for sod farms assuming application rates >4 lb ai/A. For these scenarios, MOEs reached acceptable levels at time points ranging from 3 to 7 days after application.

For the greenhouse/nursery crops using the greenhouse rose DFR data, there are risks of concern for all activities on the day of application. For these scenarios, MOEs reached acceptable levels at time points ranging from 2 to 13 days after application.

For the vegetable crops using the cauliflower DFR data, there are risks of concern for certain high contact activities on the day of application. For some of these scenarios, MOEs reached acceptable levels at time points ranging from 1 to 30 days after application; however, some scenarios still did not reach acceptable MOEs at 30 days.

For the vegetable crops using the succulent bean DFR data, there are risks of concern for all activities on the day of application. For these scenarios, MOEs reached acceptable levels at time points ranging from 1 to 19 days after application.

For tobacco using the tobacco DFR data, there are risks of concern for all activities on the day of application. For some of these scenarios, MOEs reached acceptable levels at time points ranging from 1 to 25 days after application; however, some scenarios still did not reach acceptable MOEs at 30 days.

Table 11.2.2.2. Acephate Occupational Post-application Risk Estimates Using Chemical-specific Data (Turf/MRID 44806401).							
Crop	Application Rate (lb ai/acre)	Activity	Transfer Coefficient (cm^2/hr)	DFR on 0DAT (ug/cm^2)[1]		MOE[2] (LOC = 1000)	
				Acephate	Methamidophos	0DAT	DAT on which MOE ≥ 1000 (MOE)
Golf Course	3.9	Maintenance, greens only	2500	0.096	0.00034	2,200	0
	3.9	Maintenance	3700	0.096	0.00034	1,500	0
	4.77	Maintenance, greens only	2500	0.118	0.00041	1,800	0
	4.77	Maintenance	3700	0.118	0.00041	1,200	0
	4.95	Maintenance, greens only	2500	0.122	0.00043	1,800	0
	4.95	Maintenance	3700	0.122	0.00043	1,200	0
Sod	3.02	Maintenance	6700	0.075	0.00026	1,100	0
		Harvesting, Slab					
		Transplanting/ Planting					
	3.99	Maintenance	6700	0.099	0.00034	**820**	3 (1,000)
		Harvesting, Slab					
		Transplanting/ Planting					
	4.77	Maintenance	6700	0.118	0.00041	**690**	7 (1,100)
		Harvesting, Slab					
		Transplanting/ Planting					

DAT = Day after treatment.

1 DFR = Residues of acephate and methamidophos from a turf study, adjusted to account for application rate differences.

2 MOE = POD (150 mg/kg/day) / Combined Dermal Dose. Where Combined Dermal Dose = acephate dose (mg/kg/day) + (methamidophos dose, mg/kg/day * 400), and daily dose = [DFR (µg/cm^2) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day] ÷ BW (69 kg).

Table 11.2.2.3. Acephate Occupational Post-application Risk Estimates Using Chemical-specific Data (Greenhouse Roses / MRID 44763903)							
Crop	Application Rate (lb ai/acre)	Activity	Transfer Coefficient (cm^2/hr)	DFR on 0DAT (ug/cm^2)[1]		MOE[2] (LOC = 1000)	
				Acephate	Methamidophos	0DAT	DAT on which MOE ≥ 1000 (MOE)
Floriculture Crop	0.75	Container Moving	230	0.607	0.021	**310**	2 (1,400)
		Pinching					
		Pruning, Hand					
		Weeding, Hand					
		Scouting					
		Transplanting					
		Irrigation (hand set)	1900			**38**	10 (1,300)
		Harvesting, Hand	4800			**15**	13 (1,200)
	0.99	Harvesting, Hand	230	0.801	0.028	**240**	2 (1,100)

Table 11.2.2.3. Acephate Occupational Post-application Risk Estimates Using Chemical-specific Data (Greenhouse Roses / MRID 44763903)							
Crop	Application Rate (lb ai/acre)	Activity	Transfer Coefficient (cm^2/hr)	DFR on 0DAT (ug/cm^2)[1]		MOE[2] (LOC = 1000)	
				Acephate	Methamidophos	0DAT	DAT on which MOE ≥ 1000 (MOE)
Nursery Crop (Ornamentals, Non-bearing Plants)		Pruning, Hand					
		Scouting					
		Container Moving					
		Weeding, Hand					
		Transplanting					
		Grafting					
		Propagating					
		Pinching					
		Tying/Training					
		Irrigation (hand set)	1900			**29**	11 (1,300)
Greenhouse Crop (Ornamentals, Non-bearing Plants)	1	Harvesting, Hand	230	0.809	0.029	**240**	2 (1,100)
		Pruning, Hand					
		Scouting					
		Container Moving					
		Weeding, Hand					
		Transplanting					
		Grafting					
		Propagating					
		Pinching					
		Tying/Training					

Bold MOE values are below the LOC of 1000. DAT = Days after treatment.

1 DFR = Residues of acephate and methamidophos from a greenhouse rose study, adjusted to account for application rate differences.

2 MOE = POD (150 mg/kg/day) / Combined Dermal Dose. Where Combined Dermal Dose = acephate dose (mg/kg/day) + (methamidophos dose, mg/kg/day * 400), and daily dose = [DFR (µg/cm^2) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day] ÷ BW (69 kg).

Table 11.2.2.4. Acephate Occupational Post-application Risk Estimates Using Chemical-specific Data (Cauliflower / MRID 44763904).							
Crop	Application Rate (lb ai/acre)	Activity	Transfer Coefficient (cm2/hr)	DFR on 0DAT (ug/cm^2)[1]		MOE[2] (LOC = 1000)	
				Acephate	Methamidophos	0DAT	DAT on which MOE ≥ 1000 (MOE)
Brussels Sprouts	0.99	Transplanting	230	0.331	0.005	2,500	0
		Scouting	330			1,700	0
		Irrigation (hand set)	1900			**300**	30 (1,000)
		Scouting	4200			**140**	>30
		Harvesting, Hand					

Table 11.2.2.4. Acephate Occupational Post-application Risk Estimates Using Chemical-specific Data (Cauliflower / MRID 44763904).							
Crop	Application Rate (lb ai/acre)	Activity	Transfer Coefficient (cm2/hr)	DFR on 0DAT (ug/cm^2)[1]		MOE[2] (LOC = 1000)	
				Acephate	Methamidophos	0DAT	DAT on which MOE ≥ 1000 (MOE)
		Topping					
		Weeding, Hand					
Cauliflower	0.99	Transplanting	230	0.331	0.005	2,500	0
		Scouting	330			1,700	0
		Thinning Plants					
		Weeding, Hand	1400			410	21 (1,000)
		Irrigation (hand set)	1900			300	30 (1,000)
		Scouting	4200			140	>30
		Harvesting, Hand					
		Tying/Training					
		Weeding, Hand					
Grapefruit (representative of citrus)	0.73	Orchard maintenance	100	0.244	0.004	7,800	0
		Weeding, Hand					
		Baiting/Trapping					
		Transplanting	230			3,400	0
		Scouting	580			1,300	0
		Pruning, Hand					
		Harvesting, Hand	1400			**560**	14 (1,000)
	0.99	Orchard maintenance	100	0.331	0.005	5,800	0
		Weeding, Hand					
		Baiting/Trapping					
		Transplanting	230			2,500	0
		Scouting	580			**990**	1 (1,000)
		Pruning, Hand					
		Harvesting, Hand	1400			**410**	21 (1,000)
	3.99	Orchard maintenance	100	1.334	0.019	1,400	0
		Weeding, Hand					
		Baiting/Trapping					
		Transplanting	230			**620**	11 (1,000)
		Scouting	580			**250**	>30
		Pruning, Hand	580	1.334	0.019	**250**	>30
		Harvesting, Hand	1400	1.334	0.019	**100**	>30

Bold MOE values are below the LOC of 1000. DAT = Days after treatment.

1 DFR = Residues of acephate and methamidophos from a cauliflower study, adjusted to account for application rate differences.

2 MOE = POD (150 mg/kg/day) / Combined Dermal Dose. Where Combined Dermal Dose = acephate dose (mg/kg/day) + (methamidophos dose, mg/kg/day * 400), and daily dose = [DFR ($\mu g/cm^2$) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day] ÷ BW (69 kg).

Table 11.2.2.5. Acephate Occupational Post-application Risk Estimates Using Chemical-specific Data (Succulent Bean / MRID 44763902).							
Crop	Application Rate (lb ai/acre)	Activity	Transfer Coefficient (cm^2/hr)	DFR on 0DAT (ug/cm^2)[1]		MOE[2] (LOC = 1000)	
				Acephate	Methamidophos	0DAT	DAT on which MOE ≥ 1000 (MOE)
Bean, dry, and Pea, dry	0.99	Scouting	1100	3.32	0.039	**62**	16 (1,100)
		Irrigation (hand set)	1900			**36**	19 (1,000)
Celery	0.99	Weeding, Hand	70	3.32	0.039	980	1 (1,200)
		Scouting	210			**330**	6 (1,000)
		Transplanting	230			**300**	7 (1,100)
		Harvesting, Hand	1100			**62**	16 (1,100)
		Irrigation (hand set)	1900			**36**	19 (1,000)
Cotton	0.99	Weeding, Hand	70	3.32	0.039	980	1 (1,200)
		Scouting	210			**330**	6 (1,000)
Cranberry	0.99	Pruning, Hand (shears)	70	3.32	0.039	980	1 (1,200)
		Weeding, Hand					
		Transplanting	230			**300**	7 (1,100)
		Harvesting, Hand (raking)	1100			**62**	16 (1,100)
		Scouting					
Lettuce, leaf	0.99	Weeding, Hand	70	3.32	0.039	980	1 (1,200)
		Thinning Plants					
		Scouting	210			**330**	6 (1,000)
		Transplanting	230			**300**	7 (1,100)
		Harvesting, Hand	1100			**62**	16 (1,100)
		Irrigation (hand set)	1900			**36**	19 (1,000)
Mint	0.99	Weeding, Hand	70	3.32	0.039	980	1 (1,200)
		Scouting	1100			**62**	16 (1,100)
		Irrigation (hand set)	1900			**36**	19 (1,000)
Peanut	0.99	Weeding, Hand	70	3.32	0.039	980	1 (1,200)
		Scouting	210			**330**	6 (1,000)
		Irrigation (hand set)	1900			**36**	19 (1,000)
Pepper, bell	0.99	Weeding, Hand	70	3.32	0.039	980	1 (1,200)
		Scouting	210			**330**	6 (1,000)
		Transplanting	230			**300**	7 (1,100)
		Harvesting, Hand	1100			**62**	16 (1,100)
		Tying/Training					
		Irrigation (hand set)	1900			**62**	19 (1,000)
Soybean	0.99	Weeding, Hand	70	0.677	0.039	980	1 (1,200)
		Scouting	1100			**62**	16 (1,100)

Bold MOE values are below the LOC of 1000. DAT = Days after treatment.

1 DFR = Residues of acephate and methamidophos from a succulent beans study, adjusted to account for application rate differences.
2 MOE = POD (150 mg/kg/day) / Combined Dermal Dose. Where Combined Dermal Dose = acephate dose (mg/kg/day) + (methamidophos dose, mg/kg/day * 400), and daily dose = [DFR (µg/cm^2) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day] ÷ BW (69 kg).

Table 11.2.2.6. Acephate Occupational Post-application Risk Estimates Using Chemical-specific Data (Tobacco / MRID 44763901).

Crop	Application Rate (lb ai/acre)	Activity	Transfer Coefficient (cm^2/hr)	DFR on 0DAT (ug/cm^2)[1]		MOE[2] (LOC = 1000)	
				Acephate	Methamidophos	0DAT	DAT on which MOE ≥ 1000 (MOE)
Tobacco	0.75	Weeding, Hand	90	1.72	0.033	**970**	1 (1,200)
		Scouting					
		Transplanting	230			**380**	10 (1,000)
		Harvesting, Hand	800			**110**	25 (1,100)
		Harvesting, Mechanically-assisted					
		Canopy Management					
		Irrigation (hand set)	1900			**46**	>30

Bold MOE values are below the LOC of 1000. DAT = Days after treatment.
1 DFR = Residues of acephate and methamidophos from a tobacco study, adjusted to account for application rate differences.
2 MOE = POD (150 mg/kg/day) / Combined Dermal Dose. Where Combined Dermal Dose = acephate dose (mg/kg/day) + (methamidophos dose, mg/kg/day * 400), and daily dose = [DFR (µg/cm^2) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day] ÷ BW (69 kg).

For use on cotton, HED has also assessed the post-application dermal exposure and risk estimates for workers involved in harvesting cotton bolls. Although most of cotton harvesting is done mechanically, there are still some activities with the potential for exposure that are associated with the harvesting of cotton. No chemical-specific data are available for the amount of residue available on the cotton bolls; i.e., dislodgeable boll residue (DBR) data. Such data are available from a study with the active ingredient tribufos; i.e., MRID 42701601. **Note: These data may be proprietary, and subject to the data protection provisions of FIFRA, and therefore, may trigger a data compensation issue between registrants.** Since the registered acephate labels include a 21 day pre-harvest interval for cotton, the best fit residue data used from MRID 42701601 was chosen from 21 days after harvest and then adjusted for the difference in application rates. All of the cotton harvesting activities resulted in MOEs ranging from 1,800 to 10,000, which do not exceed the LOC, and are therefore not of concern; see Table 11.2.2.7.

Table 11.2.2.7. Occupational Post-application Exposure and Risk Estimates for Cotton Harvesting Activities.

Mechanical Harvesting Activity	Appl. Rate (lb ai/A)	DBR (µg/g)[1]	Transfer Coefficient (g/hr)[2]	Dermal Dose[3] (mg/kg/day)	Dermal MOE[4]
Module Builder Operator	0.99	0.14	900	0.015	10,000
Picker Operator and Raker			2,400	0.04	3,800
Tramper			5,0500	0.084	1,800

1. Cotton Harvesting Dislodgeable Boll Residue (DBR) = Predicted DBR at 21 days using data in MRID# 42701601. Cotton boll residue adjusted for difference in application rate; assumed 5% degrades to methamidophos, and adjusted methamidophos residue for TAF of 400.
2. From Non-Foliar Transfer Coefficient Table: http://epa.gov/pesticides/science/exposac-policy-3-march2013.pdf
3. Daily Dose (mg/kg/day) = [DBR x Transfer Coefficient x Conv. Factor (0.001 mg/µg) x 8 hr/day] / Body Weight (69 kg).
4: Short- & Intermediate-term Margin of Exposure (MOE) = Short-term Dermal NOAEL (150 mg/kg/day) / Daily Dose (mg/kg/day).

Restricted Entry Interval (REI)

Current acephate products require a 24 hour REI. Based on the current post-application dermal exposure assessment (Tables 11.2.2.2 – 11.2.2.6), REIs of 12 hours to more than 30 days would be necessary to reach acceptable MOEs (i.e., MOEs ≥ 1000) from exposure to the combined residues of acephate and methamidophos.

12.0 Incident/Epidemiology Report

Incident report memo: S. Recore *et al*, 9/30/2014, D423142.

HED performed an updated Tier I review of human incidents for acephate using the following data sources: OPP's Incident Data System (IDS) database, NIOSH SENSOR, the Agency-sponsored National Pesticide Information Center (NPIC), California's Pesticide Incident Surveillance Program (PISP).[15] HED found that the acute health effects reported for acephate are consistent among the databases queried. These health effects primarily include neurological, gastrointestinal, and respiratory effects. HED did not identify any aberrant effects outside of those anticipated. These effects are generally mild/minor to moderate and resolve rapidly.

[15] California PISP identified only two reported incidents. Both were due to suicide attempt and were not further reviewed.

The available incident data from IDS, NPIC, and SENSOR-Pesticides found that residential use is responsible for most of the reported incidents. In IDS, 55% of the reported exposures are due to homeowner mixing/loading and/or applying an acephate product. NPIC data show that residential post-application, followed by residential mixing/loading and applying are responsible for the most reported incidents (65% combined). In SENSOR-Pesticides, data show that residential routine outdoor living, followed by homeowner applying and routine indoor living account for 47% of the reported incidents.

Occupational incidents were also reported to IDS, NPIC and SENSOR-Pesticides. There was one occupational incident reported to IDS, where a warehouse worker was exposed to an open package of an acephate product. NPIC reported three occupational incidents, one due to equipment malfunction, one attributed to mixing/loading and applying acephate, and one incident involving 12 agricultural workers who experienced symptoms due to post-application exposure after reentering a tobacco field. SENSOR-Pesticides reports occupational incidents due to mostly routine work (including fieldwork), followed by application, mixing/handling, and manufacture/formulation.

The trend over time for acephate incidents reported to IDS from 2004 to 2013 was analyzed. The number of reported incidents, which are primarily non-occupational cases, appear to be decreasing over time. This may be reflective of the 2001 RED decision to mitigate residential post-application risk for acephate by deleting residential indoor uses, all turfgrass uses (except golf course, sod farm, and spot or mound treatment for ant control), and establishing a 3 day pre-harvest interval (PHI) for the harvesting of sod.

The chronic disease epidemiology literature search identified only a small number of studies investigating the potential role of pesticide exposure in adverse chronic health outcomes which presented a risk estimate for the OP acephate. The current chronic disease epidemiology database lacks compelling evidence of a role for acephate in either adverse birth outcomes (hypospadias and neural tube defects examined), or adult neurological functioning based upon long-term pesticide exposures. EPA will monitor the literature for additional studies in this area, and if new evidence is identified, the data will be reviewed as appropriate or in accordance with the chemical assessment schedule.

13.0 References

F. Fort, 4/10/97, Acephate. List A Case No. 0042. Chemical No. 103301. Registant's Response to Residue Chemistry Data Requirements. CBRS Nos. 17188, 17189, 17190, 17191, 17427, 17429, D225794, D225795, D225796, D225786, D228007, D227969.

S. Recore, *et al*, 9/30/2014, Acephate: Updated Tier I Review of Human Incidents for Preliminary Risk Assessment, D423142.

R.D. Jones, 3/21/2017, Preliminary Drinking Water Assessment for Registration Review of Acephate, D421707.

K. Lowe, 3/28/18, Acephate. Revised Occupational and Residential Exposure Assessment for Registration Review, D446403.

D. Drew, 3/20/2018, Acephate. Revised Acute and Steady State Dietary (Food and Drinking Water) Exposure and Risk Assessments to Support Registration Review, D446264.

D. Drew, 3/9/2018, Acephate. Revised Residue Chemistry Chapter in Support of Registration Review, D446265.

Appendix A. Toxicology Profile and Executive Summaries

A.1. Toxicology Data Requirements

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

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	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 90-Day Oral Toxicity in Rodents	yes	yes
870.3150 90-Day Oral Toxicity in Non-rodents	yes	yes
870.3200 21/28-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	-
870.3465 90-Day Inhalation	yes	yes [a]
870.3700a Prenatal Developmental Toxicity in Rodents	yes	yes
870.3700b Prenatal Developmental Toxicity in Non-rodents	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity in Rodents	yes	yes
870.4100b Chronic Toxicity in Non-rodents	yes	yes
870.4200a Carcinogenicity in Rats	yes	yes
870.4200b Carcinogenicity in Mice	yes	yes
870.4300 Chronic Toxicity/Carcinogenicity in Rats	yes	yes
870.5100 Mutagenicity—Bacterial Reverse Mutation Test	yes	yes
870.5300 Mutagenicity—Mammalian Cell Gene Mutation Test	yes	yes
870.5375 Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotoxicity in Hens	yes	yes
870.6100b 90-Day Neurotoxicity in Hens	yes	yes
870.6200a Acute Neurotoxicity Screening Battery in Rats	yes	yes
870.6200b 90-Day Neurotoxicity Screening Battery in Rats	yes	yes
870.6300 Develop. Neurotoxicity	yes	yes
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	yes	yes
870.7800 Immunotoxicity	yes	yes
Special Studies Comparative Cholinesterase in Rats	Yes	yes

[a] 4-Week study

A.2. Toxicity Profile

Summary of OPP's ChE Policy & Use of BMD Modeling

OPP's ChE policy (USEPA, 2000[16]) describes the manner in which AChE data are used in human health risk assessment. The following text provides a brief summary of that document to provide context to points of departure selected.

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

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

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

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

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

Table A.2.1. Results of BMD Modeling (mg/kg) for Brain and RBC ChE Data on Acephate, Acute Oral Dosing Studies in Rats.					
Test	**Age Sex**	**Brain BMD_{10}**	**Brain $BMDL_{10}$**	**RBC BMD_{10}**	**RBC $BMDL_{10}$**
MRID 46151801 Acute CCA	Adult Male	1.622 [a]	1.353	NE	
MRID 46151801 Acute CCA	Adult Female	QF		NDR	
MRID 46151801 Acute CCA	PND 11 Male	0.513	0.272	NE	
MRID 46151801 Acute CCA	PND 11 Female	1.205	0.704	NE	

[a] The BMD_{10} for adults were not accurately identified in the acute CCA based on empirical evidence; however, 13% inhibition of brain AChE was observed at the lowest dose tested (0.5 mg/kg/day) in both sexes
CCA = Comparative Cholinesterase Assay
NE = Not evaluated due to obvious lack of dose response
QF = Questionable fit, all statistical tests of fit were not passed and high variance was observed in the dose groups
NDR = No dose response found upon analysis

Table A.2.2. Results of BMD Modeling (mg/kg/day) for Brain and RBC ChE Data on Acephate, Repeated Oral Dosing Studies in Rats.					
Test (Dosing Days)	**Age Sex**	**Brain BMD_{10}**	**Brain $BMDL_{10}$**	**RBC BMD_{10}**	**RBC $BMDL_{10}$**
MRID 46151806 Repeated Dose CCA (11)	Adult Male	NF		NE	
MRID 46151806 Repeated Dose CCA (11)	Adult Female	NF		NE	
MRID 46151806 Repeated Dose CCA (11)	PND 11 Male	0.516	0.315	NE	
MRID 46151806 Repeated Dose CCA (11)	PND 11 Female	1.406	1.217	NE	
MRID 46151805 Gestational CCA (15)	Dam	0.436	0.317	NDR	
MRID 46151805 Gestational CCA (15)	Fetus Male	2.479	1.961	NF	
MRID 46151805 Gestational CCA (15)	Fetus Female	1.949	1.572	NF	
MRID 44203304 13-Week Subchronic Neurotoxicity (91)	Adult Male	0.295	0.199	2.864	1.385
MRID 44203304 13-Week Subchronic Neurotoxicity (91)	Adult Female	0.354	0.298	NA	
MRID 40504819 13-Week Oral Tox (91)	Adult Male	0.470	0.340	NDR	
MRID 40504819 13-Week Oral Tox (91)	Adult Female	0.433	0.359	2.164	1.636
MRID 00084017 104-Week Chronic Tox/Carc (819)	Adult Male	0.332	0.255	0.919	0.509
MRID 00084017 104-Week Chronic Tox/Carc (819)	Adult Female	0.494	0.381	1.132	0.728

CCA = comparative cholinesterase assay
NF = No model fit the data well
NE = Not evaluated due to obvious lack of dose response
NDR = No dose response found upon analysis
NA = Result considered not accurate
Tox = Toxicity
Carc = Carcinogenicity

Table A.2.3. Results of BMD Modeling (mg/kg/day) for Brain and RBC ChE Data on Acephate, Oral Toxicity in Dogs.					
Test (Dosing Week)	**Age Sex**	**Brain BMD_{10}**	**Brain $BMDL_{10}$**	**RBC BMD_{10}**	**RBC $BMDL_{10}$**
MRID 41812001 Chronic Oral Tox (52-53)	Adult Male	0.322	0.237	0.527	0.396
MRID 41812001 Chronic Oral Tox (52-53)	Adult Female	0.361	0.196	0.433	0.319

Table A.2.4. Results of BMD Modeling (mg/kg/day) for Brain and RBC ChE Data on Acephate, Dermal Toxicity in Rats.					
Test (Dosing Days)	**Age Sex**	**Brain BMD_{10}**	**Brain $BMDL_{10}$**	**RBC BMD_{10}**	**RBC $BMDL_{10}$**
MRID 44541101 21-Day Dermal Tox (21)	Adult Male	QF		NE	
MRID 44541101 21-Day Dermal Tox (21)	Adult Female	QF		QF	

QF = Questionable fit, all statistical tests of fit were not passed; also, high variance was observed in the dose groups and/or predicted BMD did not match empirical evidence
NE = Not evaluated due to an obvious lack of dose response

Table A.2.5. Results of BMD Modeling (mg/m^3) for Brain and RBC ChE Data on Acephate, Inhalation Toxicity in Rats. [a]					
Test (Dosing Days)	**Age Sex**	**Brain BMD_{10}**	**Brain $BMDL_{10}$**	**RBC BMD_{10}**	**RBC $BMDL_{10}$**
MRID 40504818 4-Week Inhalation Tox (29)	Adult Male	2.577	2.111	6.586	4.488
MRID 40504818 4-Week Inhalation Tox (29)	Adult Female	1.581	1.205	3.938	2.764

[a] The main exposure period consisted of 21 daily six-hour, whole-body exposures over a 30-day period.

Table A.2.6.1. Toxicity Profile of Acephate

Guideline No.	Study Type	MRID #	Results	Tox. Category	Study Classification
Acute Toxicity					
81-1	Acute oral LD_{50} – rat	00014675	945 mg/kg Males 866 mg/kg Females	3	Acceptable
81-1	Acute oral LD_{50} recalculation - rat	00029686	1.4 g/kg Males 1.0 g/kg Females	3	Acceptable
81-2	Acute dermal LD_{50} - rabbit	00055602	>10 g/kg	4	Acceptable
81-3	Acute inhalation LC_{50} - rat	00015307	>61.7 mg/L	4	Acceptable
81-4	Primary eye irritation - rabbit	00014686	Non-irritant	4	Acceptable
81-5	Primary dermal irritation - rabbit	00015305	PIS = 0.1 (Intact and abraded skin)	4	Acceptable
81-6	Dermal sensitization - guinea pig	00119085	Negative	---	Acceptable

Guideline No.	Study Type	MRID #	Results	Core Grade
Subchronic Toxicity				
82-1(a) 870.3100	90-Day feeding - rat (Special ChE inhibition study)	40504819	ChE NOAEL (RBC) = 0.58 mg/kg/day Males; 0.76 mg/kg/day Females ChE LOAEL (RBC) = 8.90 mg/kg/day Males; 11.48 mg/kg/day Females ChE NOAEL (brain) = <0.12 mg/kg/day Males; <0.15 mg/kg/day Females ChE LOAEL (brain) = 0.21 mg/kg/day Males; 0.15 mg/kg/day Females (LDT)	Acceptable

82-2 870-3200	21-Day dermal – rat	44541101	NOAEL = 12 mg/kg/day LOAEL = 60 mg/kg/day based on reduced brain ChE No dermal toxicity was seen.	Acceptable

Guideline No.	Study Type	MRID #	Results	Core Grade
82-3 870-3465	4-Week inhalation – rat	40504818	Systemic NOAEL = 0.0108 mg/L Systemic LOAEL = 0.0936 mg/L based on tremors, miosis, decreased body weight and weight gain, and histopathological changes in the nasal cavity. ChE NOAEL (brain and erythrocyte) = <0.00105 mg/L (LDT) ChE LOAEL (brain and erythrocyte) = 0.00105 mg/L $BMD_{10}/BMDL_{10}$ for brain at 29 days = 2.58/2.11 mg/m^3 in males and 1.58/1.20 mg/m^3 in females. $BMD_{10}/BMDL_{10}$ for RBC at 29 days = 6.59/4.49 mg/m^3 in males and 3.94/2.76 mg/m^3 in females.	Acceptable
82-3 870-3465	4-Week inhalation – rat	40645903	Systemic NOAEL = 0.0005 mg/L HDT) ChE NOAEL (plasma, erythrocytes, and brain) = 0.0005 mg/L ChE LOAEL = >0.0005 mg/L (HDT)	Acceptable
Chronic Toxicity				
83-1(a)	1-Year chronic feeding/carcinogenicity study - rat	00084017 00101623	Systemic NOAEL = 2.5 mg/kg/day Males; >35 mg/kg/day Females Systemic LOAEL = 35 mg/kg/day based on neurotoxic signs, decreased body weight gain and food efficiency ChE (plasma, RBC, and brain) NOAEL = 0.25 mg/kg/day ChE (plasma, RBC, and brain) LOAEL = 2.5 mg/kg/day At 819 days: BMD_{10} = 0.332 mg/kg/day; $BMDL_{10}$ = 0.255 mg/kg/day in males BMD_{10} = 0.494 mg/kg/day; $BMDL_{10}$ = 0.381 mg/kg/day in females.	Acceptable

Guideline No.	Study Type	MRID #	Results	Core Grade
83-1(b) 870-4100	1-Year chronic feeding - dog	41812001	Systemic NOAEL = 3.11 mg/kg/day Systemic LOAEL = 20.16 mg/kg/day (HDT) based on decreases in hematological parameters, increase in thromboplastin time, increase in absolute liver weight and histological changes in the liver ChE NOAEL (brain) = <0.27 mg/kg/day Male; 0.27 mg/kg/day Female ChE LOAEL (brain) = 0.27 mg/kg/day Male (LDT); 3.11 mg/kg/day Female (LDT) ChE NOAEL (RBC) = 0.27 mg/kg/day ChE LOAEL (RBC) = 3.11 mg/kg/day	Acceptable
83-5 870.4300	Chronic feeding/carcinogenicity - rat	00084017	No treatment related increases in tumor incidence	Acceptable
83-2(b)	Carcinogenicity - mouse	00105197, 00077209, 00105198, 00129156	Systemic NOAEL = 7 mg/kg/day Males; 8 mg/kg/day Females Systemic LOAEL = 36 mg/kg/day Males; 42 mg/kg/day Females based on body weight gains, decreased (in males) or increased (in females) weights of livers, decreased weights of kidneys, and non-neoplastic lesions in liver and lungs At 167 mg/kg/day (HDT), increased incidence of hepatocellular carcinomas in female mice was found	Acceptable
Developmental/Reproductive Toxicity				
83-3(a)	Developmental toxicity study - rat	41081602	Maternal Toxicity NOAEL = 5 mg/kg/day LOAEL = 20 mg/kg/day based on reduced body weights, body weight gains, food consumption, and food efficiency Developmental Toxicity NOAEL = 20 mg/kg/day LOAEL = 75 mg/kg/day based on decreases in mean numbers of ossification centers per litter	Acceptable

Guideline No.	Study Type	MRID #	Results	Core Grade
83-3(b)	Developmental toxicity study - rabbit	00069684 00069683	Maternal Toxicity NOAEL = 3 mg/kg/day LOAEL = 10 mg/kg/day (HDT) based on increased abortions Developmental Toxicity NOAEL = >10 mg/kg/day (HDT)	Acceptable
83-4	Multi-generation reproduction study - rats	40323401 40605701	Parental Toxicity NOAEL = 2.5 mg/kg/day LOAEL = 25 mg/kg/day based on decreased body weights and/or weight gains Reproductive Toxicity NOAEL = 2.5 mg/kg/day LOAEL = 25 mg/kg/day based on decreased viability index (two generations and mating performance (one generation)	Acceptable
Neurotoxicity				
81-7	Acute delayed neurotoxicity - hens	00154884	No delayed neurotoxicity was found in the treated hens. However, cholinergic and neurotoxic effects occurred shortly after dosing and disappeared within 10 days. No lesions were observed in the sciatic nerve which included diarrhea, lethargy, limb weakness, and loss of coordination.	Acceptable
	Acute range finding neurotoxicity - rats	44203301	Systemic toxicity NOAEL = 5 mg/kg LOAEL = 25 mg/kg based on clinical signs such as lacrimation altered gait, and constricted pupils RBC ChE NOAEL = 2.5 mg/kg Males; <5 mg/kg Females LOAEL = 5 mg/kg (both sexes) Brain ChE NOAEL = 0.5 mg/kg Males; <5 mg/kg Females LOAEL = 2.5 mg/kg Males; <5 mg/kg Females	Acceptable

Guideline No.	Study Type	MRID #	Results	Core Grade
81-8a	Acute neurotoxicity - rats	44203303	Neurotoxicity NOAEL = <10 mg/kg LOAEL = 10 mg/kg (LDT) based on whole body tremors, decreased rotarod performance ChE NOAEL = <10 mg/kg ChE LOAEL = 10 mg/kg based on plasma, RBC, and brain ChE inhibition	Acceptable
82-7	Subchronic neurotoxicity - rats	44203304	Systemic toxicity NOAEL = 0.41 mg/kg/day Males; 0.33 mg/kg/day Females LOAEL = 58.27 mg/kg/day Males; 49 mg/kg/day Females, based on increases in clinical signs Neurotoxicity NOAEL = 3.31 mg/kg/day Males; 3.95 mg/kg/day Females LOAEL = 48.6 mg/kg/day Males; 58.3 mg/kg/day Females, based on decreased rotarod time, and increased rearing. Erythrocyte ChE NOAEL = 3.31 mg/kg Males and 3.95 mg/kg Females ChE LOAEL = 48.6 mg/kg Males and 58.3 mg/kg Females Brain ChE NOAEL = <0.33 mg/kg Males; <0.41 mg/kg Females ChE LOAEL = 0.33 mg/kg Males; 0.41 mg/kg Females $BMD_{10}/BMDL_{10}$ for brain at 91 days = 0.295/0.199 mg/kg/day in males and 0.354/0.298 mg/kg/day in females.	Acceptable
Mutagenicity				
84-2 870.5100 870.5375 870.5550	Mutagenicity studies	00119080, 00028625, 00132948, 00132947, 000132949, 00132950, 00137738, 40209101, 00132953, 00119081, 00132955, 00132949, 00132954, 00028625	Fourteen acceptable mutagenicity studies were submitted. The results from the *in vitro* studies indicated that acephate was mutagenic in bacteria, yeast, and cultured mammalian cells. Acephate also caused recombination and gene conversion in yeast, SCE in a cultured mammalian cell line, and UDS in human fibroblasts. In general, genotoxicity was limited to high concentrations and exogenous metabolic activation (S9 microsomal fraction) was not required for a positive responses. Attempts to characterize the mutagenic component(s) of acephate by investigating a series of acephate samples of varying purities in the Ames test failed; mutagenicity in these studies did not decrease with increasing purity levels of the test material. Nevertheless, the data from the *in vivo* assays with acephate clearly showed that the genotoxic activity of acephate was not expressed in whole animals. Confidence in the negative findings, particularly for the mouse somatic cell and the dominant lethal assays, is high because of the response induced in the target organ.	Acceptable

Guideline No.	Study Type	MRID #	Results	Core Grade
Metabolism				
85-1	Metabolism study- rats	00014994	Acephate is rapidly and completely absorbed from the stomach and rapidly excreted in urine. Methamidophos was not detected in urine, and the author concluded that Methamidophos was only a plant and soil metabolite of acephate.	Acceptable
85-1	Metabolism study-rats	00014219	Acephate was rapidly absorbed and rapidly eliminated by the rats. There was no tendency for acephate to concentrate in blood, liver, muscle, fat, heart, or brain. Rats converted a portion of acephate to methamidophos. Evidence was presented that the conversion took place in the small intestine and, to a lesser extent, in the stomach, and was apparently produced by microorganisms.	Acceptable

NOAEL = No Observable Adverse Effect Level
LOAEL = Lowest Observable Adverse Effect Level
LDT = Lowest Dose Tested; HDT = Highest Dose Tested
ChE = Cholinesterase
Toxicity Profile was excerpted from the previous risk assessment (D259663, 10/14/1999) and not updated to the most current format.

Table A.2.6.2. Supplementary Toxicity Profile of Acephate [a]			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3200	21/28-Day dermal toxicity (Rat)	44541101 (1998) Acceptable, guideline Main study: 0, 12, 60, or 300 mg/kg/day for 21 days (6 hours per day, 5 days per week for 3 consecutive weeks) Pilot study: 0, 5, 50, 150, or 300 mg/kg/day for 5 days	NOAEL = 150 mg/kg/day LOAEL = 300 mg/kg/day based on brain AChEI in both sexes
870.3465	21-Day inhalation toxicity (Rat)	40504818 (1987) Acceptable, guideline in conjunction with MRIDs 40504817 and 40645903 0, 1.05, 10.8, and 93.9 mg/m^3 (21 six-hour daily exposures over a 30-day period)	BMD_{10} = 1.581 mg/m^3 (adult female brain) $BMDL_{10}$ = 1.205 mg/m^3
None	Acute CCA (Rat)	46151801 (2003) Acceptable, nonguideline 0, 0.5, 1, 2.5, or 10 mg/kg	BMD_{10} = 0.513 mg/kg/day (PND 11 male pup brain) $BMDL_{10}$ = 0.272 mg/kg/day
None	Repeated Dose CCA (Rat)	46151806 (2003) Acceptable, nonguideline 0, 0.5, 1, 2.5, or 10 mg/kg/day (11 daily doses)	BMD_{10} = 0.516 mg/kg/day (PND 11 male pup brain) $BMDL_{10}$ = 0.315 mg/kg/day
None	Gestational CCA (Rat)	46151805 (2003) Acceptable, nonguideline 0, 0.5, 1, 2.5, or 10 mg/kg/day on GD 6-21	BMD_{10} = 0.436 mg/kg/day (dam brain) $BMDL_{10}$ = 0.317 mg/kg/day

[a] Data concerning the Comparative Cholinesterase Assay (CCA) is provided as these data were evaluated since the previous risk assessment. Additionally, the dermal and inhalation study are presented, because these studies were used for the points of departure and the dermal study was revised.

Evaluation of MRID 00084017, a 104-week chronic toxicity/carcinogenicity study

Table A.2.7. Brain cholinesterase (Umol/g) inhibition in rats following oral dietary exposure to acephate.					
Dose group (mg/kg/day)	**Day**				
	49	**133**	**364**	**637**	**819**
Males					
0	15.6±0.9	12.1±1.2	12.1±1.2	10.8±0.5	10.8±0.4
0.2	14.2±0.7 (↓9)	11.6±0.9 (↓4)	10.5±1.0 (↓13)	10.8±0.7 (↓0)	9.8±0.6 (↓9)
2.4	10.2±0.9 (↓35)	8.0±1.1 (↓34)	7.1±1.2 (↓41)	6.2±0.5 (↓43)	6.8±1.2 (↓37)
38.2	3.6±0.5 (↓77)	3.8±0.3 (↓69)	3.6±0.5 (↓70)	3.0±0.3 (↓72)	3.3±0.4 (↓69)
Females					
0	14.0±0.7	13.1±0.6	11.9±1.1	10.8±0.6	10.8±0.4
0.3	12.2±2.7 (↓13)	11.7±0.3 (↓11)	11.3±0.5 (↓5)	10.7±0.5 (↓1)	9.8±0.6 (↓9)
3.1	7.7±0.5 (↓45)	8.2±0.7 (↓37)	8.0±1.1 (↓33)	6.5±0.4 (↓40)	6.8±1.2 (↓37)
47.2	2.4±0.2 (↓83)	3.5±0.5 (↓73)	3.5±0.5 (↓71)	3.7±1.6 (↓66)	3.3±0.4 (↓69)

n=4-10. BMD_{10}/$BMDL_{10}$ at 819 days = 0.332/0.255 mg/kg/day in males and 0.494/0.381 mg/kg/day in females.
NOAEL based on brain cholinesterase inhibition was reported as 0.25 mg/kg/day.
Percent inhibition is included in parenthesis.
Data were obtained from MRID 00084017, 104-week chronic toxicity/carcinogenicity study.

Empirically, 10% inhibition was noted at approximately 0.2 mg/kg/day in the male brain at Day 819. The $BMDL_{10}$ was determined to be 0.255 mg/kg/day. In this case, the NOAEL was reported to be 0.25 mg/kg/day.

Evaluation of MRID 40504818, a 4-week inhalation toxicity study

Table A.2.8. Brain and RBC cholinesterase (Umol/g) inhibition in rats following whole-body inhalation exposure to acephate (21 daily six-hour exposures over a 30 day period).					
Dose group (mg/m^3)	**Brain**		**RBC**		
	Day 16	**Day 29**	**Day 16**	**Day 17**	**Day 29**
Males					
0	70.9±3.16	62.5±8.22	6.7±0.30	5.7±0.30	5.9±0.53
1	60.0±1.91* (↓15)	58.0±5.59 (↓7)	5.9±0.31* (↓12)	5.6±0.56 (↓2)	5.7±0.42 (↓3)
10	NM	42.7±4.41* (↓32)	NM	4.8±0.25* (↓16)	5.0±0.73* (15)
100	NM	22.5±2.02* (↓64)	NM	1.8±0.30* (↓68)	1.9±0.46* (↓68)
Females					
0	69.8±4.32	60.1±5.40	6.4±0.46	5.4±0.84	5.9±0.72
1	61.4±3.70* (↓12)	53.6±4.60* (↓11)	5.7±0.28* (↓11)	5.5±0.29	6.3±0.91
10	NM	37.4±3.92* (↓38)	NM	4.4±0.52 (↓19)	4.7±0.85* (↓20)
100	NM	17.6±3.98* (↓71)	NM	1.8±0.62* (↓67)	1.6±0.47* (↓73)

n=5 at Day 16 and n=10 at Day 29. $BMD_{10}/BMDL_{10}$ for brain at 29 days = 2.58/2.11 mg/m^3 in males and 1.58/1.20 mg/m^3 in females. $BMD_{10}/BMDL_{10}$ for RBC at 29 days = 6.59/4.49 mg/m^3 in males and 3.94/2.76 mg/m^3 in females. NOAEL based on cholinesterase inhibition was reported as 1.05 mg/m^3.
Percent inhibition is included in parenthesis.
NM = Not measured
Data were obtained from MRID 40504818, 4-week inhalation toxicity study.

Empirically, 10% inhibition was noted between 1 and 10 mg/m^3 in the female brain at Day 29, and the response may not be linear. The $BMDL_{10}$ for female brain is 1.20 mg/m^3. In this case, the NOAEL was reported as 1.05 mg/m^3.

Evaluation of MRID 44203304, a 13-week subchronic neurotoxicity study

Table A.2.9. Brain cortex cholinesterase (U/g) inhibition in rats following oral dietary exposure to acephate.			
Dose group (mg/kg/day)	**Day**		
	21	**49**	**91**
Males			
0	14.65±1.11	14.44±0.77	14.96±1.60
0.33	12.29±0.88 (↓16)	12.98±1.05 (↓10)	12.33±1.00 (↓18)
3.31	8.26±0.36 (↓44)	7.83±0.62 (↓46)	7.57±1.38 (↓49)
48.63	2.9±0.31 (↓80)	2.6±0.14 (↓82)	2.93±0.68 (↓80)
Females			
0	13.26±1.41	13.89±2.22	14.81±1.13
0.41	12.37±1.18 (↓7)	13.56±0.93 (↓2)	12.76±0.83 (↓14)
3.95	8.11±0.41 (↓39)	7.77±0.66 (↓44)	7.29±0.56 (↓51)
58.27	2.51±0.31 (↓81)	2.67±0.17 (↓81)	2.82±0.35 (↓81)

N=6. BMD_{10}/$BMDL_{10}$ for brain at 91 days = 0.295/0.199 mg/kg/day in males and 0.354/0.298 mg/kg/day in females. LOEL based on cholinesterase inhibition was reported as 0.33 mg/kg/day (lowest dose tested). Percent inhibition is included in parenthesis.

Data were obtained from MRID 44203304, 13-week subchronic neurotoxicity study.

Empirically, 10% inhibition was less than the lowest dose tested in the male brain at Day 91, and the response may not be linear. The $BMDL_{10}$ for male brain is 0.199 mg/m^3. In this case, a NOAEL was not observed. BMDL's were lower than the lowest dose tested, and the Cholinesterase Inhibition Team did not have the greatest confidence in these values. However, these values were similar to other values at steady-state.

A.3. Hazard Identification and Endpoint Selection.

A.3.1. Acute Dietary, Acute Reference Dose (aRfD) - Females Age 13-49 and General Population

Study Selected: Acute CCA study
MRID No.: 46151801
Executive Summary: See Appendix A.4. Executive Summaries, Non-Guideline
Dose and Endpoint for Risk Assessment: $BMDL_{10}$ = 0.272 mg/kg/day based on inhibition of brain ChE in male pups on PND 11; BMD_{10} = 0.5128 mg/kg/day
Comments about Study/Endpoint/Uncertainty Factors: This study provided the lowest POD following a single dose. Statistical tests, visual inspection, and empirical evidence indicated appropriate modeling. A UF of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for the FQPA safety factor (incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4)) results in an aPAD of 0.0003 mg/kg/day; this (FQPA) factor may be excluded for the sub-population of adults 50-99

A.3.2. Steady-State Dietary, Chronic Reference Dose (ssRfD)

Same as A.3.1. above. This study was chosen, because it provided the lowest POD from the best modeled data sets. There were 2 longer term rats studies with slightly lower PODs (0.199 and 0.255 mg/kg/day), but these data sets did not model as well as the chosen study. Additionally, five other data sets from 4 studies also provided a $BMDL_{10}$ of approximately 0.3 mg/kg/day (0.298-0.358 mg/kg/day). The rationale for study selection is presented in greater detail in Section 4.8.

A.3.3. Incidental Oral Exposure (Steady-State)

Same as A.3.1. above for the reasons provided in brief for the steady-state dietary and in greater detail in Section 4.8.

A.3.4. Dermal Exposure (Steady-State)

Study Selected: 5-day and 21-day dermal rat toxicity studies in rats
MRID No.: 44541101 (data for 5-day pilot study are presented in Appendix M of the MRID)
Executive Summary: See Appendix A.7. Cholinesterase Inhibition of Acephate in Dermal Studies.
Dose and Endpoint for Risk Assessment: NOAEL = 150 mg/kg/day; LOAEL = 300 mg/kg/day based on brain cholinesterase inhibition in both sexes
Comments about Study/Endpoint/Uncertainty Factors: This study provided the lowest point of departure for the dermal route of exposure. BMD modeling results were questionable; therefore, the NOAEL approach was used. The use of an absorption factor with an oral study would be overly conservative. The rationale for study selection is presented in greater detail in Section 4.8. The total UF is 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation and 10X for FQPA/database uncertainty).

A.3.5. Inhalation Exposure (Steady-State)

Study Selected: 4-week inhalation toxicity study
MRID No.: 40504818

Executive Summary: See Appendix A.4. Executive Summaries, 870.3465 and Appendix A.8. Cholinesterase Inhibition from Acephate in Inhalation Studies.
Dose and Endpoint for Risk Assessment: $BMDL_{10}$ = 1.205 mg/m^3 based on inhibition of brain ChE in female adults on Day 29; BMD_{10} = 1.581 mg/m^3. HED ranges from 0.096 to 0.498 mg/kg/day, and HEC ranges from 0.00060 to 0.00251 mg/L.
Comments about Study/Endpoint/Uncertainty Factors: This study provided the lowest point of departure for the inhalation route of exposure. Statistical tests, visual inspection, and empirical evidence indicated appropriate modeling. The total UF is 300X (3X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA/database uncertainty). The interspecies factor was reduced from 10X to 3X, due to the HEC calculation accounting for pharmacokinetic interspecies differences. The rationale for study selection is presented in greater detail in Section 4.8.

A.4. Executive Summaries.

The following presentation is not all-inclusive.

A.4.1 Subchronic Toxicity

870.3100 90-Day Oral Toxicity – Rat

Not included in this report.

870.3100 90-Day Oral Toxicity – Mouse

Not included in this report.

870.3150 90-Day Oral Toxicity – Dog

Not included in this report.

870.3200 21/28-Day Dermal Toxicity – Rat

See Appendix A.7.

870.3465 90-Day Inhalation – Rat

In a subchronic inhalation toxicity study (MRID 40504818, 40504817), Acephate (assumed 100%, lots 1) SX-1725; 2) SX-1725, SX-1768) was administered by whole body exposure to Fischer 344 [CDF(F-344)/Crl BR] rats at concentrations of 0 (house air only), 1.05, 10.8, and 93.9 mg/m^3 (25/sex/group for controls, 15/sex/group for low dose, 10/sex/group for mid dose, and 20/sex/group for high dose). The main exposure period consisted of 21 six-hour exposures over a 30-day period (10 animals/sex/group). Five animals/sex from control and low dose groups received 12 exposures over a 16-day period, at which time they were sacrificed for determination of plasma, erythrocyte, and brain cholinesterase (ChE) activities. In addition, 10 animals/sex from control and high dose groups were retained for 4 additional weeks after cessation of exposure (recovery group).

At post-exposure observations, the study authors reported tremors and increased secretory responses in high dose males and females (data not provided). In addition, 2 high dose females exhibited tremors, and 6 exhibited polypnea during clinical observations. High dose females (7/10) exhibited miosis at week 4, and week 8 (2/10; recovery phase). High dose males (2/10) only had this at week 8.

Body weights were significantly less for high-dose females during the study and for mid dose females only at week 4 (week 4: 151, 156, 145*, 145* gm, control to high dose, respectively). Body weight gains were significantly decreased during weeks 0-4 for high dose males (88, 95, 99*, 79* gm, control to high dose, respectively) and females (43, 48*, 38, 36* gm, control to

high dose, respectively). There were treatment related effects in food consumption, hematology or clinical chemistry parameters (other than ChE).

Cholinesterase was only affected in the main study, not the range finding study. **Brain ChE** was significantly decreased in all treated animals at all time points in the main study, except for low-dose males at days 29-30 (range: 29-36% of controls for high-dose, 62-28% of controls for mid-dose, and 62-93% for low-dose during treatment; 83-84% of controls for high dose after the 4 week recovery period). **Plasma** and **erythrocyte ChE** activities were significantly inhibited for mid- and high-dose groups for males and females during the treatment phase (29-68% of controls for high-dose plasma; 62-90% of controls for mid-dose plasma; 27-33% of controls for high dose erythrocyte; 80-85% of controls for mid-dose erythrocyte). Erythrocyte ChE activity was inhibited in low-dose males and females on day 16 only (88-89% of control levels). During the recovery phase, plasma ChE activity was significantly inhibited in high-dose males only at day 44 (89% of control levels); erythrocyte ChE activity was inhibited in high-dose males and females (82-84% of control levels) at day 44; plasma and erythrocyte ChE activities returned to normal by day 59 for both sexes.

There were no treatment related gross pathological findings. Histopathological examination demonstrated increased incidence of "induced exudate in the lumen, suppurative inflammation, individual cell necrosis, and regenerative epithelium of the middle and posterior sections of nasal turbinate (nasal passages)" of high dose males and females. After the 4-week recovery period, histopathological findings included "reduced cellularity and intraepithelial cysts of the middle and posterior sections of nasal turbinates. No similar lesions were found in the mid dose group.

The systemic LOAEL is 93.6 mg/m^3 (0.0936 mg/L) based on tremors, miosis, decreased body weight and weight gain, and histopathological findings. The systemic NOAEL is 10.8 mg/m^3 (0.0108 mg/L).

The LOAEL for plasma ChE inhibition is 10.8 mg/m^3 (0.0108 mg/L). The NOAEL is 1.05 mg/m^3 (0.00105 mg/L).

The LOAEL for erythrocyte and brain ChE inhibition is 1.05 mg/m^3 (0.00105 mg/L). The NOAEL is < 1.05 mg/m^3.

This subchronic inhalation toxicity study in the rat is acceptable/guideline when combined with the range finding (MRID 40504817) and satellite (MRID 40645903) studies and satisfies the guideline requirement for a subchronic inhalation study OPPTS 870.3465; OECD 413 in the rat.

****

SATELLITE STUDY

In a subchronic inhalation toxicity study (MRID 40645903) Acephate (assumed 100%, lot SX-1768) was administered by whole body exposure to Fischer 344 [CDF(F-344)/Crl BR] rats at concentrations of 0 (house air only), 0.187, and 0.507 mg/m^3. The exposure period consisted of 21 six-hour exposures over a 30-day period (10/sex/group).

There were no treatment related effects on mortality, clinical signs, body weight, weight gain, food consumption, hematology, clinical chemistries, gross and histopathology, or ChE activities.

The systemic and ChE LOAEL is 0.507 mg/m^3 (0.0005 mg/L, HDT) and the systemic NOAEL is 0.507 mg/m^3.

This subchronic inhalation toxicity study in the rat is acceptable/guideline when combined with the range finding (MRID 40504817) and main (MRID 40504818) studies and satisfies the guideline requirement for a subchronic inhalation study OPPTS 870.3465; OECD 413 in the rat.

A.4.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study – Rat

In a developmental (teratology) study (MRID # 41081602), virgin female rats (Strain: Crl:CD®(SD)BR from Source: Charles River Breeding Laboratories, Inc., Raleigh, North Carolina) received either 0, 5, 20, or 75 mg/kg/day Acephate Technical (Purity: 99.7% a.i.; Lot No.: SX-1725) in reverse osmosis membrane processed deionized water (R.O. Deionized water) by oral gavage from gestation days 6 through 15.

The maternal animals of the high dose group presented with statistically significantly ($p \leq 0.01$) increased incidence of rats with tremors and decreased motor activity. The mid and high dose had reduced body weights and body weight gains during the dosing period (gestation days 6-16; 47.1-84.2% of control for body weight gains) the period including the post dosing period (gestation days 6-20; 80.4-90.3% for body weight gains and when corrected for gravid uterine weights; 37.3-71.0%) and the entire gestation period (gestation days 0-20; 86.3-92.0% for body weight gains and when corrected for gravid uterine weights; 71.2-84.2%). There was a rebound *in* body weights *in* the high dose group during the period following dosing (gestation days 16-20) and a decrease in body weight gain during the same period when corrected for gravid uterine weight. There was also reduced food consumption and food efficiency in the mid and high dose groups during the dosing period (73.1-92.4%; statistically significant reduced food consumption for both doses, statistics were not performed on food efficiency), for the dosing plus post dosing period (81.4-93.7%; statistically significant reduced food consumption for both doses) and for the entire gestation period (87.3-95.9%; statistically significant reduced food consumption for the high dose only).

The Maternal Toxicity NOEL was 5 mg/kg/day, and the Maternal Toxicity LOEL was 20 mg/kg/day based reduced body weights and body weight gain, reduced food consumption and reduced food efficiency.

Developmental Toxicity was noted in the high dose group as slight decreases in the mean number of ossified caudal vertebrae, sternal centers, metacarpals and the fore- and hindlimb phalanges with the hindlimb phalanges statistically significantly reduced. The Developmental Toxicity NOEL was 20 mg/kg/day, and the Developmental Toxicity LOEL was 75 mg/kg/day based on decreases in mean numbers of ossification centers per litter.

This study is classified as Acceptable-Guideline and satisfies the guideline requirements (§83-3a) for a teratology study in rats.

870.3700a Prenatal Developmental Toxicity Study – Rat

In a teratogenicity study (MRID # 00014695), 5 groups of female rats were administered by gavage of Orthene (Acephate) technical dissolved in distilled water (vehicle) at 0, 25, 50, 100 or 200 mg/kg/day (n=21, except n=22 at 200 mg/kg/day) from Day 6 through 15 of gestation. On Day 20 of gestation all females were sacrificed and maternal and fetal parameters evaluated.

At 200 mg/kg/day, 1 female died on the 6th day of treatment. Maternal weights decreased in all treated groups during the treatment period. Pregnancy rate was 21/21, 18/21, 17/21, 20/21, and 19/22 for 0, 25, 50, 100 and 200 mg/kg/day. 1.3 resorptions/female were noted at 200 mg/kg/day compared to 0.5 resorptions/female in controls. Caudal renal ectopia was observed at 100 (3/95) and 200 (3/65) mg/kg/day. Other malformations, such as small and large atria, appeared in control and treated groups.

The study was planned and executed satisfactorily. The study demonstrated that the test material given to pregnant rats by gavage resulted in maternal toxicity (decreased maternal body weight gain) at all dose levels used, decreased pregnancy rate in treated groups, increased embryo lethality at the high dose (increased Resorptions), and increased malformations (caudal renal ectopia) in fetuses of 100 and 200 mg/kg/day groups.

870.3700b Prenatal Developmental Toxicity Study – Rabbit

In this developmental toxicity study (83-3b; MRIDs: 00069684 [main study] and 00069683 [pilot study]), artificially inseminated and then chorionic gonadotropin-injected (to induce ovulation) Dutch Belted rabbits, 16/group, received by gavage 0, 1, 3 and 10 mg/kg/day of Technical RE-12420 (Acephate; purity: 92.8%) from gestation day (GD) 6 through 27. The test material was administered as an aqueous solution at a constant volume of 1 mL/kg of body weight. Doses selected for this study were based on the results of the pilot study in which doses of 3, 10, 30 and 100 mg/kg/day of Technical RE-12420 (purity: 92.8%) were tested; (40% deaths and 10% weight loss were observed on GD 24 in the 30 mg/kg group). In the current study, the rabbits were observed daily and weighed every 6 days, and also on day 28 before they were sacrificed. The following parameters were examined at study termination: (1) Gross necropsy on the dams; (2) Determination of the uterine weights, number of implantations, post implantation losses, resorptions, corpora lutea/dam, living and dead fetuses, and sex and body weights of fetuses; and (3) Examination of fetuses for malformations, variations and skeletal defects.

Two rabbits in the 10 mg/kg group aborted and were sacrificed and discarded without examination, one on GD 25 and another on GD 27. A slight increase in nasal discharge, possibly

treatment-related, was observed in the 3 and 10 mg/kg groups, when compared with the controls. With the exception of these two findings, Technical RE-12420 had no effect on the maternal and developmental (teratogenic, fetotoxic) parameters examined.

Based on 2/16 (12.5%) abortions in the high-dose group and none in the controls, the LOEL and NOEL for maternal toxicity are 10 mg/kg/day (HDT) and 3 mg/kg/day, respectively. The NOEL for developmental toxicity is > 10 mg/kg/day.

This study is Acceptable-guideline and satisfies the guideline requirement for the developmental (teratology) toxicity study in the rabbit (83-3b).

A.4.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects – Rat

In this 3-generation reproduction study (83-4; MRIDs: 40323401 [main study] and 40605701 [corrections]), Charles River rats, 30 males and 30 females/group, were fed diets containing Acephate Technical (purity: 98.7%) for 75 days before they were bred to produce F1a, F1b, F2a and F2b litters. Because of low fertility in all groups, including the controls, for the F1b and F2b litters, a third generation (F3a) was produced from the F2b litters. All rats were continuously exposed to the test material or the control diets either directly in their feed or through the mothers' milk during lactation. The nominal doses used were 0, 25, 50 and 500 ppm, and were based on the results of an earlier (1983) rat reproduction study (MRID 00129508) in which a reproductive NOEL was not determined. Using the FDA/HEW conversion factor (1 ppm in food = 0.05 mg/kg/day, for the older rat; Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, 1959), these doses were equivalent to 0, 1.25, 2.5 and 25 mg/kg/day, respectively. Parameters examined were those routinely examined in a multigeneration rat reproduction study.

Treatment-related effects were observed only in the 500 ppm group and included: (1) Decreased body weights and/or weight gains for adult males (in each generation) and females (in some generations) and for pups in the F2a and F3a generations; (2) Increases in food consumption for males and females during the premating period and decreases in food consumption for females during the gestation and lactation periods; (3) Clinical signs in males (increased incidence of alopecia in the first generation and increased incidence of soft or liquid stools in the second and third generations); (4) Decreases in mating performance for the F2b generation; (5) Decreases in mean litter size (25-30%, $p<0.01$) for the F1b, F2a, F2b and F3a generations; and (6) Significant ($p<0.01$) decreases in pup survival to day 4 for the F1a (3.2%) and the F2a (6.3%) generations.

Based on decreased body weights and/or weight gains for adult males (each generation), and for adult females and pups (some generations), decreased food consumption during gestation and lactation periods, and decreases in litter size (some generations), the parental LOEL and NOEL are 500 ppm (25 mg/kg/ day) and 50 ppm (2.5 mg/kg/day), respectively. Based on decreases in viability index (two generations) and in mating performance (one generation), the reproductive LOEL and NOEL are also 500 ppm (25 mg/kg/day) and 50 ppm (2.5 mg/kg/day), respectively.

This study is Acceptable-guideline and satisfies the guideline requirement for a reproduction study in the rat (83-4).

870.3800 Reproduction and Fertility Effects – Rat

In this 2-generation reproduction study (83-4; MRID 00129508), four-week old Charles River rats, 12 males and 23-24 females/ group, were fed diets containing Technical RE-12420 (Acephate; purity: 93%) for 15-17 weeks before they were mated to produce the F1 and F2 generations. The F2 offsprings were not fed RE-12424 and were not bred. The nominal doses used (based on preliminary studies) were 0, 50, 150 and 500 ppm. The actual intake of RE-12420 (calculated by the testing facility from the analytical content of RE-12420 in diets, food consumption and body weight) was 0/0, 3.30/3.43, 9.80/10.21 and 34.53/36.82 mg/kg/day for the F0/F1 control, low-dose, mid-dose and high-dose males, respectively. The corresponding values for the F0/F1 females were 0/0, 4.04/4.12, 12.13/12.35 and 41.82/45.12 mg/kg/day, respectively. Parameters examined were those routinely examined in a multigeneration rat reproduction study.

Various effects on reproduction (low pregnancy rate, high loss of total litters, high fetal losses, decreased size and weight of total litters, and decreased number of young born alive) were observed in rats fed 50 ppm (LDT) of the test material. Systemic effects noted in the 50 ppm group included decreased body weight gain in the females and decreased food utilization in males and females.

Based on the above findings, the reproductive NOEL is < 50 ppm (4.08 mg/kg/day; LDT) and the systemic NOEL is also < 50 ppm.

This study is Acceptable but does not satisfy the guideline requirement for the rat reproduction study (83-4) because the reproductive NOEL was not definitively determined.

A.4.4 Chronic Toxicity

870.4100a (870.4300) Chronic Toxicity – Rat

In a chronic feeding/carcinogenicity study (MRIDs 00084017 [main study] and 00101623 [additional data], Sprague-Dawley rats, 45 days old at study initiation, 75 males and 75 females/group, received Technical RE-12420 (Acephate; purity: 92.5%) in the diet for 28 months at the following nominal doses: 0, 5, 50 and 700 ppm. Using the FDA/HED conversion factor (1.0 ppm in food = 0.05 mg/kg/day, for the older rat; Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, 1959), these doses were equivalent to 0, 0.25, 2.5 and 35.0 mg/kg/day, respectively. No justification was presented for the selection of doses. Parameters examined for all rats in the study included daily observations, body weights, food consumption, food efficiency (during the first 8 weeks) ophthalmological examination, hematology, clinical chemistry (including cholinesterase [ChE] activities in plasma, erythrocytes [RBC] and brain), urinalysis, necropsy, histopathology of some 40 organs/tissues (including brain, eyes, spinal cord and sciatic nerve), organ weights and organ/body weight ratios (for adrenals, brain, heart,

kidneys, liver, lungs, spleen, testes/ovaries and thyroid gland - for all scheduled sacrifices). Plasma and RBC ChE activities were determined during weeks 6, 7, 19 and 28, and months 12, 18, 22, 24 and 28, using randomly selected 4, 5 or 10 rats/sex/group. Brain ChE activity was determined during weeks 7 and 19, and months 12, 22 and 28.

The following treatment-related findings were observed in the high-dose (700 ppm) male rats: (1) Hyperactivity in some (8%) of the males during the initial 5 months of the study; (2) Increased incidence of aggressive behavior (31% vs 5% in the controls), also during the initial 5 months of the study; (3) Decreased body weight gain (6-18%; p<=0.01) during study weeks 8-106, when compared with the controls; and (4) Significantly (p<=0.01) decreased food efficiency during the entire testing interval (weeks 1-8). Aggressive behavior was also observed in 13% of the low-dose and 13% of the mid-dose male rats.

Relative to the control values, plasma ChE activity was inhibited at all sampling times in the high-dose males (10-50%) and females (50-72%; p<=0.01). In the mid-dose group, the inhibitions were 0-29% for the males and 0-38% for the females. Plasma ChE activity was not inhibited in the low-dose males and slightly inhibited (0-19%) in the females. Erythrocyte ChE activity was decreased (p<=0.01) at all sampling times in the high-dose males (21-67%) and females (21-61%). In the mid-dose groups, ChE inhibitions in RBC were 0-31% and 0-42% for males and females, respectively. In the low-dose group, RBC ChE activity was decreased 0-13% (males) and 0-29% (females). Relative to the control values, the inhibitions of brain ChE activity in the low-dose, mid-dose and high-dose males were 0-13%, 34-43% and 69-77%, respectively. The corresponding values for the female rats were 1-13%, 33-45% and 66-83%, respectively. Most of these inhibitions were statistically significant (p<=0.01).

There was a higher incidence of adrenal medullary tumors (pheochromocytomas) in the treated male rats than in the concurrent control males. However, the reported incidences for the 5, 50 and 700 ppm groups (9.7, 15.5 and 12.2%, respectively) were within the historical control range. The historical incidence of medullary tumors was 0-20.3% and the concurrent incidence, 2.7%. All of the tumors, but two, in the current study were benign.

Based on the above findings, the systemic LOEL and NOEL for the male rats are 700 ppm (35 mg/kg/day) and 50 ppm (2.5 mg/kg/day), respectively. The systemic NOEL for the female rats is >700 ppm. The LOEL and NOEL for the inhibition of plasma, RBC and brain ChE activities in males and females are 50 ppm (2.5 mg/kg/day) and 5 ppm (0.25 mg/kg/day; borderline value), respectively. Technical RE-12420 (Acephate) was not carcinogenic in this study.

This study is Acceptable and satisfies the guideline requirement for the chronic feeding study (83-1a) and carcinogenicity study (83-2a) in the rat.

870.4100b Chronic Toxicity – Dog

In a chronic feeding study (MRID 41812001), beagle dogs (4.0-4.5 months old), 5/sex/group, received Acephate Technical (purity: 99.9%) in the diet for one year at the following (nominal) doses: 0, 10, 120 and 800 ppm (analytical values: 0, 0.27, 3.11 and 20.16 mg/kg/day,

respectively). Doses used in this study were based on the results of a 4-week preliminary study (No. HWA 2107-164) in which 8, 20, 250 500 ppm doses of Acephate Technical were tested. Parameters examined for all dogs in the current study included daily observations, physical and ophthalmological examinations, body weight gains, food consumption and utilization, hematology, clinical chemistry (including cholinesterase [ChE] levels in plasma, erythrocytes [RBC] and brain), urinalysis, necropsy, histopathology of some 40 organs/tissues (including brain, eyes, spinal cord and sciatic nerve), and absolute and relative (organ/terminal body weight and organ/brain weight ratios) weights for 12 organs. Plasma and RBC ChE levels were determined for all dogs during the study weeks -3, -2, -1, 4, 13, 26 and 52, whereas brain ChE levels were assayed only at study termination. Substrates used for ChE determinations were acetylthiocholine (RBC and brain) and butyrylthiocholine (plasma).

The primary treatment-related effect observed in this study was the inhibition of ChE levels in brain and RBC. Relative to the control values, brain ChE levels (µMol/g) were significantly ($p<0.05$) inhibited in all male groups (17, 53 and 66%, respectively) and in the mid-dose and high-dose female groups (49 and 66%, respectively). Erythrocyte ChE levels (µMol/mL) were significantly ($p<0.05$) inhibited in the mid-dose (42-55%) and high-dose (76-87%) groups of both sexes. Plasma ChE levels (µMol/mL) were inhibited in the mid-dose (13-18%) and high-dose (6-10%) male groups and in all female groups (6-30%), but the inhibitions were dose-unrelated and statistically insignificant. Despite severe brain ChE inhibition in the mid-dose and high-dose groups of both sexes, symptoms usually associated with ChE inhibition (tremors, ataxia) were not observed.

Other treatment-related statistically significant ($p<0.05$) effects were: (1) Decrease in RBC count (13-26%), hemoglobin concentration (14-21%) and hematocrit (6-9%), all in the high-dose males); (2) Increase in activated partial thromboplastin time (34-96%), in the high-dose males; (3) Increase in the absolute weight of liver, in the high-dose males (29%) and females (17%); and (4) Perivascular infiltration and pigment in the livers (reticuloendothelial cells) of one mid-dose male and most high-dose males and females.

Based on decreases in hematological parameters (RBC, hemoglobin and hematocrit), increase in thromboplastin time, increase in absolute liver weight and histological changes in the liver (perivascular infiltration and pigment in reticuloendothelial cells), the LOEL and NOEL for systemic effects are 20.16 mg/kg/day (800 ppm; HDT) and 3.11 mg/kg/day (120 ppm), respectively (both sexes). The LOELs for cholinesterase (ChE) inhibition are as follows: Brain: 0.27 mg/kg/day (10 ppm), LDT, (males) and 3.11 mg/kg/day (females); RBC: 3.11 mg/kg/day (both sexes); and Plasma: >20.16 mg/kg/day (both sexes). The NOELs for ChE inhibition are as follows: Brain: <0.27 mg/kg/day (males) and 0.27 mg/kg/day (females); RBC: 0.27 mg/kg/day (both sexes); and Plasma: 20.16 mg/kg/day (both sexes).

This study is Acceptable-guideline and satisfies the guideline requirements for the chronic feeding study in the dog (83-1b).

A.4.5 Carcinogenicity

870.4200a Carcinogenicity Study – Rat

See 870.4300 above.

870.4200b Carcinogenicity (Feeding) – Mouse

In a carcinogenicity study (MRIDs: 00105197 [main study]; and 00077209, 00105198 and 00129156 [additional data]), Charles River CD1 mice, 75/sex/group, were fed diets containing Orthene Technical (RE-12420; Acephate; purity: 92.6%) at nominal doses of 0, 50, 250 and 1000 ppm. The analytical doses were 0, 7, 36 and 146 mg/kg/day, respectively, for males and 0, 8, 42 and 167 mg/kg/day, respectively, for females. No explanation was given for the selection of dose levels. Ten mice/sex/group were sacrificed after 12 months of feeding the test material and the remaining mice, after 24 months. Parameters examined for all mice in the study included daily observations, body weight gains, food consumption, hematology (for 10 mice/sex/group at study termination), necropsy, histopathology of some 40 organs/tissues (including brain, eyes, spinal cord and sciatic nerve) at study termination, and absolute and relative (% of body weight) weights of brain with stem, heart, liver, gonads and kidneys (at study termination). Tissues from mice which died during the study or were sacrificed moribund were also examined microscopically.

Female mice, fed 1000 ppm (167 mg/kg/day) of Orthene Technical, had higher incidence of hepatocellular carcinomas (HC) and hyperplastic nodules (HN) than did the concurrent controls. The incidence of HC in the control, 50, 250 and 1000 ppm female groups was 1.3, 1.3, 0 and 15.8%, respectively. The corresponding values for the male groups were 5.3, 2.7, 4.0 and 4.0%, respectively. All of these HC were observed at the terminal sacrifice. The incidence of HN in the control, 50, 250 and 1000 ppm groups was 2.7, 1.3, 0 and 19.7%, respectively. The corresponding values for the male groups were 13.3, 9.3, 5.3 and 17.3%, respectively. Most of the nodules (14.5 and 12.0% in the 1000 ppm females and males, respectively) were observed at the terminal sacrifice. The incidence of HC in the historical controls (22 studies; 1630 CD1 mice) ranged from 0 to 6%.

Other treatment-related findings were: (1) Liver lesions (hypertrophy of hepatocytes, karyomegaly and intracellular inclusion bodies) in the mid-dose (250 ppm) and high-dose (1000 ppm) males and females; (2) Lung lesions (dark pigmented alveolar macrophages, eosinophilic foreign bodies and alveolar hyalinosis) and lesions in nasal cavity (acute rhinitis) in the mid-dose and high-dose males and females; (3) Significantly ($p<=0.01$) decreased body weight gains in the mid-dose males (8-11%) and females (6-14%) during the study weeks 52-104, and in the high-dose males (15-30%) and females (14-29%) during the study weeks 13-104, when compared with the controls; and (4) Significant ($p<=0.01$) changes in organ weights at the high-dose level in the males (smaller livers and kidneys) and the females (larger livers and smaller kidneys, brains and ovaries), when compared with the controls.

Based on decreased body weight gains, decreased (in males) or increased (in females) weights of livers, decreased weights of kidneys, and non-neoplastic lesions in liver and lungs, the systemic

LOEL is 250 ppm (mg/kg/day: 36 and 42) and the systemic NOEL is 50 ppm (mg/kg/day: 7 and 8). Based on the increased incidence of hepatocellular carcinomas in the 1000 ppm (167 mg/kg/day; HDT) females, Orthene Technical (Acephate) was carcinogenic to female mice in this study.

This study is Acceptable-guideline and satisfies the guideline requirements for the carcinogenicity study in the mouse (83-2b).

A.4.6 Mutagenicity

870.5100 Bacterial reverse mutation assay MRID 00028625 Acceptable/Guideline (in conjunction with MRID Nos. 00119080, 00132947, and 00132948)	*Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TAl00 were exposed (first assay) to 1-1000 µg/plate acephate (93.5%) ±S9. In a second assay, the same strains were exposed to 105000 µg/plate ±S9. Additional testing was carried out with TAl00 using dose ranges of 100010,000 µg/plate ±S9; and 2500-10,000 µg/plate ±S9, and with Escherichia coli WP2 (first assay: 1-1000 µg/plate ±S9; second assay: 500-10,000 µg/plate ±S9; third assay: 2500-10,000 µg/plate ±S9). Weak, reproducible positive responses (≤1.4-fold increase in number of revertants) were seen for *S. typhimurium* TAl00 at doses ≥5000 µg/plate ±S9 (the text indicates there was a noticeable effect at 2500 µg/plate) but there was no indication of a mutagenic response in the other *S. typhimurium* strains at up to 5000 µg/plate ±S9. Weak, but not reproducible, positive findings were also seen for *E. coli* WP2 (uvrA) at ≥5000 µg/plate ±S9. The S9 fraction was derived from Aroclor 1254-induced rat livers and the test material was delivered to the test system in either dimethyl sulfoxide or ethanol.
870.5100 Bacterial reverse mutation assay MRID 00119080 Acceptable/Guideline (in conjunction with MRID Nos. 00028625, 00132947, and 00132948)	*Salmonella tvphimurium* strains TA 98, TA 100 and TA 1537 were exposed to technical acephate. (92.9%) at concentrations ranging from 0.001 to 10 mg/plate ±S9 for TA 100, and 1-10 mg/plate ±S9 for TA 98 and TA 1537. Most of the assays were conducted using plate incorporation, but some spot tests were also performed. Because there was a weak positive response in TA 100, additional tests were conducted with this strain using both technical (92.9%) and analytical-grade acephate (99.3%) at doses of up to 50 mg/plate; it is not indicated whether these additional tests were conducted with or without S9. The S9 was derived from Aroclor-induced Sprague-Dawley rat livers. It is not certain whether or not the test material was delivered to the system in DMSO. There was an increased incidence of revertants in strain TA 100, both with and without S9 activation, but at relatively high doses (first assay: no indication of an increase at 1 mg/plate ±S9, but an increase in revertants: 1.6-fold increase - S9 and a 1.5-fold increase +S9, at the next dose level, 10 mg/plate). In a second assay with TA 100 and doses of 1-10 mg/plate -S9 there was a dose response with the peak response (1.5-fold) at 10 mg/plate. Additional testing with orthene technical (92. 9% acephate) showed dose-related increases ranging from 1.5-fold at 10 mg/plate to 1.9-fold at 50 mg/plate. Similarly, analytical grade orthene (99.3% acephate) induced l.8-fold and 2.2-fold increases in revertants at 20 and 50 mg/plate respectively. It is noted that the usual criterion for a positive response in strain TA 100 is a doubling in number of revertants. However, the reproducibility of the data suggests that the response is valid. There was no indication of any effect on strains TA 98 and/or TA 1537.

870.5100 Bacterial reverse mutation assay MRID 00132947 Acceptable/Guideline (in conjunction with MRID Nos. 00028625, 00119080, and 00132948)	Eight acephate technical samples, at doses usually ranging from 2 to 50 mg/plate, were tested for mutagenic activity in the absence of S9 activation in a partial Ames assay, utilizing *S. typhimurium* strain TA 100. Four of these acephate samples were also tested for mutagenic activity (at doses of 10 and 50 mg/plate) in the absence of S9 activation against *S. typhimurium* strains TA 98 and TA 1537. The test materials were delivered to the test system in distilled water. Seven of the eight samples showed mutagenic activity against strain TA 100 -S9; the one sample that was negative had a reported purity of 100%. The response at 50 mg/plate ranged from a 2.6-fold (samples SX-911 and SX-941) to a 1.8-fold (sample SX-357) increase in revertants vs. 120 revertants for the control. With the exception of the 100% pure sample (SX-976), no clear pattern of reduced mutagenic activity with increasing purity was noted. No activity was observed against strains TA 98 and TA 1537.
870.5100 Bacterial reverse mutation assay MRID 00132948 Acceptable/Guideline (in conjunction with MRID Nos. 00028625, 00119080, and 00132947)	Five acephate technical samples, at doses ranging from 2 to 50 mg/plate, were tested for mutagenic activity in the absence of S9 activation in a partial Ames assay utilizing *S. typhimurium* strain TA 100. A sixth acephate technical (SX-986, 99+%) was tested at considerably lower doses, ranging from 0.1 to 0.5 mg/plate. The test materials were delivered to the test system in distilled water. All six samples (including SX-986, 99+%) showed evidence (~1.8-fold increase in number of revertants at the highest dose tested vs. 145 mutants in controls) of mutagenic activity against strain TA 100 -S9 at the highest doses tested. The response ranged from a 2.6-fold increase at 50 mg/plate for sample SX-911 (99.6%) to 1.8-fold for sample SX-984 (92.6%), Hence, there was no trend of decreased genotoxicity with increasing purity. Test material SX-986 (99+%) was severely cytotoxic at doses above 0.5 mg/plate, whereas the other samples were tested at doses up to and including 50 mg/plate.
870.5200 Mouse visible specific locus MRID 40209101 Acceptable/Guideline	In a mouse somatic cell mutation assay (MRID 40209101) groups (ranging in number from 134-169) of C57Bl/B6 female mice which had been mated to T-strain males were fed diets during gestation days 8.5-12.5 containing 0 (negative control), 50, 200, 600 or 800 ppm technical acephate (98.8%). A positive control group received ethylnitrosourea (ENU) at 50 mg/kg. The mutagenic potential was determined from the number of pups having recessive color spots on lactation days l4 and 28. The test material was administered at a sufficiently adequate dose, as symptoms of toxicity (including tremors, hunched back, labored breathing) were observed in the majority of animals in both the 600 and 800 ppm groups. Thirty (23%) treatment-related maternal deaths occurred in the 800 ppm females. The total numbers of pups were decreased in the 600 and 800 ppm groups. Similarly, the percentages of pups surviving to day 28 in the diet control, positive control, 50, 200, 600 and 800 ppm groups were 80, 77, 77, 77, 25 and 26%, respectively. Significant ($p \leq 0.05$) decreases in pregnancy rates were observed in the 200 and 600 ppm groups. There was no indication of an increase in numbers of white midventral spots or recessive coat spots in any of the acephate-treated groups. The positive control group showed significant increases in both of these parameters.
870.5300 *In vitro* mammalian cell assay	Cultured L5178Y mouse lymphoma cells were exposed (±S9) to doses of acephate technical (93.5%) ranging from 2429-5000 µg/mL with 4-hr exposure

Mammalian cell gene mutation assay in cultures of mouse lymphoma (L5178Y) cells MRID 00137738 Acceptable/Guideline	time. The S9 homogenate was derived from Aroclor-induced rat livers. The test material was delivered to the test system in sterile deionized water. There was no evidence of cytotoxicity at the highest dose level of 5000 µg/mL. There were consistent and dose-related increases in the mutation frequency (>2x the solvent control value) observed at all dose levels of acephate, both in the presence and absence of metabolic activation. The positive controls elicited the appropriate responses.
870.5300 Gene Mutation *In vitro* mammalian cell assay Mammalian cell gene mutation assay in cultures of mouse lymphoma (L5178Y) cells MRID 00132950 Acceptable/Guideline	Cultured L5178Y mouse lymphoma cells were exposed (±S9) to doses of acephate technical (93.5%) ranging from 1000-5000 µg/mL with 4 hr exposure time. One S9 activated and two non-activated trials were performed following preliminary cytotoxicity tests utilizing doses ranging from l1000 µg/mL acephate +S9 and 1000-5000 µg/mL -S9. The S9 homogenate was derived from Aroclor-induced rat (Fischer 344) livers. The test material was delivered to the test system in DMSO. There was some evidence of cytotoxicity (69.1 to 85% relative suspension growth -S9; 69.1 to 72.6% relative growth +S9) at the highest dose level of 5000 µg/mL. There were consistent and generally dose-related increases in the mutation frequency (MF) to >2x the solvent control value observed at non-activated doses ≥2000 µg/mL. With S9, >2-fold increases in MF were seen at ≥3000 µg/mL. The positive controls elicited the appropriate responses.
870.5395 *In vivo* Cytogenetics Micronucleus assay in mouse bone marrow cells MRID 00132953 Acceptable/Guideline	In an *in vivo* bone marrow micronucleus assay in male Swiss mice, 8 animals/dose/sacrifice time were gavaged twice with technical acephate (93.5%) at doses of 2 x 75, 2 x 150 and 2 x 300 mg/kg. Doses were administered 24 hours apart. Bone marrow cells were harvested at 48, 72 and 96 hours after the first treatment. A positive control group of 8 males received 2 x 1000 mg trimethyl phosphate by ip injection, with sacrifice 48 hours after administration of the first dose. The dosage was on the basis of a published oral LD50 value for acephate in mice of 361 mg/kg; it is noteworthy that there were no mortalities in this study at even the highest dose level (2 x 300 mg/kg), although there was a "dose-related increase in weight loss in treated animals." Bone marrow smears were made, and 500 polychromatic erythrocytes (PCEs)/mouse were examined for micronucleated polychromatic erythrocytes (MPCEs). There was no significant increase in the frequency of MPCEs after any treatment time at any dose level of acephate. However, it is reported that elevated PCE to RBC ratios observed in all groups at 48 hours were thought to be an artifact. The pH of the stain was apparently lower than 6.8, giving very pale staining of mature cells, which were therefore difficult to count. A new pH meter electrode was used at 72 and 96 hours. This indicates the stain used for the 48-hr preparations was not optimal; however, since micronuclei normally stain so heavily, this would not have affected their detection.
870.5450 *In vivo* Cytogenetics Rodent dominant lethal assay MRID 00119081 Acceptable/Guideline	Groups of 12 male CD-1 mice/dose level were fed diets containing 0 negative control), 50, 500 or 1000 ppm acephate technical (99%) for five days, (equivalent to 5.8, 60 or 71 mg/kg/day) then each was mated with 2 CD-1 female mice/week over the next 8 weeks. A positive control group was injected i.p. with 0.3 mg/kg triethylenemelamine (TEM) shortly before the first mating. There were no consistent indications of any dominant lethal effects associated with dietary exposure to acephate in the parameters which were evaluated (including percentage of pregnant females, total number of implants, average number of implantation sites per female per male, early fetal deaths per group). The 1000 ppm acephate group had a reduced pregnancy index during week l

	(75% vs. a control value of 96%), but this was not statistically significant. The positive control group showed significant effects involving a number of these parameters for matings during the first 3 weeks. The highest dose level (1000 ppm) is adequate, based on an 18% weight loss during the week of dosing, and a marked (52%) decrease in food consumption during the week of dosage.
870.5550 Other Genotoxicity Unscheduled DNA synthesis in WI-38 human diploid cells MRID 00028625 Acceptable/Guideline	WI-38 cells were exposed to acephate ±S9 (3-hr exposure to acephate in the absence of S9; 1-hr exposure to acephate in the presence of S9; in both cases followed by subsequent 3-hr incubation with 3H-Thymidine and hydroxyurea). In the first assay, doses of acephate ranged from 0.1-1000 µg/mL ±S9; in the second assay doses of 125-2000 µg/mL -S9 and 250-4000 µg/mL +S9 were tested. DNA was extracted and its radioactivity was measured. In the first assay -S9, there was a slight (24%) increase in radioactivity at the highest dose level of 1000 µg/mL; in the second assay -S9, there was a 36% increase in radioactivity at 1000 µg/mL and a significant ($p<0.01$) 44% increase at 2000 µg/mL. Based on the evidence of dose responsiveness and this significant increase, the study was considered positive under non-activated conditions. There were no consistent indications of an effect +S9. The positive controls elicited appropriate responses.
870.5575 Other Genotoxicity *Saccharomyces* yeast reverse mutation assay and mitotic gene conversion MRID 00132949 Acceptable/Guideline	In two independently conducted *in vitro* mutagenicity assay with *Saccharomyces cerevisiae* D7, acephate (93.5%), at concentrations ranging from 1-5% ±S9 (first assay) and 3-5% ±S9 (second assay) was tested for its ability to induce crossing over, gene conversion and reverse mutation. Acephate induced mitotic crossing over and gene conversion, both with and without metabolic activation. The response for all three genetic endpoints was generally dose-related over the concentration range of 1-5%. The report states that acephate induced reverse mutations only in the presence of S9 (from Aroclor 1254-induced rat liver), but examination of the data suggests the possibility of a weak positive response -S9 as well.
870.5900 *In vitro* sister-chromatid exchange assay MRID 00132954 Acceptable/Guideline	Chinese hamster ovary (CHO) cells were exposed for 21.5 hrs to technical acephate at doses of from 8 to 2000 µg/mL without S9 activation, and for 2 hrs (with a wash and subsequent incubation) to doses of from 312.5 to 5000 µg/mL technical acephate with S9 activation. Dose levels were based on a preliminary cytotoxicity assay. The S9 fraction was derived from Aroclor 1254-induced male Fischer rat livers. The test material was delivered to the test system in 95% ethanol. There were statistically significant dose-response increases in the numbers of SCEs/chromosome, both without and with S9 activation. At the highest dose levels (2000 µg/mL -S9; 5000 µg/mL +S9) there were 3.97x and 1.28x the number of SCEs/chromosome as compared to the respective negative controls. Acephate technical (percentage active not reported) was found to be positive in this assay, both in the presence and absence of S9 activation. The positive controls elicited appropriate responses.

A.4.7 Neurotoxicity

870.6100 Delayed Neurotoxicity Study – Hen

In this acute delayed neurotoxicity study (81-7; MRID 00154884), 53-week old white leghorn hens were intubated with single doses of the following test substances: water (negative control), Acephate Technical, 785 mg/kg and TOPC (tri-o-tolyl phosphate; positive control), 600 mg/kg. Acephate (purity: 99%) was administered in water and TOPC (purity: 95%) in corn oil. After the initial dosing, the hens were observed for 21 days and then the negative control group and the Acephate-treated group were re-dosed with water and Acephate (785 mg/kg), respectively. Both groups were sacrificed 21 days later (on study day 43), whereas the TOPC-treated group was sacrificed after study day 21. All Acephate-treated hens received also an intramuscular injection of atropine sulfate at dosing and at 4, 8, 12 and 21 hours after dosing. The dose of 785 mg/kg (LD50) was selected by the sponsor and was based on the results of two acute oral LD50 studies conducted in February and March, 1985 and included in the main report).

Toxic signs observed in the Acephate-treated group were: (1) Mortality (9/16 or 56% hens died, due to cholinergic effects, during days 3-7 after dosing); (2) Weight losses after initial dosing and redosing; (3) Diarrhea, lethargy, weakness in lower limbs, loss of coordination, wing droop and reduced reaction to sound and movement - each sign occurring at about 3 hours after dosing and redosing, and persisting through day 10); (4) Ataxia (during the first 7 days after each dosing and decreasing in severity thereafter); and (5) Swelling (minimal) of axis cylinder of the sciatic nerve in one hen only.

In the TOPC-treated group, toxic signs (loss of coordination, weakness in lower limbs, ataxia and staggering gait) were observed during days 14-21 after dosing and increased in severity with time after exposure. Lesions (minimal to moderate) were observed mostly in the sciatic nerve and in all hens. These lesions included lymphocytic foci, swollen and fragmented axons, nerve fiber and myelin degeneration, and Schwann cell hyperplasia.

Based on the cholinergic and neurotoxic effects occurring shortly after dosing and disappearing within some 10 days and on the absence of lesions in the sciatic nerve (except for a slight swelling in one hen), Acephate Technical was negative for acute delayed neurotoxicity at 785 mg/kg (only dose tested). Based on the cholinergic and neurotoxic effects observed 14-21 days after dosing and increasing in severity with time, and on the prominent lesions in the sciatic nerve, in all hens, Tri-o-tolyl phosphate (TOPC; 600 mg/kg; positive control), caused acute delayed neurotoxicity.

This study is Acceptable-guideline and satisfies the guideline requirement for an acute delayed neurotoxicity study in the hen (81-7).

A.4.7 Neurotoxicity

870.6200 Acute Neurotoxicity Screening Battery

In the acute neurotoxicity study (81-8; MRID 44203303), ORTHENE® Technical (acephate; purity: 99%) was administered in a single gavage dose to groups of 30 male and 30 female non-fasted Sprague-Dawley rats (Crl:CD® BR strain). The doses used (0, 10, 100 or 500 mg/kg) were based on the results of two range-finding studies (MRID 44203301 and 44203302) and were administered as solutions in deionized water. Parameters examined included: (1) daily observations for changes in clinical condition - for all animals; (2) body weights before dosing, on dosing day (day 0), and on days 7 and 14 or 15 after dosing – for all animals; (3) functional observational battery (FOB), for 12 animals/sex/group - before dosing, at 2.5 hours after dosing ("peak effect"), and on study days 7 and 14; (4) locomotor activity (MA), after the completion of the FOB; (5) cholinesterase (ChE) activities in plasma, erythrocytes (RBC) and 6 brain regions (brain stem, cerebellum, cortex, hippocampus, midbrain and olfactory), for 6 animals/ sex/group/sampling time – before dosing, at 2. 5. hours after dosing, and on study days 7 and 14; (6) whole and regional brain weights for all ChE animals; (7) whole brain weights and brain dimensions for the FOB/MA animals; and (8) microscopic examination of selected central and peripheral nervous tissues from 5 animals/sex in the control and 500 mg/kg FOB/MA group, at the termination of the study (day 15).

The following treatment-related findings were observed in the 500 mg/kg and 100 mg/kg male and female groups: (l) whole body and/or limb tremors; ataxia, weakness in hindlimbs and repetitive movement of mouth and jaws; alterations in posture, gait and mobility; low arousal and no approach and touch responses; decreased rearing and motor activities, rotarod performance, and body temperature; increased righting reflex and time to first step; and lacrimation, salivation and soiled fur; (2) decreased body weight gains in males only (41-45% and 15% in the high-dose and mid-dose groups, respectively); and (3) inhibition of cholinesterase activities in plasma (86-88%), RBC (53-55%) and brain (the six regions tested: 83-88%). Findings observed only in the 500 mg/kg male and female groups were: increased catalepsy time and clonic convulsions; absence of the pinch, startle, pupil and olfactory responses; decreased hindlimb footsplay and forelimb and hindlimb grip strength; chromodacryorrhea; and clear or colored (tan, red, brown and/or yellow) staining/matting material on various body surfaces.

The following treatment-related findings were observed in the 10 mg/kg male and female groups: Whole body tremors (single occurrences) in one male and one female; inhibition of ChE activities in plasma (31-34%), RBC (18-19%) and brain region’s (37-48%); and decreased rotarod performance in males on day 0 (when compared with that of the controls).

Toxic signs occurred within 0.5-2.5 hours after dosing and persisted for 4-8 hours or longer, but were not observed during the next day (study day 1). Plasma and RBC ChE activities were inhibited significantly ($p<0.01$) only during the dosing day. Brain ChE activities were inhibited ($p<0.01$) during dosing day (all regions) , day 7 after dosing (all regions but olfactory) and day 14 (midbrain only) . Other parameters examined in this study were not affected by ORTHENE® Tech.

Based on the above findings, the LOEL and NOEL for neurotoxicity, for both sexes, are 10 mg/kg (LDT) and <10 mg/kg, respectively. The LOELs and NOELs for the inhibition of plasma, RBC and brain cholinesterase activities are also 10 mg/kg and <10 mg/kg, respectively.

This study is ACCEPTABLE and satisfies the guideline requirement for an acute neurotoxicity study in the rat (81-8).
2

870.6200 Subchronic Neurotoxicity Screening Battery

In a subchronic (13-week) neurotoxicity study (MRID # 44203304), Acephate (99% purity) was administered to Sprague Dawley rats (30/sex/group) at 0, 5, 50, or 700 ppm in the diet (mean compound intake was 0.33, 3.31, and 48.63 mg/kg/day for males, 0.41, 3.95, and 58.27 mg/kg/day for females, respectively) for 13 weeks. Body weights were recorded weekly, food consumption was recorded twice weekly, and clinical observations were recorded daily. Cholinesterase activity was determined in plasma, erythrocytes, and brain (6 regions) at Weeks 3, 7, and at study termination in 6 animals/sex/group. Neurobehavioral assessment (functional observation battery and motor activity testing) was performed in 12 animals/sex/group prior to compound administration and during Weeks 3, 7, and 12. Brain weights (whole brain and regional) were determined during Weeks 3, 7, and at study termination in non-perfused animals (6/sex/group). At study termination, 12 animals/sex/group were euthanized and perfused in situ for neuropathological examination; brain weights and measures were determined. Of the perfused animals, 5/sex for control and 700 ppm groups were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

The only effects seen at the 5 ppm dose were inhibition of brain cholinesterase (significant in at least one sex for all brain regions; inhibition ranged from 2 to 28%).

At 50 ppm dose, there was significant inhibition of brain cholinesterase in all regions for both sexes (ranging from 18-55%). Plasma cholinesterase was inhibited at 50 ppm for males and females at Week 3 (25-41%). Erythrocyte cholinesterase was not significantly inhibited, but was decreased by 26% in females at Week 3. Thus, the NOEL for plasma cholinesterase inhibition was 5 ppm, with a LOEL of 50 ppm. Other effects seen at 50 ppm included a slight increase in clinical signs, specifically hair loss.

At the 700 ppm dose, brain and plasma cholinesterase were significantly inhibited in both sexes at all time points (range 55-74% inhibition for plasma, 63-82% inhibition for brain). Erythrocyte cholinesterase was significantly inhibited in both sexes at all time points (37-46%) except for week 13 females (25% inhibition). Thus, the NOEL for erythrocyte cholinesterase was 50 ppm, with a LOEL of 700 ppm. Additional effects seen at 700 ppm included decreased body weight (males) and body weight gain (males and females); increased food consumption (when measured as g/kg/day); increased grooming, increased rearing, and decreased rotarod time in males; decreased motor activity in females.

Based on the effects seen in this study, the LOEL for systemic effects (increases in clinical signs) was 50 ppm (3.31 or 3.95 mg/kg/day for males or females, respectively), with a NOEL of 5 ppm (0.33 or 0.41 mg/kg/day for males and females, respectively). The LOEL for neurotoxicity (FOB findings and decreased motor activity) was 50 ppm (3.31 or 3.95 mg/kg/day for males or females, respectively), with a NOEL of 5 ppm (0.33 or 0.41 mg/kg/day for males and females, respectively). The LOEL for erythrocyte cholinesterase inhibition was 700 ppm (48.63 or 58.27 mg/kg/day for males or females, respectively), with a NOEL of 50 ppm (3.31 or 3.95 mg/kg/day for males or females, respectively). The LOEL for plasma cholinesterase inhibition was 50 ppm (3.3l or 3.95 mg/kg/day for males and females, respectively), with a NOEL of 5 ppm (0.33 or 0.41 mg/kg/day for males and females, respectively). The LOEL for brain cholinesterase inhibition was 5 ppm (0.33 or 0.41 mg/kg/day for males and females, respectively), with the NOEL less than 5 ppm (the lowest dose tested).

This study is classified as acceptable, guideline and satisfies the guideline requirement for a subchronic neurotoxicity study in the rat (82-7).

870.6300 Developmental Neurotoxicity Study

In a developmental neurotoxicity study (MRID 46151802), Acephate technical (99.2% a.i.; Lot #: AS 40s) in deionized water was administered daily by oral gavage to pregnant Crl:CD® (SD)IGS BR VAF/Plus® rats (25/dose) at doses of 0, 0.5, 1, or 10 mg/kg/day from gestation day (GD) 6 through lactation day (LD) 6. Additionally the F_1 pups were similarly dosed on postnatal days (PNDs) 7-21. Dams were allowed to deliver naturally and were sacrificed on LD 6. On PND 4, litters were standardized to 10 pups/litter (5 males and 5 females when possible); the remaining offspring were sacrificed and examined grossly and for cholinesterase activity. Subsequently, 10 pups/sex/group were allocated to Subsets 1-4 and up to 10 pups/sex/group to Subset 5. Selected subsets were examined for detailed clinical and functional observational battery, motor activity, auditory startle habituation, passive avoidance and water maze learning and memory tests, brain weight, neuropathology, and/or brain and blood cholinesterase determinations. Pups were weaned on PND 21, and all offspring were sacrificed by PND 71.

No treatment-related effect was observed on maternal mortality, clinical signs, abbreviated functional observations, body weight, food consumption, reproductive performance, and gross pathology.

The maternal NOAEL is 10 mg/kg/day (HDT). A maternal LOAEL is not established.

Treatment had no adverse effects on offspring survival, body weight, body weight gain, food consumption, clinical signs, FOB, developmental landmarks, auditory startle reflex, learning and memory, brain weights, brain morphology or neuropathology. Assessment for motor activity revealed a non-significant but dose-related decrease in the number of movements (↓19% at 1 mg/kg/day to ↓30% at 10 mg/kg/day) that was accompanied by non-significant but comparable dose-related decreases in time spent in movement (↓19% at 1 mg/kg/day to ↓28% at 10 mg/kg/day)

in females on Day 21. However, it was determined that no conclusions can be drawn regarding the effect of acephate on motor activity because the variability in the data was so high.

No treatment-related cholinesterase inhibition (ChEI) was seen in the brains, plasma or red blood cells of male or female pups at PND 4. On Day 21, dose-depended and statistically significant ChEI of the brain were seen. Inhibition at the low, mid and high dose groups were 29%, 34% and 62%, respectively, in males and 25%, 25%, and 58%, respectively, in females. There were also significant ($p<0.01$) reductions in plasma (46% in males and 43% in female) and RBC (50% in males and 63% in females) ChEI in males at the high-dose males at PND 21.

The offspring LOAEL is 0.5 mg/kg/day (LDT), based on statistically significant and dose-depended inhibition of brain cholinesterase activity in male and female pups on Day 21. An offspring NOAEL was not established.

This study is classified **Acceptable/Non-Guideline** and may be used for regulatory purposes. It does not, however, satisfy the guideline requirement for a developmental neurotoxicity study in rats (OPPTS 870.6300, §83-6); OECD 426 (draft) due to the inadequacies in the assessment of motor activity in the offspring and the pending comprehensive review of the positive control data.

A.4.8 Metabolism

870.7485 Metabolism – Rat

In a rat metabolism study (MRID 46366201), ^{14}C-S-methyl-labeled acephate (^{14}C-acephate; product # 516; lot # 000619; purity >95% a.i) in water was administered by oral gavage to Sprague-Dawley Crl:CD (SD)IGS BR rats (3 or 4 rats/sex/dose) at dose levels of 25 or 100 mg/kg. In the first phase of the study (Toxicokinetic Phase), two dose groups (Groups 1 and 2; each with 2 sub-groups) consisting of 6 animals per gender were treated with single doses at 25 or 100 mg/kg. Blood samples were collected from both dose groups of rats following dosing (Subgroup A: 0.5, 2, 8, 48, and 96 hours; Subgroup B: 1, 4, 24, 72, 168 hours), and the plasma was isolated. The toxicokinetic data obtained from Groups 1 and 2 were used to establish the time points for determination of tissue distribution in the second phase. The plasma concentrations of radioactivity were determined at various time points up to 168 hours post dosing, and the toxicokinetic (TK) parameters were calculated from the plasma concentration versus time curves.

In the second phase of the study (Metabolism Phase), two dose groups (Groups 3 and 4) consisting of 4 animals per gender were treated with single doses at 25 or 100 mg/kg per time point (0.5, 1, 2, 8, and 24 hours). The concentrations of radioactivity in tissues and excreta were determined, and metabolites in the urine were identified and quantified. The 24-hour animals were used to provide excreta for metabolite profiling and mass balance.

Tissue concentrations appeared to be dose proportional and exhibited no gender differences; no differences in absorption or excretion were observed between the sexes and dose levels; there

were no gender differences at either dose level with respect to TK parameters, which were proportional to dose.

Acephate was absorbed rapidly by rats of both sexes as the time point of maximum plasma concentration (T_{max}) was observed 0.5 hours after dosing with 25 and 100 mg/kg. After having reached peak levels, plasma concentrations declined continuously. Following an acute oral dose of 25 mg/kg, both the C_{max} values (21.9 and 24.9 ug/g) and AUC_{0-168} values (148 and 150 µg-h/g) were similar for males and females, respectively. The elimination rate constant values were 0.014 and 0.012 h^{-1} and the terminal phase half-lives were 50 and 58 hours for males and females, respectively, demonstrated similarity between the sexes.

Following an acute oral dose of 100 mg/kg, C_{max} values were 84 and 98 ug/g and AUC_{0-168} values were 576 and 545 µg-h/g for males and females, respectively. The elimination rate constant values were 0.014 and 0.13 h^{-1} and the terminal phase half-lives were 49 and 52 hours for males and females, respectively, demonstrating similarity between the sexes.

Total recoveries of radioactivity ranged from 103.4-105.6% and 97.3-98.0% of the administered dose following an oral dose of 25 and 100 mg/kg, respectively, with no differences observed between sexes and dose levels. In the 25 mg/kg animals, the urine, feces and expired carbon dioxide accounted for 86.1%, 2.3% and 9.5% of the administered dose in males and 88.9%, 2.4% and 9.7% of the administered dose in females, respectively. In the 100 mg/kg animals, the urine, feces and carbon dioxide accounted for 82.7%, 3.0% and 5.7% of the administered dose in the males and 87%, 1.8% and 4.6% of the administered dose in the females, respectively. In the 25 and 100 mg/kg animals, cage wash, tissues, GI tract and carcass each account for <3.3% of the administered dose.

The highest concentrations of radioactivity were found in tissues at 0.5 h or 1 h after administration at 25 and 100 mg/kg. Tissues concentration of acephate decreased, generally, by an order of magnitude or more by 24-h post-dosing. The highest concentrations of radioactivity (in terms of *u*g equivalents/g tissue) in the 25 and 100 mg/kg groups at 24-h post-dosing were found in liver (2.54-7.87), kidney (2.40-6.28), lung (2.10-6.19), spleen (2.14-7.55), bone (1.4-5.55), GI tract (2.59-7.93), adrenal glands (2.86-11.98) and GI tract contents (1.36-17.69). Overall, tissue concentrations appeared to be dose proportional and exhibited no gender differences. At 24-h post-dosing, the highest levels of radioactivity (in terms of % of the administered dose) were found in liver (0.27-0.47%), GI tract (0.28-0.52%) and GI tract contents (0.18-0.69%). All other tissues contained less than 0.1% of the administered dose.

Based on the TLC analyses of urine samples collected at 6, 12, and 24 h post-dosing of ^{14}C-acephate at 25 or 100 mg/kg, there was no difference in the metabolic profile of urine between sexes and dose levels. The major radioactive component in urine from rats dosed with ^{14}C-acephate at 25 and 100 mg/kg was unmetabolized acephate (77-80% of dose; approximately 90% of radioactivity in urine sample). The only significant metabolism of acephate is the formation of $^{14}CO_2$ (9-10% of dose). Small quantities of methamidophos (4% of dose) and 3 unknown components (<4% of dose) were found in the urine. The unknown components were des-acetamidoacephate (DMPT), 0-desmethyl acephate (SMPT), and 0-desmethyl methamidophos

(SMPAA). However, metabolic origins of methamidophos and these 3 metabolites are uncertain because they were present as contaminants in the dosing solutions at about the same percentage.

This metabolism study is classified **acceptable/guideline** and satisfies the guideline requirements for a metabolism study [OPPTS 870.7485, OECD 417] in rats.

870.7600 Dermal Absorption – Rat

In a dermal absorption study (MRID 00154886), male Sprague-Dawley rats (age: 144-151 days; weight: 498-618 g), 4/dose/exposure period, received single applications of a mixture of Acephate Technical and radioactive (14C) Acephate, and were sacrificed after 0 (immediately after dosing), 2, 8 and 24 hours of exposure. The purity of Acephate Technical was 98.7% and the radiochemical purity of 14C-Acephate was 99.1%. The concentrations of Acephate applied in 0.05 mL of a dosing solution (distilled H_2O + 0.1% w/w Tween 80) were 0.5 mg (4,421,000 dpm) and 5.0 mg (4,435,000 dpm) per rat or 0.899 mg/kg and 9.333 mg/kg (actual mean values), respectively. Acephate was labeled in the carbon atom of the *CH_3S-group of the molecule. After the applications on the intact (shaved) dorsal trunk, the rats were housed singly in metabolic cages and had unlimited access to food and water.

Acephate Technical was absorbed slowly through the intact skin of the male rats. At 24 hours after dosing, the recovery of applied radioactivity (expressed as 14C-Acephate) was 78.3% and 90.6% in the 0.5 mg/rat and 5.0 mg/rat groups, respectively. Most of this radioactivity was recovered from the surface of the skin (application site). Systemic absorption was defined as the percentage of the recovered dose in the carcass, blood, urine, feces, CO_2 trap and cage wash. In the 0.5 mg/rat group, 2.1, 3.0 and 10.5% of the recovered dose (radioactivity) was absorbed in 2, 8 and 24 hours, respectively. The corresponding values for the 5.0 mg/rat group were 1.6, 3.6 and 7.6%, respectively. Most of the absorbed radioactivity was found in urine (6.0% in the low-dose group and 4.4% in the high-dose group at 24 hours after exposure). Systemic absorption was not examined immediately after dosing (0 time).

This study is Acceptable-guideline and satisfies the guideline requirement for a dermal absorption study in the rat (85-2).

A.4.9 Immunotoxicity

870.7800 Immunotoxicity

In an immunotoxicity study (MRID #48774001), Acephate Technical (98.8% a.i., Batch no. 09-750-10) was administered to male Sprague-Dawley rats (10/dose) in the diet at dose levels of 0, 5, 50, or 700 ppm (equivalent to 0, 0.42, 4.06 or 61.18 mg/kg/day, respectively) for 4 weeks. On the study Day 27, the positive control group (8 males) was administered cyclophosphamide 50 mg/kg (5mg/mL) via intraperitoneal injection. During the study, clinical condition, bodyweight, food and water consumption, organ weight, brain and blood (plasma and red blood cell) cholinesterase levels and macroscopic pathology were evaluated. On Day 25, all animals in all

groups received a single intravenous dose of sheep red blood cells (SRBC, $2x10^8$ cells/mL, 1.0 mL/animal) in 0.9% saline. At sacrifice on Day 29, selected organs were removed and weighed (brain, spleen, and thymus). The anti-SRBC antibody (T-cell dependent antibody) response was measured with a Jerne Plaque- Forming Cell (PFC) assay.

There were no premature deaths, and no treatment-related clinical signs. No treatment related effects on food and water consumption at 5 or 50 ppm. There was slightly low food consumption during the first week at 700 ppm group, but slightly higher food consumption in these animals during the remaining 3 weeks of treatment. There was no effect of treatment on bodyweights in 5 and 50 ppm groups. Between Day 1 and 4, there was statistically significant reduction of weight gain (approximately 51% of vehicle control group) in males at 700 ppm; however, subsequent weight gain of these animals was similar to those of the controls. The overall weight gain was slightly low (8% reduction) when compare with the vehicle control group. Slightly higher absolute thymus weight and statistically significant ($P< 0.01$) increase in relative thymus weight were found at 700 ppm. There was no treatment related effect on thymus weights of 5 or 50 ppm groups. There was no effect of treatment on brain and spleen weight in all treated groups. After 4 weeks of treatment, there was a statistically significant ($p<0.01$) reduction of erythrocyte and brain acetylcholinesterase levels at all dietary concentrations of acephate in a dose-related manner when compare to the vehicle controls. The reduction was 20, 35 and 79% for erythrocyte cholinesterase and 14, 48 and 84% for brain cholinesterase at 5, 50 and 700 ppm respectively.

The systemic LOAEL was 5 ppm (equivalent to 0.42 mg/kg/day) based on decreased acetylcholinesterase levels. The systemic toxicity no-observed-adverse-effect level (NOAEL) was < 5 ppm.

There were no statistically significant differences observed in either Specific Activity ($PFC/10^6$ cells) or Total Spleen Activity (PFC/spleen) in treated groups when compare to the vehicle control group. High inter-individual variability was noted in all the treatment groups as well as in the control group. Evaluation of the individual animal data of this study did not show any trend or distribution that would demonstrate significant suppression of T-cell dependent anti-SRBC PFC response. Positive control group had statistically significant ($p<0.001$) decrease of the PFC response. This confirmed the ability of the test system to detect immunosuppressive effects and confirmed the validity of the study design.

The Natural Killer (NK) cells activity was not evaluated in this study. The toxicology database for acephate technical does not reveal any evidence of immunotoxicity. The overall weight of evidence suggests that the chemical does not directly target the immune system. Under HED guidance a NK cell activity assay is not required at this time.

The NOAEL for immunotoxicity was 700 ppm (equivalent to 61.18 mg/kg/day), the highest dose tested; the LOAEL for immunotoxicity was not established.

This immunotoxicity study is classified **acceptable/guideline** and satisfy the guideline requirement for an immunotoxicity study (OPPTS 870.7800) in the rats.

A.4.9 Special/Other Studies

Comparative cholinesterase assay

In a series of special comparative cholinesterase inhibition (ChEI) studies, Acephate technical (99.2% a.i., LOT No. AS 40s, Batch No. VLD-622-37a) was administered by gavage to groups of Crl:CD(SD)IGS BR rats. For time-course evaluation, groups of 14 adult rats/sex were given single oral doses of 0, 2.5, or 10 mg/kg (MRID 46151803) and groups of 14 PND 11 and 14 PND 21 pups/sex were given single oral doses of 0, 5, or 10 mg/kg (MRID 46151804); two rats/sex/dose were sacrificed 0, 1, 2, 3, 4, 8, and 24 hours later. MRID 46151803 also included a range-finding study for repeat exposures in adult rats. In MRID 46151804, groups of 8 PND 11 and groups of 8 PND 21 pups/sex were given single oral doses of 0, 0.5, 2.5, 5, or 10 mg/kg and observed for 24 hours for clinical signs and mortality. In the same study (MRID 46151804), groups of 4 PND 11 pups/sex were given 11 repeat doses, PND 11 through 21, and observed for clinical signs and mortality. In the definitive acute study (MRID 46151801), groups of adult, PND 11, and PND 21 rats, 10/sex/age group, were given single oral doses of 0, 0.5, 1, 2.5, or 10 mg/kg and sacrificed 3 hours later (time of peak effect). In the definitive repeat oral dosing study (MRID 46151806) groups of 10 adult and 10 PND 11 rats/sex were given 11 daily oral doses of 0, 0.5, 1, 2.5, or 10 mg/kg/day. In a study of comparative maternal and fetal sensitivity (MRID 46151805), groups of 8 pregnant dams were given doses of 0, 0.5, 1, 2.5, or 10 mg/kg/day on gestation days (GD) 6 through 21. Plasma, red blood cell (RBC), and brain ChE activities were measured in all animals in each study except the clinical observation part of study MRID 46151804.

All adult male and female rats and all pups survived to scheduled sacrifice. No treatment-related clinical signs of toxicity were observed in any animal during the studies. No treatment-related lesions were observed at necropsy. Body weight was comparable among the control and treated groups for both male and female adults and for both male and female pups in all studies (both the single and repeat-dose studies). Fetuses from treated dams had body weight comparable to those in the control group. Reproduction performance, gestation, and implantation were not affected by treatment in dams, nor were litter size, viability, sex ratio, or post implantation affected.

The acute ChEI data were often variable and did not follow clear dose-response patterns (MRID 46151801). Acute exposure at doses ≥1 mg/kg resulted in biologically significant (≥20%) inhibition of enzyme activity in the brain compartment of most groups. At 1 mg/kg, brain enzyme activity was biologically or statistically significantly inhibited in adult males and females, PND 11 males, and PND 21 females. PND 11 female pups and PND 21 male pups were affected at 2.5 and 10 mg/kg, respectively. RBC activities were generally unaffected by acute treatment up to and including 10 mg/kg, the exception being PND 21 male pups which were affected at 10 mg/kg. Plasma ChE activity showed a clearer dose-response pattern than the other compartments. Plasma ChEI occurred at 2.5 mg/kg (adult males and PND 11 male pups) and 10 mg/kg (adult females, PND 21 male pups, and PND 11 and PND 21 female pups). For all compartments, pups were no more sensitive to acute exposures than were adults except for RBC in PDN 21 male pups. Where adults and pups were affected at the same dose, e.g., brain ChEI at 1 mg/kg, the inhibition in pups (23-25%) was similar to that in adults (30-35%).

Data for brain ChEI were also variable after 11-day repeated dosing in both adults and neonates (MRID 46151806). LOAELs were 1 mg/kg for adult males and females and PND 21 male pups and 2.5 mg/kg for PND 21 female pups.

The LOAELs for acute and repeated exposures in adults are fairly similar. The brain ChEI data for pups were variable, with acute and repeat dose LOAELs for PND 21 male pups of 10 and 1 mg/kg, respectively, and for PND 21 females of 1 and 2.5 mg/kg, respectively. Treatment had no effect on RBC cholinesterase activity, with the exception of PND 21 male pups, affected at the highest dose (30% ChEI at 10 mg/kg/day). Plasma ChEI LOAELs ranged from 1 to 10 mg/kg/day with no clear relationship to sex or age.

In the repeat-exposure gestation study, lack of a dose-response relationship between 0.5 and 1 mg/kg/day for ChEI in several compartments for both dams and fetuses precluded establishing a LOAEL (of 0.5 mg/kg/day).

For acute exposures:

the adult LOAEL for brain ChEI is 1 mg/kg (both sexes)
the adult NOAEL for brain ChEI is 0.5 mg/kg (both sexes);

the PND 11 LOAEL for brain ChEI is 1 mg/kg (males), 2.5 mg/kg (females)
the PND 11 NOAEL for brain ChEI is 0.5 mg/kg (males), 1 mg/kg (females);

the PND 21 LOAEL for brain ChEI is 10 mg/kg (males), 1 mg/kg (females)
the PND 21 NOAEL for brain ChEI is 2.5 mg/kg (males), 0.5 mg/kg (females);

the adult LOAEL for RBC ChEI is >10 mg/kg (both sexes)
the adult NOAEL for RBC ChEI is ≥10 mg/kg (both sexes);

the PND 11 LOAEL for RBC ChEI is >10 mg/kg (both sexes)
the PND 11 NOAEL for RBC ChEI is ≥10 mg/kg (both sexes);

the PND 21 LOAEL for RBC ChEI is 10 mg/kg (for males), >10 mg/kg (for females)
the PND 21 NOAEL for RBC ChEI is 2.5 mg/kg (for males), ≥10 mg/kg (for females);

the adult LOAEL for plasma ChEI is 2.5 mg/kg (for males), 10 mg/kg (for females)
the adult NOAEL for plasma ChEI is 1 mg/kg (for males), 2.5 mg/kg (for females);

the PND 11 LOAEL for plasma ChEI is 2.5 mg/kg (for males), 10 mg/kg (for females)
the PND 11 NOAEL for plasma ChEI is 1 mg/kg (for males), 2.5 mg/kg (for females);

the PND 21 LOAEL for plasma ChEI is 10 mg/kg (both sexes)
the PND 21 NOAEL for plasma ChEI is 2.5 mg/kg (both sexes).

For acute exposure, the overall adult LOAEL for cholinesterase inhibition in rats is 1 mg/kg based on enzyme inhibition in brain; the adult NOAEL is 0.5 mg/kg.

For acute exposure, the overall offspring LOAEL for cholinesterase inhibition in rats is 1 mg/kg based on enzyme inhibition in brain; the offspring NOAEL is 0.5 mg/kg.

For repeated exposure:

the adult LOAEL for brain ChEI is 1 mg/kg/day (both sexes)
the adult NOAEL for brain ChEI is 0.5 mg/kg (both sexes);

the offspring LOAEL for brain ChEI is 1 mg/kg/day (males), 2.5 mg/kg (females)
the offspring NOAEL for brain ChEI is 0.5 mg/kg/day (males), 1 mg/kg/day (females);

the adult LOAEL for RBC ChEI is >10 mg/kg (both sexes)
the adult NOAEL for RBC ChEI is ≥10 mg/kg/day (both sexes);

the offspring LOAEL for RBC ChEI >10 mg/kg (males), 10 mg/kg/day (females)
the offspring NOAEL for RBC ChEI is ≥10 mg/kg/day (males), 2.5 mg/kg/day (females);

the adult LOAEL for plasma ChEI is 2.5 mg/kg/day (for males), 1 mg/kg/day (for females)
the adult NOAEL for plasma ChEI is 1 mg/kg/day (for males), 0.5 mg/kg/day (for females);

the offspring LOAEL for plasma ChEI is 10 mg/kg/day (males), 2.5 mg/kg (females)
the offspring NOAEL for plasma ChEI is 2.5 mg/kg/day (males), 1 mg/kg/day (females).

For repeated exposure, the overall adult LOAEL for cholinesterase inhibition in rats is 1 mg/kg/day based on enzyme inhibition in brain and plasma; the adult NOAEL is 0.5 mg/kg.

For repeated exposure, the overall offspring LOAEL for cholinesterase inhibition in rats is 1 mg/kg/day based on enzyme inhibition in brain; the offspring NOAEL is 0.5 mg/kg/day.

The cholinesterase activity measurements following an acute oral dose of acephate technical demonstrate approximately equal susceptibility between juvenile and adult rats. Following an acute exposure, brain enzyme inhibition in male and female adults and male and female pups was similar (LOAELs at 1 mg/kg, 23-35%). Repeated exposures show that sensitivity is still similar between adults and PND 21 rats (LOAELs at 1 mg/kg, 21-29%). In both adults and pups the brain ChE activity appeared to be more sensitive than RBC or plasma enzyme activity, although the brain data were variable and some groups were not affected at 1 mg/kg, e.g., acute exposure of PND 11 females and PND 21 males. This compartment susceptibility was observed in terms of the dose level at which an effect was observed (i.e., the LOAEL for cholinesterase inhibition was generally lower for brain than for RBC or plasma). RBC enzyme activity was largely unaffected in adults and pre-weaning rats of both sexes and following acute and repeated exposures. Following repeated exposures, LOAELs for brain enzyme activity were variable among sexes and age groups, but showed no greater sensitivity in pups than in adults. The ChEI

data for both dams and GD 21 fetuses were variable, but showed no greater susceptibility in brain enzyme activity of GD 21 fetuses when compared to dams, following maternal exposure from GD 6-21.

Taken together, these studies are classified **Acceptable/Non-guideline** for the determination of plasma, RBC and brain cholinesterase activities following treatment with acephate technical in adult, fetal, and juvenile rats.

Cholinesterase Inhibition in a Subchronic Oral Test in Rats

In this special cholinesterase (ChE) inhibition study (MRID 40504819), Sprague-Dawley rats (about 45 days old at the start of dosing), 30 males and 30 females/group, received Acephate Technical (purity: 98.2%) in the diet for 13 weeks at the nominal doses of 0, 2, 5, 10 and 150 ppm. The actual intake of the test material was 0, 0.12, 0.21, 0.58 and 8.90 mg/kg/day, respectively, for males and 0, 0.15, 0.36, 0.76 and 11.48 mg/kg/ day, respectively, for females. Cholinesterase activities in brain, erythrocytes (RBC) and plasma were determined on 10 rats/ sex during weeks 4, 9 and 13. Other parameters examined for all rats studied were signs of toxicity, body weights (weekly) and necropsy.

Relative to the control values, Acephate Technical had no effect on body weights and no toxic signs were observed in this study. Tissue abnormalities were not observed at necropsy and there was no mortality.

Brain ChE activity was significantly ($p<0.01$) inhibited in the 2 ppm group, during week 13 in the males (7%) and during weeks 9 and 13 in the females (9% each). In the remaining groups, brain ChE activity was significantly ($p<0.01$) inhibited at all times as follows: 5-10%, 10-16% and 44-53% in the 5 ppm, 10 ppm and 150 ppm groups, respectively. The inhibitions were similar in males and females. Erythrocyte ChE activity was significantly inhibited (32-48%; $p<0.01$) only in the 150 ppm group, in males during weeks 4 and 9, and in females during weeks 9 and 13. Plasma ChE activity was significantly inhibited (43%; $p<0.01$) only in the 150 ppm females and only during week 13.

Brain cholinesterase was slightly inhibited in male and female rats at 2 ppm (0.12 mg/kg/day in males and 0.15 mg/kg/day in females), the lowest dose level tested. However, the response was not dose-dependent. Therefore, the Committee considered the 2 ppm to be a NOEL for brain cholinesterase. The NOEL/LOEL for erythrocyte cholinesterase inhibition were 10 ppm (0.58 mg/kg/day in males and 0.76 mg/kg/day in females) and 150 ppm (8.90 mg/kg/day in males and 11.48 mg/kg/day in females), respectively. The NOEL/LOEL for plasma cholinesterase inhibition were 10 ppm and 150 ppm, respectively, for both males and females. Acceptable.

This study is classified as acceptable, nonguideline (a special subchronic ChE inhibition study).

Recovery from Cholinesterase Inhibition in Rats

In this special cholinesterase (ChE) inhibition study (MRID 00063463), the purpose of this study was to feed a diet containing Technical Orthene (75 ppm) to Sprague-Dawley male rats (age at start: 43 days) until brain cholinesterase activity became inhibited at least 25%, and then to monitor the recovery period.

During the initial test days 6-7, brain, plasma and RBC cholinesterase activities were inhibited 30-34%, 18-25% and 11-21%, respectively. The recovery period as started on the test day 8, when an Orthene-containing diet was replaced with an Orthene-free control) diet.

The recovery from cholinesterase inhibition in plasma and RBC was rapid. Complete recovery (return to control values) occurred within the first week of feeding an Orthene-free diet.

The recovery from cholinesterase inhibition in brain tissue was rapid initially, but incomplete, and slow thereafter. During the recovery Week 1, brain cholinesterase activity was inhibited only 8.7%, but it was still inhibited 5.5% during the recovery Week 6.

Classification of Study: Acceptable. [Special ChE study not intended to satisfy a guideline requirement.]

Acute Dermal (ChE Inhibition) Study in Rats

In this special cholinesterase (ChE) inhibition study (MRID 40504820), Sprague-Dawley rats, five 52-day old males and five 59-day old females per group, were treated dermally with the following single doses of Acephate Technical (purity: 98.2%): 0, 2, 10, 30 and 60 mg/rat. These doses were equivalent to 0, 7.9, 36.7, 107.0 and 201.0 mg/kg, respectively, for males and 0, 9.4, 51.7, 153.9 and 305.5 mg/kg, respectively, for females. The test material, dissolved in 0.1% (w/v) aqueous Tween 80, was applied (0.2 mL) on the shaved backs and the rats were then fitted with Queen Anne's collars until sacrifice (3 days later). Parameters examined included daily observations for toxic signs and (at study termination), body weights, gross pathology, histopathology, hematocrit, brain protein, and ChE activities in plasma, erythrocytes (RBC) and brain. The substrates used in ChE assays were acetylthiocholine (RBC and brain) and butyrylthiocholine (plasma).

With the exception of ChE activities in plasma, RBC and brain, Acephate Technical had no effect on all of the remaining parameters examined. Relative to the control values, ChE activities were statistically significantly inhibited at the following dose levels and above: Plasma: 34% in the 10 mg/rat male group and 41% in the 30 mg/rat female group ($p<0.05$; both groups); RBC: 59% ($p<0.05$) in the 60 mg/rat female group only; and Brain: 30% ($p<0.05$) and 38% ($p<0.01$) in the 30 mg/rat male and female group, respectively.

Based on the statistically significant inhibitions of ChE activities, the NOELs for male and female rats are as follows: Plasma, 2 mg/rat (7.9 mg/kg ♂) and 10 mg/rat (51.7 mg/kg ♀); RBC, >60 mg/ rat (>201 mg/kg HDT ♂) and 30 mg/rat (153.9 mg/kg ♀); and Brain, 10 mg/rat (36.7 mg/kg ♂ and 51.7 mg/kg ♀).

Based on the statistically significant inhibitions of ChE activities, the LOELs for male and female rats are as follows: Plasma, 10 mg/rat (36.7 mg/kg ♂) and 30 mg/rat (153.9 mg/kg ♀); RBC, 60 mg/rat (305.5 mg/kg ♀); and Brain, 30 mg/rat (107.0 mg/kg ♂ and 153.9 mg/kg ♀).

This study is Acceptable as a special acute dermal (ChE inhibition) Non-Guideline study.

90-Day Inhalation – Rat

In a subchronic inhalation toxicity study (MRID 45134302), acephate (tech., 98.8% a.i.) aerosol was administered by nose-only inhalation exposure to 10 Crl:CD®(SD)IGS BR rats/sex/concentration at levels of 0, 0.001064, 0.003123 or 0.005550 mg/L (target concentrations of 0, 0.001, 0.003 or 0.005 mg/L) for 4 weeks (5 days/week and 6 hrs/day; total of 20 exposures).

At 0.003123 mg/L, slightly decreased brain cholinesterase activity in males (-9.9% less than controls, $p<0.01$; females showed a very slight but not significant decrease of -5.2%); plasma cholinesterase in males on days 1 and 5 (-13.5% and -17.1%) and erythrocyte activity in females on day 5 (-21.4%; $p<0.05$) were observed. At 0.005550 mg/L, inhibition of cholinesterase activity in plasma (males -13.5%, $p<0.05$ to -18%, $p<0.01$ on days 1 and 5), erythrocytes (females -30%, day 5) and brain (-14.3%, males and -13.1%, $p<0.01$) was observed along with labored breathing in 25% to 33% of the animals during exposure on 3 days during the last week of the study. (A decrease of -11.6%, $p<0.05$, in plasma cholinesterase activity in males on day 5 at 0.001064 mg/L was considered insufficient for establishing an adverse effect). There were no treatment-related effects on body weight/weight gain, food consumption, organ weights, gross pathology or microscopic findings in the selected tissues that were examined (see DER).

Ophthalmological examinations, hematology, clinical chemistry and a complete histopathology examination were not performed. The ChE LOAEL is 0.003123 mg/L, based on inhibition of plasma and brain cholinesterase activities in males and erythrocyte cholinesterase in females. The ChE NOAEL is 0.001064 mg/L.

This subchronic inhalation toxicity study in the rat is classified Acceptable/nonguideline (§82-4a). Although the study lacks evaluations of several parameters that are normally conducted in a subchronic inhalation study, it is considered acceptable, when taken together with previously conducted 4-week subchronic whole-body exposure inhalation toxicity studies (MRIDs 40504818 and 40645903; HED Doc. No 012433), for determination of ChE and systemic toxicity NOAELs, because the most sensitive endpoint, cholinesterase inhibition of blood and brain, was evaluated.

Acute Neurotoxicity Screening Battery Range-Finder

In an acute, range-finding study (MRID 44203301), young adult, non-fasted Sprague-Dawley rats (Crl:CD®BR strain) received single gavage ·doses of ORTHENE® Tech. (acephate; purity: 99.4%; lot number: SX1725) as follows: **PART A:** 0 (deionized water; vehicle), 25, 50, 75, 150,

300, 450, 600 or 900 mg/kg (2 males and 2 females/dose, for doses 0-450 mg/kg and 1 male and 1 female/dose for the remaining doses; dosing date: 3/25-26/93); **PART B:** 0, 10 or 500 mg/kg (1 male and 1 female/ group; dosing date: 4/5/93); and **PART C:** 0, 5 or 500 mg/kg (5 male and 5 female/group; dosing date; 4/23/93). The rats were observed for 7 days and were sacrificed on day 8. Parameters examined included daily observations for toxic signs, daily detailed clinical examination, body temperatures and weights, and necropsy (performed only on animals found dead or killed moribund).

Both animals in the 900 mg/kg group, one (female) in the 600 mg/kg group and one (male) in the 500 mg/kg group died within 1-3 days after dosing. Toxic signs observed in the nonsurvivors within 15 min. to 6 hours after dosing were: (1) gait alterations (rocking, lurching or swaying, prostration and/or high carriage), tremors (whole body and/or forelimb/hindlimb) , salivation, lacrimation, constricted pupils and impaired air righting reflex; (2) reduced forelimb/hindlimb grasp, hypoactivity, hypothermia, swelling of the face and exophthalmus; (3) Labored respiration and head twitch; (4) staining (clear, yellow and/or tan) on the forelimbs, urogenital area and around the mouth; and (5) red ocular discharge, red material around the eyes and nose, and decreased urination and defecation. Most of these toxic signs persisted for 8 hours, some (like gait alterations) for 24 hours and labored breathing, until death. Macroscopic examination of the females revealed dark red contents in the ileum and a reddened cortico-medullary junction in each kidney (one female). The 900 mg/kg male had a distended and gas-filled duodenum and jejunum, a hemorrhagic thymus gland, and a reddened and enlarged mediastinal lymph node. No gross lesions were observed in the 500 mg/kg male which apparently died from blood loss caused by a pulled out claw.

Toxic signs observed in the surviving male and female rats were similar to those observed in the non-survivors. These signs occurred at dose levels of 25-900 (HDT) mg/kg. No toxic signs were noted at the two other levels of ORTHENE® Tech. tested, 5 and 10 mg/kg. The minimum effect dose levels (LOELs) and the estimated times of peak effect for each predominant sign are summarized in Table A.

Table A. Toxic Signs Observed in Rats Sacrificed on Day 8 after Single Dosing [a]

	Min. Effect Dose (mg/kg)		Peak Effect (min.)	
Toxic Sign	**Males**	**Females**	**Males**	**Females**
Gait alterations	25	25	90-120	90-120
Tremors	75	50	90	90
Constricted pupils	25	25	3 hrs.	4 hrs.
Lacrimation	50	25	90	90-150
Exophthalmus	50	25	90-150	90-150
Salivation	300	50	2-3 hrs.	2-3 hrs.
Hypoactivity	150	300	6 hrs.	5 hrs.
Impaired air righting reflex	150	150	90	4 hrs.
Decreased body temperature	25	25	2-4 hrs.	2-4 hrs.
Decreased body weight gain	300	150	---	---

[a] This table is based on data reported on pages 26-38 in the submitted report (MRID 44203301).

Based on the above data, the LOEL and NOEL for neurotoxic effects, for both sexes, are 25 mg/kg and 10 mg/kg, respectively, and the highest nonlethal dose is 500 mg/kg. It was, therefore, recommended that **(1)** the highest dose for the main acute neurotoxicity study with rats (81-8; MRID 44203303) should not exceed 500 mg/kg of ORTHENE® Tech. and **(2)** the time of peak effect should be 150 minutes after dosing. These recommendations appear to be supported by data reported in this range-finding study.

Acute Neurotoxicity Screening Battery Range-Finder

In an acute, range-finding study (MRID 44203302), young adult, fasted (about 18 hours) Sprague-Dawley rats (Crl:CD®BR strain) received single gavage doses of ORTHENE® Tech. (acephate purity: 99.0%; lot number: SX1725) as follows: **Phase I:** 0 (deionized water; vehicle), 5, 25, 125 or 500 mg/kg (2 males and 2 females/group; dosing date: 9/22/95) and **Phase II:** 0, 0.5, 2.5 or 5.0 mg/kg (5 females/group; dosing date: 10/25/95). All rats were killed at 2.5 hours after dosing. Parameters examined included observation for toxic signs, body weights (on Day -1, prior to dosing and prior to sacrifice), brain and brain regions weights, and cholinesterase activities (at the termination of the study) in plasma, erythrocytes (RBC), and brain regions (hippocampus, midbrain, brain stem, cerebellum and cortex).

There were no unscheduled deaths in this study; body, brain and brain region weights were not affected at all dose levels; and no clinical signs were observed in the 0.5-5.0 mg/kg groups.

Treatment-related toxic signs in the 25 mg/kg group were tremors of the mouth (repetitive movement) and twitching of both ears. These signs were observed at the terminal sacrifice (2.5 hours after dosing) in one male rat.

The most prominent findings in the 125 mg/kg male and female groups were tremors of the mouth, forelimbs/hindlimbs and/or whole body; altered gait (rocking, lurching or swaying); and salivation and twitching of both ears. These signs were first observed at 1-2 hours after dosing and were still present at study termination.

The most prominent findings in the 500 mg/kg males and females were the same as those observed in the 125 mg/kg group, plus hypothermia and hypoactivity. These signs were also first observed at 1-2 hours after dosing.

Cholinesterase (ChE) activities, determined at the termination of the study (2.5 hours after dosing), were inhibited in a dose-related manner in males and females as follows: **(1)** In plasma, at dose levels of 2.5 mg/kg (female) and 5.0 mg/kg (male), and above; **(2)** in RBC, at dose level of 5.0 mg/kg and above; and **(3)** in brain, at dose level of 0. 5 mg/kg and above. The ChE inhibition data are summarized in **TABLES AA and AB.**

TABLE AA. Percent Inhibition (Relative to Control) of Cholinesterase Activities in Plasma, Erythrocytes and Brain Regions of Rats at 2. 5 Hours After Dosing with ORTHENE® Tech. (Study Termination) - Phase I [a]								
	5 mg/kg		25 mg/kg		125 mg/kg		500 mg/kg	
Matrix	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
Plasma	30	26	55	44	75	70	84	91
Erythrocytes	115	13	29	31	45	46	49	50
Hippocampus	32	31	56	63	74	76	78	84
Midbrain	25	30	53	58	71	74	75	80
Brain Stem	28	25	56	60	73	73	78	80
Cerebellum	18	26	50	54	66	71	75	79
Cortex	28	30	55	62	73	75	78	80

[a] This table is based on data reported on page 24 in the submitted report (MRID 44203302). n=2.

TABLE AB. Percent Inhibition (Relative to Control) of Cholinesterase Activities in Plasma, Erythrocytes and Brain Regions of Female Rats at 2. 5 Hours After Dosing with ORTHENE® Tech. (Study Termination) - Phase II [a]			
Matrix	**0.5 mg/kg**	**2.5 mg/kg**	**5.0 mg/kg**
Plasma	0	14	10
Erythrocytes	8	3	19
Hippocampus	8	13	30
Midbrain	4	21	30
Brain Stem	7	22	34
Cerebellum	0	20	33
Cortex	0	21	31

[a] This table is based on data reported on page 26 in the submitted report (MRID 44203302). n=5. Zero (0) inhibition means ChE activities were the same or greater than those for the respective control groups.

Based on the clinical signs, **the NOEL and LOEL for systemic toxicity,** for both sexes, were 5 mg/kg and 25 mg/kg, respectively. Based on the ChE activities data, the NOELs and LOELs for ChE inhibitions were:
Plasma ChE NOEL = 0. 5 mg/kg (F) and < 5.0 mg/kg (M; LDT); **LOEL =** 2.5 mg/kg (F) and 5.0 mg/kg (M).
RBC ChE NOEL = 2.5 mg/kg (F) and < 5.0 mg/kg (M); **LOEL =** 5 mg/kg· (both sexes).
Brain ChE NOEL = 0.5 mg/kg (F) and < 5 mg/kg (M); **LOEL =** 2.5 mg/kg (F) and < 5.0 mg/kg (M).

Considering the findings in this range-finding study and those in the earlier range-finding study (MRID 44203301), doses of 10, 100 and 500 mg/kg and a time peak of approximately 2.5 hours after dosing (day 0) were selected for the main acute neurotoxicity study with ORTHENE® Technical (81-8; MRID 44203303). However, considering the ChE inhibition data in this range-finding study, the 10 mg/kg dose appears to be too high for the lowest dose in the acute neurotoxicity study.

Metabolism – Rat

In this metabolism study (MRID 00014994), male and female Sprague-Dawley rats were intubated daily with nonradioactive Orthene (Acephate; analytical grade; 25 mg/kg) for 7 consecutive days. On Day 8, the animals were dosed with radioactive Acephate (S-methyl-^{14}C-Orthene; purity: >99.5%; 25 mg/kg) and were sacrificed 3 days later.

Acephate was rapidly and completely absorbed from the stomach and was rapidly excreted in urine. About 87% and 95% of the administered radioactivity (^{14}C) was excreted, respectively, during the first 6 and 12 hours after dosing. Most of the remaining ^{14}C was found in the exhaled air (probably CO2; 1-4.5%), feces (1%) and tissues (0.4%). The ^{14}C found in urine was unchanged Acephate (O,S-dimethyl acetylphosphoramidothioate; 73-77%), DMPT (O,S-dimethyl phosphorothioate; 3-6%) and S-Methyl acetylphosphoramidothioate; 3-4%). Methamidophos (O,S-dimethyl phosphoramidothioate; ORTHO 9006) was not detected in urine, and the author concluded that Methamidophos was only a plant and soil metabolite of Acephate. Of the 0.4% ^{14}C recovered in tissues, most (0.13-0.26%) was in the liver and least (0.001-0.004%) in the brain. Male and female rats had the same excretion pattern.

This study is classified as Acceptable, Non-guideline. It provides information on the metabolism of Acephate by the rat, but does not satisfy (even partially) the guideline requirement for the metabolism studies (85-1).

Metabolism – Rat

The purpose of this metabolism study (MRID 00014219) was to investigate whether Methamidophos (ORTHO 9006) was formed from Orthene (Acephate) in rats. Six-week old male and female Sprague -Dawley rats were dosed (gavage) with nonradioactive Acephate (purity: 99.94%) at 100 mg/kg for 4 days. Two rats were sacrificed 3 hours after each dose (except the third) and the whole carcasses were quickly frozen and then analyzed (by GLC) for Acephate and Methamidophos. In addition, 3 male and 3 female rats were sacrificed 3 hours after the fourth dose for Acephate and Methamidophos analyses in tissues. Excreta were collected for analyses (by GLC) during the 24 hours following the third dose. The rats were sacrificed at 3 hours after being dosed because it was estimated that Methamidophos would be at or near maximum concentration at that time.

Acephate was rapidly absorbed and rapidly eliminated by the rats. The carcasses contained only 12-48% and the gastrointestinal tracts 3-14% of the final dose at 3 hours after dosing. The excreta (chiefly urine) contained 54-56% of the final dose at 6 hours after dosing. There was no tendency for Acephate to concentrate in blood, liver, muscle, fat, heart and brain.

Rats converted a portion of Acephate to Methamidophos. Evidence was presented that the conversion took place in the small intestine and, to a lesser extent, in the stomach, and was apparently effected by the microorganisms. Methamidophos was then absorbed from the stomach and intestines, and distributed throughout the body. At 3 hours after the last dose, the carcass contained 0.6-1.6% and the excreta (chiefly urine) 1.1-1.5% of the final dose of Acephate

as Methamidophos. There was no tendency for Methamidophos to accumulate in blood, liver, muscle, fat and heart. Concentrations of Methamidophos in these tissues varied from 0.2 to 1.1 ppm. Highest concentrations of Methamidophos were found in kidneys (4.1-11.5 ppm), testes (2.4-3.9 ppm) and brain (2.1-2.5 ppm).

This study is classified as acceptable, non-guideline. It provides information on the metabolism of Acephate by the rat, but does not satisfy (even partially) the guideline requirement for the metabolism studies (85-1).

A.5. Lifestage Sensitivity to Acephate-Induced Acetyl Cholinesterase (AChE) Inhibition in the Brain of Rats Following Oral Treatment

MRID # Test	Lifestage Sex	BMD_{10} (mg/kg/day)	Nearest Dose to 90% of Control (% of Control) [b]	Fold-Difference [c]	Conclusion
Acute					
Pup vs Adult					
46151801 Acute CCA	Adult Male	1.62	**0.5** (87%)	0.97	The pup is not more sensitive than the adult.
46151801 Acute CCA	Pup (PND 11) Male	**0.513**	0.5 (90%)		
46151801 Acute CCA	Adult Female	8.95	**0.5** (87%)	0.42	The pup is not more sensitive than the adult.
46151801 Acute CCA	Pup (PND 11) Female	**1.20**	1 (93%)		
Steady State					
Pup vs Adult					
46151806 Repeated Dose CCA	Adult Male	NF	0.5 (72%)	Can't calculate, because no value near 90% for adult male.	The pup is not more sensitive than the adult.
46151806 Repeated Dose CCA	Pup Male	0.516	0.5 (95%)		
46151806 Repeated Dose CCA	Adult Female	NF	**0.5** (92%)	0.5	The pup is not more sensitive than the adult.
46151806 Repeated Dose CCA	Pup Female	1.41	**1** (91%)		
Fetus vs Dam					
46151805 Gestational CCA	Dam	**0.436**	0.5 (83%)	Dam vs male fetus: 0.176 Dam vs female fetus: 0.872	The fetus is not more sensitive than the mother.
46151805 Gestational CCA	Male Fetus	**2.48**	2.5 (89%)		
46151805 Gestational CCA	Female Fetus	1.57	**0.5** (86%)		
Pregnant vs Non-Pregnant					
46151805 Gestational CCA	Dam	**0.436**	0.5 (83%)	1.01	No difference in pregnant vs. non-pregnant female. BMD of 0.494 in non-pregnant female from chronic toxicity/ carcinogenicity study supports this conclusion.
40504819 13W Subchronic	Adult Female (Not Pregnant)	**0.433**	0.36 (91%)		

[a] No data available to compare fetus vs dam or pregnant vs non-pregnant lifestages following a single dose.
[b] Doses tested for all CCA studies were 0, 0.5, 1, 2.5, and 10 mg/kg/day. Doses tested in the subchronic oral toxicity test were 0, 0.15, 0.36, 0.76, and 11.48 mg/kg/day.

[c] Upper Row ÷ Lower Row of Merged Cell. When BMD did not agree with empirical evidence, the dose tested which provided inhibition nearest 10% was used instead of BMD_{10}. Bolded values were used to calculate fold-difference. So, when comparing acute affects in the adult male vs pup: 0.5 ÷ 0.513 = 0.97.
NF Indicates that the data did not fit well any of the tested models

Other conclusions: At 0.5 mg/kg/day, comparing the adult male and female demonstrates a comparable sensitivity in the acute CCA (87% of control in both sexes) and in the repeated dose CCA (72% of control in males and 92% of control in females). In the pups, males were more sensitive than females in the acute CCA study (males: 90% of control at 0.5 mg/kg/day; females: 93% of control at 1 mg/kg/day) and perhaps also in the repeated dose CCA study (males: 95% of control at 0.5 mg/kg/day; females: 91% of control at 1 mg/kg/day). Comparison of the sexes as pups is limited only to the CCA studies; therefore, confidence in conclusions is also limited. It is possible that no sex difference is present in pups just like there is none in adults.

The brain AChE is typically more sensitive than the RBC AChE to acephate. For instance in the 13-week subchronic oral toxicity study (MRID 40504819), the BMD_{10} was 2.2 mg/kg/day in the female's RBC, but only 0.4 mg/kg/day in the female's brain. Please consult Appendix 2 (Tables A.2.1 - A.2.5) for additional data.

A.6. Analysis of the Effect of Two Different Estimations of the Toxicity Adjustment Factor on Risk Assessment.

Table 1. Toxicity adjustment factors and points of departures for orally administered acephate.

Route of Administration	Methamidophos BMD_{10} (mg/kg/day)	Acephate BMD_{10} (mg/kg/day)	Toxicity Adjustment Factor [a]	Acephate POD (mg/kg/day)
Oral (pups)	0.186 [b]	0.513 [c]	2.76	0.272 [d]
Oral (adults)	0.07 [e]	0.77 [e]	11.0	0.41

[a] Values were obtained by dividing the acephate BMD_{10} by the methamidophos BMD_{10}. Multiplying the measured methamidophos residues by the toxicity adjustment factor provides a measure of acephate-equivalents.
[b] Value was obtained from D382498, 1/25/2011.
[c] Acephate BMD_{10} value in the current study is 0.513 mg/kg/day and is presented in the BMD Modeling Summary table. Although 0.51 mg/kg/day is reported in D382498, 1/25/2011, this value has actually just been rounded, because the TAF is reported as 2.76.
[d] This value is 0.304 mg/kg/day as reported in D382498, 1/25/2011; however, the POD calculated for pups in the current risk assessment (0.272 mg/kg/day) was used for the purposes of comparing the use of the TAF for pups to adults.
[e] Values were obtained from the Organophosphorus Cumulative Risk Assessment, 2006, Table I.B-4.

The POD selected for all oral exposure scenarios was derived from pup brain ChEI; consequently, the TAF will be 2.76. When the crop field residues of methamidophos are much less than acephate, the TAFs for adults and pups are similar after considering the PODs that were selected from the studies. This fact is shown mathematically below, with exposure showing the relative levels of the two compounds.

Test A: Acephate: Methamidophos (10:1), pups

	TAF	exposure	TAF-adjusted exposure
Acephate	1	10	10
Methamidophos	2.76	1	2.76
total			12.76
MOE-like metric			**0.021317**

Test A: Acephate: Methamidophos (10:1), adults

	TAF	exposure	TAF-adjusted exposure
Acephate	1	10	10
Methamidophos	11	1	11
total			21
MOE-like metric			**0.019524**

The MOE-like metric was calculated as the acephate POD ÷ the total TAF-adjusted exposure. Thus, 0.272 ÷ 12.76 = 0.021317 and 0.41 ÷ 21 = 0.019524. Comparison of the MOE-like metrics yields approximately a value of 1 (no difference): 0.021317 ÷ 0.019524 = 1.09. When

acephate residues exceed methamidophos residues by 10:1, this comparison indicates that using either the pup or the adult TAF will yield a very similar result when considering the analyses' corresponding PODs.

A second scenario is examined below where the relative amount of methamidophos is increased compared to the first scenario:

Test B: Acephate: Methamidophos (7:3), pups

	TAF	exposure	TAF-adjusted exposure
Acephate	1	7	7
Methamidophos	2.76	3	8.28
total			15.28
MOE-like metric			**0.017801**

Test B: Acephate: Methamidophos (7:3), adults

	TAF	exposure	TAF-adjusted exposure
Acephate	1	7	7
Methamidophos	11	3	33
total			40
MOE-like metric			**0.01025**

Comparison of the MOE-like metric shows a slight difference (less than 2-fold): 0.017801 ÷ 0.01025 = 1.74. This comparison indicates that using either the pup or the adult TAF will yield a somewhat similar result when considering the analyses' corresponding PODs. However, as methamidophos levels increase relative to acephate, the adult and pup TAFs will result in MOEs that also differ more.

The BMD analysis used to compare toxicity of methamidophos and acephate in pups (presented in the table above) is the same procedure used to calculate the BMD_{10}s for acephate in the current risk assessment. The chosen POD was based on brain ChEI in pups. The BMD analysis does not support the conclusion that the adults are more sensitive than the pups. Infants are expected to be the subpopulation at greatest risk. Based on these facts, it was considered most appropriate to use the pup TAF for all oral risk assessment scenarios.

A.7. Cholinesterase Inhibition of Acephate in Dermal Studies.

In a 21-day dermal toxicity study (MRID 44541101), Acephate Technical (97.8% a.i.; batch no. 224T020619) was administered to 10 Sprague-Dawley rats/sex/dose via the skin (≈10% of the body surface area) at dose levels of 0, 12, 60, or 300 mg/kg/day for 21 days (6 hours per day, 5 days per week for 3 consecutive weeks). Dose selection was based on acetylcholinesterase (AChE) inhibition noted in rats in a 5-day pilot study conducted with groups of three rats/sex/dose, dermally exposed to 5, 50, 150, or 300 mg/kg/day.

In the pilot study, there were no effects on survival, clinical signs, or body weight, and there was no indication of dermal irritation at any dose. In the main 21-day study, all rats survived until study termination, and there were no clinical signs of toxicity. There was also no dermal response. No adverse effects were observed on body weight, food consumption, hematology, clinical chemistry, and organ weights, and gross and microscopic findings were comparable among the dose groups for both sexes.

In the pilot study (n=3), the dose-response relationship was not clear for the males (see the table below), but there was an apparent inhibition at 150 (↓12%) and 300 (↓10%) mg/kg/day in male brain AChE. In comparison at 150 mg/kg/day, brain AChE levels were decreased by 12% in males but increased by 13% in females; however, the overall database does not suggest a difference in ChEI based on sex in adults. Male brain AChE levels were decreased by 12% at 150 mg/kg/day in the pilot study (n=3), but were only decreased by 9% at 300 mg/kg/day in the main study (n=10). Because of these reasons, there was little confidence of an adverse effect at 150 mg/kg/day in the pilot study. Conversely, a clear effect on brain cholinesterase inhibition was noted at 300 mg/kg/day in the main study ($p \leq 0.05$; ↓9% males; ↓14% females) and in the pilot study (↓10% males; ↓14% females).

Additionally at 300 mg/kg/day, RBC cholinesterase inhibition (not statistically significant) was observed in males (↓9%) and females (↓13%). However, a similar inhibition was not observed in the pilot study.

The LOAEL was 300 mg/kg/day based on brain cholinesterase inhibition. The NOAEL was 150 mg/kg/day.

This study is classified as **acceptable, guideline** and satisfies the guideline requirements (OPPTS 870.3200; OECD 410) for a 21-day dermal toxicity study in rats.

COMMENTS: This is a revised Executive Summary. The LOAEL was changed from the original review, based on the data from the two studies considered in conjunction and the conclusion that the magnitude of the brain inhibition in the females at 60 mg/kg/day (↓6%) is not considered adverse. Tables are included below to support the conclusions.

COMPLIANCE: Signed and dated GLP Compliance, Quality Assurance, No Data Confidentiality, and Flagging statements were provided.

This is a copy of the revised Executive Summary for the DER of MRID 44541101. For additional information, please consult the DER and MRID.

Males	Pilot Study Data Individual Cholinesterase Determinations					Appendix M
Group (mg/kg)	Animal Number	Pretest PCHE	Pretest RCHE	Termination PCHE	Termination RCHE	BCHE
I	1008	0.501	1.250	0.437	1.163	17.250
0	1009	0.791	1.488	0.694	1.225	19.000
	1010	0.593	1.150	0.494	1.113	19.083
	Mean	**0.628**	**1.296**	**0.542**	**1.167**	**18.444**
	S.D.	**0.148**	**0.174**	**0.135**	**0.056**	**1.035**
	N	**3**	**3**	**3**	**3**	**3**
II	2008	0.835	0.950	0.779	0.988	19.383
5	2009	0.616	1.188	0.578	1.350	18.150
	2010	0.496	1.925	0.451	1.225	19.150
	Mean	**0.649**	**1.354**	**0.603**	**1.188**	**18.894**
	S.D.	**0.172**	**0.508**	**0.165**	**0.184**	**0.655**
	N	**3**	**3**	**3**	**3**	**3**
III	3008	0.595	1.175	0.536	1.138	18.617
50	3009	0.504	2.138	0.406	1.250	16.533
	3010	0.766	2.025	0.565	1.088	16.217
	Mean	**0.622**	**1.799**	**0.502**	**1.159**	**17.122**
	S.D.	**0.133**	**0.526**	**0.085**	**0.083**	**1.304**
	N	**3**	**3**	**3**	**3**	**3**
IV	4008	0.740	1.325	0.573	1.063	16.483
150	4009	0.532	1.313	0.424	0.925	16.350
	4010	0.539	1.513	0.429	1.300	16.183
	Mean	**0.604**	**1.384**	**0.475**	**1.096**	**16.339**
	S.D.	**0.118**	**0.112**	**0.085**	**0.190**	**0.150**
	N	**3**	**3**	**3**	**3**	**3**
V	5008	0.687	1.363	0.527	1.225	15.817
300	5009	0.546	1.500	0.462	1.163	17.383
	5010	0.673	1.200	0.564	1.175	16.717
	Mean	**0.635**	**1.354**	**0.518**	**1.188**	**16.639**
	S.D.	**0.078**	**0.150**	**0.052**	**0.033**	**0.786**
	N	**3**	**3**	**3**	**3**	**3**

Copied from page 346 of Appendix M in MRID 4454101.

Females	Pilot Study Data Individual Cholinesterase Determinations					Appendix M
Group (mg/kg)	Animal Number	Pretest PCHE	Pretest RCHE	Termination PCHE	Termination RCHE	BCHE
I	1508	1.100	1.375	1.473	1.038	17.450
0	1509	1.112	1.188	1.405	1.175	17.317
	1510	0.947	1.413	1.214	1.100	16.267
	Mean	**1.053**	**1.325**	**1.364**	**1.104**	**17.011**
	S.D.	**0.092**	**0.120**	**0.134**	**0.069**	**0.648**
	N	**3**	**3**	**3**	**3**	**3**
II	2508	0.975	1.263	1.296	1.300	19.617
5	2509	0.879	1.725	1.036	1.338	18.150
	2510	1.339	1.000	1.909	0.975	18.383
	Mean	**1.064**	**1.329**	**1.414**	**1.204**	**18.717**
	S.D.	**0.243**	**0.367**	**0.448**	**0.200**	**0.788**
	N	**3**	**3**	**3**	**3**	**3**
III	3508	1.012	1.325	0.961	1.038	20.083
50	3509	1.347	1.338	1.673	1.163	15.217
	3510	1.013	1.338	0.976	1.025	17.200
	Mean	**1.124**	**1.334**	**1.203**	**1.075**	**17.500**
	S.D.	**0.193**	**0.007**	**0.407**	**0.076**	**2.447**
	N	**3**	**3**	**3**	**3**	**3**
IV	4508	1.247	1.225	1.608	1.125	17.800
150	4509	0.832	1.713	1.077	1.138	17.717
	4510	1.023	1.175	1.211	1.738	22.017
	Mean	**1.034**	**1.371**	**1.299**	**1.334**	**19.178**
	S.D.	**0.208**	**0.297**	**0.276**	**0.350**	**2.459**
	N	**3**	**3**	**3**	**3**	**3**
V	5508	1.363	1.450	1.577	0.950	14.067
300	5509	0.811	1.125	0.812	1.088	15.350
	5510	0.971	1.238	0.995	1.075	14.717
	Mean	**1.048**	**1.271**	**1.128**	**1.038**	**14.711**
	S.D.	**0.284**	**0.165**	**0.399**	**0.076**	**0.642**
	N	**3**	**3**	**3**	**3**	**3**

Copied from page 347 of Appendix M in MRID 4454101.

Males	Mean Cholinesterase Determination Values Termination	Table 11

	Plasma Cholinesterase		Erythrocyte Cholinesterase		Brain Cholinesterase	
	IU/mL	% Inhibition from Control	IU/mL	% Inhibition from Control	IU/g	% Inhibition from Control
GROUP I - 0 mg/kg						
MEAN	0.609	-	1.308	-	18.270	-
S.D.	0.15		0.451		0.806	
N	10		10		10	
GROUP II - 12 mg/kg						
MEAN	0.622	0	1.267	3	18.173	1
S.D.	0.136		0.349		1.183	
N	10		10		10	
GROUP III - 60 mg/kg						
MEAN	0.610	0	1.304	0	17.303	5
S.D.	0.101		0.415		1.425	
N	10		10		10	
GROUP IV - 300 mg/kg						
					**	
MEAN	0.578	5	1.185	9	16.628	9
S.D.	0.085		0.167		0.515	
N	10		10		10	

Copied from page 80 of MRID 4454101.
** Statistically different from the control at $p \leq 0.01$

Females	Mean Cholinesterase Determination Values Termination	Table 11

	Plasma Cholinesterase		Erythrocyte Cholinesterase		Brain Cholinesterase	
	IU/mL	% Inhibition from Control	IU/mL	% Inhibition from Control	IU/g	% Inhibition from Control
GROUP I - 0 mg/kg						
MEAN	1.374	-	1.303	-	18.317	-
S.D.	0.38		0.319		0.715	
N	10		10		10	
GROUP II - 12 mg/kg						
MEAN	1.465	0	1.487	0	18.652	0
S.D.	0.294		0.776		0.834	
N	10		10		10	
GROUP III - 60 mg/kg						
MEAN	1.462	0	1.253	4	17.137**	6
S.D.	0.483		0.223		0.722	
N	10		10		10	
GROUP IV - 300 mg/kg						
MEAN	1.292	6	1.137	13	15.787**	14
S.D.	0.282		0.259		0.553	
N	10		10		10	

Copied from page 80 of MRID 4454101.
** Statistically different from the control at $p \leq 0.01$

Dose Response Analysis of Brain Cholinesterase Data

Males

Group	BCHE (IU/g)	Percent Inhibition from Control (%)
0 mg/kg/day (pilot)	18.444	-
0 mg/kg/day (main)	18.270	-
5 mg/kg/day (pilot)	18.894	0%
12 mg/kg/day (main)	18.173	1%
50 mg/kg/day (pilot)	17.122	7%
60 mg/kg/day (main)	17.303	5%
150 mg/kg/day (pilot)	16.339	12%
300 mg/kg/day (pilot)	16.639	10%
300 mg/kg/day (main)	16.628	9%**

Females

Group	BCHE (IU/g)	Percent Inhibition from Control (%)
0 mg/kg/day (pilot)	17.011	-
0 mg/kg/day (main)	18.317	-
5 mg/kg/day (pilot)	18.717	0%
12 mg/kg/day (main)	18.652	0%
50 mg/kg/day (pilot)	17.500	0%
60 mg/kg/day (main)	17.137	6%**
150 mg/kg/day (pilot)	19.178	0%
300 mg/kg/day (pilot)	14.711	14%
300 mg/kg/day (main)	15.787	14%**

BCHE - brain cholinesterase
**$p \leq 0.01$

Copied from the Acephate: Toxicology Chapter for the RED (D238147, 1/26/98).

A.8. Cholinesterase Inhibition from Acephate in Inhalation Studies

The methods and dosimetry equations described in EPA's RfC guidance (1994) are suited for calculating HECs based on the inhalation toxicity NOAEL for use in MOE calculations. The procedure provided in the Office of Pesticide Programs Inhalation Risk Assessment Guidance on the Applications of the RfC Methodology (2014) were followed.

The regional deposited-dose ratio (RDDR), which accounts for the particulate diameter (mass median aerodynamic diameter [MMAD] and geometric standard deviation [σ_g] of aerosols), can be used to estimate the different dose fractions deposited along the respiratory tract. The RDDR is also based on interspecies differences in ventilation and respiratory-tract surface areas. Thus, the RDDR can be used to adjust an observed inhalation particulate exposure of an animal to the predicted inhalation exposure for a human.

The RfC methodology applies a dosimetric adjustment that takes into consideration not only the differences in ventilation rate (MV) but also the physicochemical properties of the inhaled compound, the type of toxicity observed (e.g., systemic vs. portal-of-entry) and the pharmacokinetic (PK) (but not pharmacodynamic) differences between animals and humans. Based on the EPA's RfC guidance (1994), the methodology for RfCs derivation is an estimate of the quantitative dose-response assessment of chronic non-cancer toxicity for individual inhaled chemicals and includes dosimetric adjustment to account for the species-specific relationships of exposure concentration to deposited/delivered dose. This adjustment is influenced by the physicochemical properties of the inhaled compound as well as the type of toxicity observed (e.g., systemic vs. portal-of-entry), and takes into consideration the PK differences between animals and humans. Though the RfC methodology was developed to estimate toxicity of inhaled chemicals over a lifetime, it can be used for other inhalation exposures (e.g., acute and short-term exposures) since the dosimetric adjustment incorporates mechanistic determinants of disposition that can be applied to shorter duration of exposures provided the assumptions underlying the methodology are still valid.

Acephate is not volatile in ambient conditions. The vapor pressure of acephate is only 1.7×10^{-6} mm Hg/Torr; 5.1×10^{-13} atm mole/m^3. Acephate would be inhaled as an aerosol. Calculations used to estimate the inhalation risk to humans from aerosols are dependent on the regional deposited dose ratio (RDDR). Inhalation studies using aerosols characterize particulate exposure by defining the particulate diameter (mass median aerodynamic diameter [MMAD]) and the geometric standard deviation (σ_g), which is then used to determine the RDDR. The RDDR is a multiplicative factor used to adjust an observed inhalation particulate exposure concentration of an animal (A) to the predicted inhalation particulate exposure concentration for a human (H) that would be associated with the same dose delivered to the rth region or target tissue.

$$RDDR_r = (RDD_r/\text{Normalizing Factor})_A \div (RDD_r/\text{Normalizing Factor})_H$$

As with calculations for gases, the r regions and potential target tissues are the three respiratory regions (ET, TB, PU). The RDDR is easily calculated by using a software program designed specifically for computing the RDDR from the MMAD and σ_g defined from an aerosol inhalation study. The values for the species-specific parameters used to calculate the RDDR are

provided in the EPA document "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry."

The most sensitive endpoint of toxicity for acephate is cholinesterase inhibition, an extrarespiratory effect. Portal of entry effects were observed at 100 mg/m^3 (but not at lower doses) in the nasal turbinates of both sexes as induced exudate in the lumen, suppurative inflammation, individual cell necrosis, and regenerative epithelium of the middle and posterior sections. The $BMDL_{10}$ for female brain ChEI was 1.205 mg/m^3. The lowest dose group (1 mg/m^3) approximated the $BMDL_{10}$ for this study; therefore, the MMAD and GSD data from this dose group was used. The overall average MMAD and GSD reported for Days 1, 6, and 16 as measured by GC impactor (Table 2A on page 74 of MRID 40504818) was used to calculate the RDDR. These values are MMAD = 1.85 and GSD = 2.73. The resulting RDDRs (as shown below) are 2.773 in males and 2.818 in females.

Regional Deposited Dose Ratio (RDDR) for Acephate in Males

MMAD = 1.85
Sigma g = 2.73

SPECIES	Body weight(g)	VE(ml)	Extrathoracic SA(cm^2)	dep	Tracheobronchial SA(cm^2)	dep	Pulmonary SA(m^2)	dep
rat	267	189.8	15.000	0.400	22.500	0.049	0.340	0.046
human	70000	13800.0	200.000	0.349	3200.000	0.074	54.000	0.221
RATIO	0.004	0.014	0.075	1.145	0.007	0.662	0.006	0.210

RDDR 0.210 1.295 0.458

	Thoracic SA(m^2)	dep	Total RT SA(m^2)	dep	Extrarespiratory BW(g)	dep
rat	0.342	0.095	0.344	0.495	267	0.495
human	54.320	0.125	54.340	0.644	70000	0.644
RATIO	0.006	0.760	0.006	0.769	0.004	0.769

RDDR 0.705 1.672 2.773

V. 2.3

Regional Deposited Dose Ratio (RDDR) for Acephate in Females

MMAD = 1.85
Sigma g = 2.73

SPECIES	Body weight(g)	VE(ml)	Extrathoracic SA(cm^2)	dep	Tracheobronchial SA(cm^2)	dep	Pulmonary SA(m^2)	dep
rat	204	152.2	15.000	0.365	22.500	0.056	0.340	0.059
human	70000	13800.0	200.000	0.349	3200.000	0.074	54.000	0.221
RATIO	0.003	0.011	0.075	1.044	0.007	0.757	0.006	0.267

RDDR 0.153 1.188 0.468

	Thoracic SA(m^2)	dep	Total RT SA(m^2)	dep	Extrarespiratory BW(g)	dep
rat	0.342	0.115	0.344	0.480	204	0.480
human	54.320	0.125	54.340	0.644	70000	0.644
RATIO	0.006	0.918	0.006	0.745	0.003	0.745

RDDR 0.683 1.298 2.818

V. 2.3

To calculate the HEC and HED, a point of departure (POD) value of 0.001025 mg/L and RDDR of 2.773 were entered into the March 2016 version of the RDDR Excel spreadsheet program. This program implements the Office of Pesticide Programs Inhalation Risk Assessment Guidance on the Application of the RfC Methodology (February 11, 2014). Briefly, the following steps are performed: (i) POD is adjusted for exposure duration using Haber's Law; (ii) the dosimetry adjustment factor (DAF) is derived which compares the minute ventilation rate, deposition fraction for aerosols, and surface area of the affected respiratory tract in the test animal to humans; (iii) the human equivalent concentration (HEC) is estimated as the product of duration-adjusted POD and the DAF, and (iv) the HEC is converted to the human equivalent dose (HED), with the consideration of volume respired per unit time. Formulas and a more detailed explanation are provided in the cited document. The following results were calculated:

Exposure Scenario	HED (mg/kg/day)
Occupational Handler	0.20
Residential Handler	0.07
Residential Outdoor Postapp	0.08
Residential Indoor Postapp	0.05
Residential Bystander	0.001 mg/L HEC

Appendix B. Use Summary for Acephate

Use Site	Formulation	Application Method Type	Application Method Equipment	Maximum Application Rate	RTI (days)	PHI (days)	Restrictions
Beans and Lima beans (dry and succulent forms)	DF	Broadcast	Aerial and Groundboom	0.99 lb ai/A	3 to 10	14 for dry bean; 1 for lima (succulent)	
	WSP						
Beans grown for seed	DF						
Brussels sprouts and Cauliflower	DF	Broadcast	Aerial and Groundboom	0.99 lb ai/A	3 to 7	14	
	WSP						
Celery	DF	Broadcast	Aerial and Groundboom	0.99 lb ai/A	3 to 7	21	
	WSP						
Christmas tree plantations	DF	Broadcast	Aerial, Groundboom, and Handheld	0.487 lb ai/A or 0.005 lb ai/gal	3 to 7	NA	
	WSP						
Indoor Commercial and Industrial Buildings (such as Restaurants, Warehouses, Stores, Hospitals, Hotels, Manufacturing Plants and Ships)	DF	Spot/Crack and crevice treatment	Handheld equipment (including paintbrush)	0.085 lb ai/gal		NA	Not for indoor residential use. Aerosol can size: 18 oz can; use with the supplied actuator and injection tubes or other Whitmire Micro-Gen equipment. [a]
	PRL	Crack and crevice treatment.	Aerosol can	0.011 lb ai/can			
	WSP	Spot/Crack and crevice treatment	Handheld equipment	0.084 lb ai/gal			
	WSP	Mound treatment	Handheld equipment	0.009 lb ai/mound			
Container Grown Nursery Stock (Ornamentals)	DF	Broadcast	Handheld equipment	0.007 lb ai/gal	3 to 7	NA	
	G	Broadcast or Spot	Tractor drawn spreader or Handheld equipment	1 lb ai/A or 0.024 lb ai/1000 sq ft	NS		
	WSP	Broadcast	Handheld equipment	0.75 lb ai/100 gal	NS		
Cotton	DF	Broadcast	Aerial and Groundboom	0.99 lb ai/A	3 to 7	21	
	WSP						
	G	Soil in-furrow treatment.	Tractor drawn spreader	1 lb ai/A	NS	NA	
Cotton seed	WSP	Seed treatment	Slurry-type seed treater	0.004 lb ai/lb seed	NA	NA	
	DF						

Use Site	Formulation	Application Method Type	Application Method Equipment	Maximum Application Rate	RTI (days)	PHI (days)	Restrictions
Cranberry	DF WSP	Broadcast	Aerial, Chemigation and Groundboom	0.99 lb ai/A	NA (1 app per season)	90	
Golf course turf	DF	Broadcast	Groundboom	4.77 lb ai/A	3 to 7	NA	*label states not to exceed 4 lb ai/A for golf course, but higher rate can be calculated based on use directions
	G	Broadcast	Tractor drawn spreader	4.95 lb ai/A	7	NA	
	WSP	Broadcast	Groundboom	3.9 lb ai/A	NS	NA	
Golf course turf (ant mound treatment)	WSP	Mound treatment	Handheld equipment	0.009 lb ai/mound	NA	NA	
Greenhouse nursery stock	G	Broadcast or Spot	Groundboom or Handheld equipment	1 lb ai/A or 0.024 lb ai/1000 sq ft	NA	NA	
Lettuce	DF	Broadcast	Aerial and Groundboom	0.974 lb ai/A	3 to 7	21	
	WSP			0.9975 lb ai/A			
Mint / Peppermint / Spearmint	WSP	Broadcast	Aerial and Groundboom	0.99 lb ai/A	7	14	
	DF			0.974 lb / a			
Non-bearing citrus	DF	Broadcast	Airblast	0.73 lb ai/A	7	365	
				3.99 lb ai/A (FL only)			
	WSP			0.99 lb ai/A			
Non-bearing Citrus (ant mound treatment)	DF	Mound treatment	Handheld equipment	0.009 lb ai/mound	NS	365	
	WSP						
Non-Crop Areas (field borders, fencerows, roadsides, ditchbanks, borrow pits)	DF	Broadcast	Groundboom	0.24 lb ai/A	NA	NA	
	WSP	Broadcast	Aerial and Groundboom	0.252 lb ai/A	NA (1 app per year)	NA	
Non-Crop Areas (field borders, fencerows, roadsides, ditchbanks, borrow pits) (ant mound treatment)	WSP	Mound treatment	Handheld equipment	0.012 lb ai/mound	NA	NA	
	G						
Nursery Stock including Non-Bearing Deciduous Fruit and Nut Trees and Vines, including: Almond, Pistachio, Pecan, Walnut, Apple, Kiwi, Pear, Apricot, Cherry, Plum, Prune, Grape	DF	Broadcast	Aerial and Groundboom	0.99 lb ai/A	14 days	365 days	

Use Site	Formulation	Application Method Type	Application Method Equipment	Maximum Application Rate	RTI (days)	PHI (days)	Restrictions
Ornamental lawns and turf	DF	Perimeter /Spot treatment	Handheld equipment	1.164 lb /gal			Do not apply with low pressure handwand. Not for use on residential lawns. Do not apply by air to lawns.
	WSP			0.09 lb ai/gal		NA	
Ornamental lawns and turf (ant mound treatment)	WSP	Mound treatment	Handheld equipment	0.009 lb ai/mound	NA (1 app per year)	NA	
Ornamental plants grown for cut flower production	WSP	Broadcast	Groundboom or Handheld equipment	0.005 lb ai/gal	3 to 7	NA	
				0.75 lb ai/A	NS		
Ornamental Trees and Shrubs	RTU Capsule	Tree injection treatment.	Injection equipment	0.003 lb ai / capsule and 1 capsule every 6 inches of tree	NS	NA	
	WSP			0.1 lb ai/tree			
	WSP			0.32 lb ai/tree			
	RTU liquid injection unit			0.003 lb ai / injection unit and 1 unit every 4 to 6 inches in tree			
	DF	Soil treatment.	Soil injector equipment	0.06 lb ai/gal			
	DF (Pellets)	Broadcast	Airblast	0.974 lb / a			
	WSP	Broadcast	Handheld	0.01 lb ai/gal	14		Do not apply with low pressure handwand
	WSP	Broadcast	Mist blower	4.4 lb ai/A	3 to 7		Assumed maximum application rate from label; used airblast as surrogate for mist blower
	DF (Pellets)	Bark treatment.	Paintbrush	14 lb ai/gal	3 to 7		
	WSP			11 lb ai/gal			
	WSP			11.52 lb ai/gal			
Ornamentals in a commercial greenhouse	PRL	Fogger	Total release fogger	0.045 lb ai/can or 0.017 lb ai/1000 ft^2	NS	NA	
Peanut seed treatment	WSP	Seed treatment.	Hopper box.	0.002 lb ai/lb seed	NA	NA	
Peanuts	DF (Pellets)	Broadcast	Aerial and Groundboom	0.99 lb ai/A	3 to 7	14	
	WSP						
Pepper (bell)	WSP	Broadcast		0.9975 lb ai/A	3 to 7	7	

Use Site	Formulation	Application Method Type	Application Method Equipment	Maximum Application Rate	RTI (days)	PHI (days)	Restrictions
	DF		Aerial and Groundboom	0.974 lb ai/A			
Pepper (non-bell)	DF	Broadcast	Groundboom	0.5 lb ai/A	3 to 10	7	
	WSP						
Residential lawns (ant mound treatment)	D	Mound treatment	Handheld equipment	0.009 lb ai/mound	NS	NA	
	G						
	WP						
Residential ornamentals	L	Broadcast	Handheld equipment	0.012 lb ai/gal	7 to 10	NA	
	G	Soil treatment.		17.51 lb ai/A	6 weeks		
Residential ornamentals (ant mound treatment)	DF	Mound treatment	Handheld equipment	0.007 lb ai/mound	NS	NA	
Residential, Recreational, and Commercial Turf (ant mound treatment)	DF	Mound treatment	Handheld equipment	0.009 lb ai/mound	NS	NA	
	G				NS	NA	
	WSP			0.012 lb ai/mound	NS	NA	
Sod farms	WSP	Broadcast	Groundboom	3.99 lb ai/A	7	3	label states not to exceed 3 lb ai/A for sod farms, but can calculated higher rate from use directions
	DF			3.02 lb ai/ a			
				4.77 lb ai/A			
	G		Tractor drawn spreader	3 lb ai/A			
Sod farms (ant mount treatment)	WSP	Mound treatment	Handheld equipment	0.009 lb ai/mound	NA	NA	
Southern pine seed orchards	DF	Broadcast	Aerial and Airblast	2.997 lb ai/A	14 days	NA	
Soybeans	DF	Broadcast	Aerial and Groundboom	0.99 lb ai/A	3 to 7	14	
	WSP					14	
Structural / Foundation (outdoor) treatment	WSP	Perimeter treatment.	Paintbrush.	0.075 lb ai/gal	NA	NA	
Tobacco	WSP	Broadcast	Aerial and Groundboom	0.75 lb ai/A	7	3	
	DF	Transplant water treatment.	Groundboom	1.125 lb / a	NA	NA	Added directly to soil along with transplanted plants.
		Broadcast	Aerial and Groundboom	0.73 lb ai/A	3 to 7	3	
		Broadcast	Greenhouse	0.73 lb ai/A	7	NA	
Tobacco (ant mound treatment)	WSP	Mound treatment	Handheld equipment	0.009 lb ai / mound	only 1 per crop cycle	3	
	DF						

DF = dry flowable; WSP = water soluble packet; G – granular; L = liquid; D = dust; WP = wettable powder; DF (pellets) = dry flowable in a pellet form; DF (prills) = dry flowable in a prill form; RTU = ready to use

a. Inject into cracks and crevices or void spaces where insects may be harboring, living and breeding. Place injector tip into cracks, crevices, holes and other small openings. Release approximately 1 second of product. For light infestations, move injector tip along cracks while treating at the rate of 3 ft/sec. For heavy infestations, move injector tip along at 1 ft/sec. For closed voids calculate the void's cubic area and treat at the, rate of 5 - 10 sec/3 ft3. Several holes may be required in long-running voids. Treatment of cracks, crevices and voids from the exterior of the structure is also permitted.

Appendix C. Occupational Handler Risk Summary

Table C1. Occupational Handler Exposure and Risk Estimates for the Foliar Uses of Acephate.

Formulation[1]	Crop / Target Category[2]	Application Rate (lb ai/A unless otherwise noted)[3]	Amount Handled / Area Treated[4]	Dermal MOE[5] (LOC = 1000)		Inhalation MOE (LOC = 300)				ARI			
				SL/G	EC	No-R	PF5 R	PF10 R	EC	SL/G + No-R	SL/G + PF5 R	SL/G + PF10 R	EC
Mixer/loaders for Aerial (Broadcast) Applications													
DF/WDG	non-bearing citrus (FL only)	3.99	350 acres	**140**	**750**	**1.1**	**5.5**	**11**	**41**	**0.0036**	**0.016**	**0.029**	**0.12**
	Southern Pine tree Orchards	2.99	350 acres	**190**	1,000	**1.5**	**7.4**	**15**	**55**	**0.0049**	**0.022**	**0.04**	**0.15**
	Field crop, high-acreage	0.99	1200 acres	**170**	**890**	**1.3**	**6.5**	**13**	**48**	**0.0042**	**0.019**	**0.035**	**0.14**
	Field crop, typical	0.99	350 acres	**580**	3,000	**4.5**	**22**	**45**	**170**	**0.015**	**0.065**	**0.12**	**0.48**
	Nursery (ornamentals, vegetables, trees, container stock)	0.97	60 acres	3,400	18,000	**26**	**130**	**260**	990	**0.085**	**0.38**	**0.69**	2.8
	Non-bearing citrus	0.73	350 acres	**790**	4,100	**6**	**30**	**60**	**230**	**0.02**	**0.089**	**0.16**	**0.65**
	Tobacco	0.73	350 acres	**790**	4,100	**6**	**30**	**60**	**230**	**0.02**	**0.089**	**0.16**	**0.65**
	Non-bell pepper	0.5	350 acres	1,100	6,000	**8.8**	**44**	**88**	330	**0.029**	**0.13**	**0.23**	0.93
	Christmas Tree farm	0.48	350 acres	1,200	6,300	**9.1**	**46**	**91**	340	**0.03**	**0.14**	**0.24**	0.96
	Non-crop areas	0.24	350 acres	2,400	13,000	**18**	**91**	**180**	680	**0.059**	**0.27**	**0.48**	1.9
DF/WDG (pellets)	non-bearing citrus (FL only)	3.99	350 acres	**450**	No Data	**160**	810	1,600	No Data	**0.24**	**0.39**	**0.41**	No Data
	Southern Pine tree Orchards	2.99	350 acres	**600**		**220**	1,100	2,200		**0.33**	**0.52**	**0.55**	
	Field crop, high-acreage	0.99	1200 acres	**530**		**190**	950	1,900		**0.29**	**0.45**	**0.49**	
	Field crop, typical	0.99	350 acres	1,800		650	3,300	6,500		0.98	1.5	1.7	
	Nursery (ornamentals, vegetables, trees, container stock)	0.97	60 acres	11,000		3,900	19,000	39,000		6	9.4	10	

Table C1. Occupational Handler Exposure and Risk Estimates for the Foliar Uses of Acephate.													
Formulation[1]	**Crop / Target Category[2]**	**Application Rate (lb ai/A unless otherwise noted)[3]**	**Amount Handled / Area Treated[4]**	**Dermal MOE[5] (LOC = 1000)**		**Inhalation MOE (LOC = 300)**				**ARI**			
				SL/G	**EC**	**No-R**	**PF5 R**	**PF10 R**	**EC**	**SL/G + No-R**	**SL/G + PF5 R**	**SL/G + PF10 R**	**EC**
	Non-bearing citrus	0.73	350 acres	2,500		880	4,400	8,800		1.3	2.1	2.3	
	Tobacco	0.73	350 acres	2,500		880	4,400	8,800		1.3	2.1	2.3	
	Non-bell pepper	0.5	350 acres	3,600		1,300	6,500	13,000		2	3.1	3.3	
	Christmas Tree farm	0.48	350 acres	3,800		1,400	6,700	14,000		2.1	3.2	3.5	
	Non-crop areas	0.24	350 acres	7,500		2,700	14,000	27,000		4.1	6.5	6.9	
DF/WDG (prills)	non-bearing citrus (FL only)	3.99	350 acres	**220**	No Data	**28**	**140**	**280**	No Data	**0.066**	**0.15**	**0.18**	No Data
	Southern Pine tree Orchards	2.99	350 acres	**290**		**38**	**190**	380		**0.088**	**0.2**	**0.24**	
	Field crop, high-acreage	0.99	1200 acres	**260**		**33**	**170**	330		**0.077**	**0.18**	**0.21**	
	Field crop, typical	0.99	350 acres	**880**		**110**	570	1,100		**0.26**	**0.6**	**0.71**	
	Nursery (ornamentals, vegetables, trees, container stock)	0.97	60 acres	5,200		680	3,400	6,800		1.6	3.6	4.2	
	Non-bearing citrus	0.73	350 acres	1,200		**150**	770	1,500		**0.35**	**0.82**	0.97	
	Tobacco	0.73	350 acres	1,200		**150**	770	1,500		**0.35**	**0.82**	0.97	
	Non-bell pepper	0.5	350 acres	1,700		**230**	1,100	2,300		**0.53**	1.2	1.4	
	Christmas Tree farm	0.48	350 acres	1,800		**230**	1,200	2,300		**0.54**	1.2	1.5	
	Non-crop areas	0.24	350 acres	3,600		470	2,300	4,700		1.1	2.4	2.9	
G	Nursery (ornamentals, vegetables, trees, container stock)	1	60 acres	25,000	20,000	**140**	680	1,400	2,800	**0.46**	2.1	3.9	6.4
WSP	Sod	3.99	350 acres	No Data	**750**	No Data			**41**	No Data			**0.12**

Table C1. Occupational Handler Exposure and Risk Estimates for the Foliar Uses of Acephate.													
Formulation[1]	**Crop / Target Category[2]**	**Application Rate (lb ai/A unless otherwise noted)[3]**	**Amount Handled / Area Treated[4]**	**Dermal MOE[5] (LOC = 1000)**		**Inhalation MOE (LOC = 300)**				**ARI**			
				SL/G	**EC**	**No-R**	**PF5 R**	**PF10 R**	**EC**	**SL/G + No-R**	**SL/G + PF5 R**	**SL/G + PF10 R**	**EC**
	Non-bearing citrus	0.99	350 acres		3,000				**170**				**0.48**
	Field crop, typical	0.99	350 acres		3,000				**170**				**0.48**
	Field crop, high-acreage	0.99	1200 acres		**890**				**48**				**0.14**
	Nursery (ornamentals, vegetables, trees, container stock)	0.97	60 acres		18,000				990				2.8
	Tobacco	0.75	350 acres		4,000				**220**				**0.62**
	Non-bell pepper	0.5	350 acres		6,000				330				0.93
	Christmas Tree farm	0.48	350 acres		6,300				340				0.96
	Non-crop areas	0.25	350 acres		12,000				660				1.9
Mixer/loaders for Airblast (Broadcast) Applications													
DF/WDG	non-bearing citrus (FL only)	3.99	40 acres	1,300	6,600	**9.7**	**48**	**97**	360	**0.032**	**0.14**	**0.26**	1
	Southern Pine tree Orchards	2.99	40 acres	1,700	8,800	**13**	**65**	**130**	480	**0.042**	**0.19**	**0.35**	1.4
	Nursery (ornamentals, vegetables, trees, container stock)	0.97	20 acres	10,000	55,000	**79**	400	790	3,000	**0.26**	1.2	2.1	8.5
	Non-bearing citrus	0.73	40 acres	6,800	36,000	**53**	**260**	530	2,000	**0.17**	**0.77**	1.4	5.6
	Christmas Tree farm	0.48	40 acres	10,000	55,000	**80**	400	800	3,000	**0.26**	1.2	2.1	8.5
DF/WDG (pellets)	non-bearing citrus (FL only)	3.99	40 acres	4,000	No Data	1,400	No Data			2.2	No Data		
	Southern Pine tree Orchards	2.99	40 acres	5,300		1,900				2.9			
	Nursery (ornamentals, vegetables, trees, container stock)	0.97	20 acres	33,000		12,000				18			
	Non-bearing citrus	0.73	40 acres	22,000		7,800				12			
	Christmas Tree farm	0.48	40 acres	33,000		12,000				18			

Table C1. Occupational Handler Exposure and Risk Estimates for the Foliar Uses of Acephate.													
Formulation[1]	**Crop / Target Category[2]**	**Application Rate (lb ai/A unless otherwise noted)[3]**	**Amount Handled / Area Treated[4]**	**Dermal MOE[5] (LOC = 1000)**		**Inhalation MOE (LOC = 300)**				**ARI**			
				SL/G	**EC**	**No-R**	**PF5 R**	**PF10 R**	**EC**	**SL/G + No-R**	**SL/G + PF5 R**	**SL/G + PF10 R**	**EC**
DF/WDG (prills)	non-bearing citrus (FL only)	3.99	40 acres	1,900	No Data	**250**	1,200	2,500	No Data	**0.58**	1.3	1.5	No Data
	Southern Pine tree Orchards	2.99	40 acres	2,500		330	1,700	3,300		**0.76**	1.7	2	
	Nursery (ornamentals, vegetables, trees, container stock)	0.97	20 acres	16,000		2,000	10,000	20,000		4.7	11	13	
	Non-bearing citrus	0.73	40 acres	10,000		1,400	6,800	14,000		3.2	6.9	8.2	
	Christmas Tree farm	0.48	40 acres	16,000		2,100	10,000	21,000		4.9	11	13	
WSP	Nursery (ornamentals, vegetables, trees, container stock)	4.4	20 acres	No Data	12,000	No Data			650	No Data			1.8
	Non-bearing citrus	0.99	40 acres		27,000				1,400				4
	Nursery (ornamentals, vegetables, trees, container stock)	0.97	20 acres		55,000				3,000				8.5
	Christmas Tree farm	0.48	40 acres		55,000				3,000				8.5
	Mixer/loaders for Chemigation (Broadcast) Applications												
DF/WDG	Field crop, typical	0.97	350 acres	**590**	3,100	**4.5**	**23**	**45**	**170**	**0.015**	**0.068**	**0.12**	**0.48**
DF/WDG (pellets)				1,900	No Data	670	No Data	No Data	No Data	1	No Data	No Data	No Data
DF/WDG (prills)				**900**	No Data	**120**	580	1200	No Data	**0.28**	**0.61**	**0.73**	No Data
WSP				No Data	3,000	No Data	No Data	No Data	**170**	No Data	No Data	No Data	**0.48**
	Mixer/loaders for Groundboom (Broadcast) Applications												
DF/WDG	Sod	4.77	80 acres	**520**	2,800	**4**	**20**	**40**	**150**	**0.013**	**0.059**	**0.11**	**0.42**
	Sod	3.02	80 acres	**830**	4,400	**6.4**	**32**	**64**	**240**	**0.021**	**0.095**	**0.17**	**0.68**
	Golf course (fairways, tees, greens)	4.77	40 acres	1,000	5,500	**8.1**	**40**	**81**	300	**0.026**	**0.12**	**0.21**	**0.85**
	Golf course (tees and greens only)	4.77	5 acres	8,400	44,000	**65**	320	650	2,400	**0.21**	**0.95**	1.7	6.8
	Tobacco (transplant water)	1.125	20 acres	8,900	47,000	**68**	340	680	2600	**0.22**	1	1.8	7.3
	Field crop, high-acreage	0.99	200 acres	1,000	5,300	**7.8**	**39**	**78**	**290**	**0.025**	**0.12**	**0.21**	**0.82**
	Field crop, typical	0.99	80 acres	2,500	13,000	**19**	**97**	**190**	730	**0.062**	**0.29**	**0.51**	2

Table C1. Occupational Handler Exposure and Risk Estimates for the Foliar Uses of Acephate.													
Formulation[1]	**Crop / Target Category[2]**	**Application Rate (lb ai/A unless otherwise noted)[3]**	**Amount Handled / Area Treated[4]**	**Dermal MOE[5] (LOC = 1000)**		**Inhalation MOE (LOC = 300)**				**ARI**			
				SL/G	**EC**	**No-R**	**PF5 R**	**PF10 R**	**EC**	**SL/G + No-R**	**SL/G + PF5 R**	**SL/G + PF10 R**	**EC**
	Field-grown ornamental crops	0.97	40 acres	5,200	27,000	**40**	**200**	400	1500	**0.13**	**0.59**	1.1	4.2
	Nursery (ornamentals, vegetables, trees, container stock)	0.97	60 acres	3,400	18,000	**26**	**130**	**260**	990	**0.085**	**0.38**	**0.69**	2.8
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.75	60 acres	4,500	23,000	**34**	**170**	340	1,300	**0.11**	**0.5**	**0.91**	3.6
	Tobacco	0.73	80 acres	3,400	18,000	**26**	**130**	**260**	990	**0.085**	**0.38**	**0.69**	2.8
	Non-bell pepper	0.5	80 acres	5,000	26,000	**39**	**190**	390	1400	**0.13**	**0.56**	1	4
	Christmas Tree farm	0.48	40 acres	10,000	55,000	**80**	400	800	3000	**0.26**	1.2	2.1	8.5
	Non-crop areas	0.24	80 acres	10,000	55,000	**80**	400	800	3000	**0.26**	1.2	2.1	8.5
DF/WDG (pellets)	Sod	4.77	80 acres	1,700	No Data	590	3,000	5,900	No Data	**0.91**	1.5	1.6	No Data
	Sod	3.02	80 acres	2,600		940	4,700	9,400		1.4	2.2	2.4	
	Golf course (fairways, tees, greens)	4.77	40 acres	3,300		1,200	5,900	12,000		1.8	2.8	3	
	Golf course (tees and greens only)	4.77	5 acres	27,000		9,500	47,000	95,000		15	23	25	
	Tobacco (transplant water)	1.125	20 acres	28,000		10,000	50,000	100,000		15	24	26	
	Field crop, high-acreage	0.99	200 acres	3,200		1,100	5,700	11,000		1.7	2.7	2.9	
	Field crop, typical	0.99	80 acres	8,000		2,900	14,000	29,000		4.4	6.8	7.4	
	Field-grown ornamental crops	0.97	40 acres	16,000		5,800	29,000	58,000		8.8	14	15	
	Nursery (ornamentals, vegetables, trees, container stock)	0.97	60 acres	11,000		3,900	19,000	39,000		6	9.4	10	
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.75	60 acres	14,000		5,000	25,000	50,000		7.6	12	13	
	Non-bell pepper	0.5	80 acres	16,000		5,600	28,000	56,000		8.6	14	15	
	Tobacco	0.73	80 acres	11,000		3,900	19,000	39,000		6	9.4	10	
	Christmas Tree farm	0.48	40 acres	33,000		12,000	59,000	120,000		18	28	30	
	Non-crop areas	0.24	80 acres	33,000		12,000	59,000	120,000		18	28	30	

Table C1. Occupational Handler Exposure and Risk Estimates for the Foliar Uses of Acephate.													
Formulation[1]	**Crop / Target Category[2]**	**Application Rate (lb ai/A unless otherwise noted)[3]**	**Amount Handled / Area Treated[4]**	**Dermal MOE[5] (LOC = 1000)**		**Inhalation MOE (LOC = 300)**				**ARI**			
				SL/G	**EC**	**No-R**	**PF5 R**	**PF10 R**	**EC**	**SL/G + No-R**	**SL/G + PF5 R**	**SL/G + PF10 R**	**EC**
DF/WDG (prills)	Sod	4.77	80 acres	**800**	No Data	**100**	520	1000	No Data	**0.24**	**0.55**	**0.65**	No Data
	Sod	3.02	80 acres	1,300		**160**	820	1600		**0.38**	**0.88**	1	
	Golf course (fairways, tees, greens)	4.77	40 acres	1,600		**210**	1000	2100		**0.49**	1.1	1.3	
	Golf course (tees and greens only)	4.77	5 acres	13,000		1,700	8300	17000		3.9	8.8	11	
	Tobacco (transplant water)	1.125	20 acres	14,000		1,800	8700	18000		4.2	9.4	11	
	Field crop, high-acreage	0.99	200 acres	1,500		**200**	1000	2000		**0.46**	1	1.2	
	Field crop, typical	0.99	80 acres	3,800		500	2500	5000		1.2	2.6	3.1	
	Field-grown ornamental crops	0.97	40 acres	7,900		1,000	5100	10000		2.3	5.4	6.4	
	Nursery (ornamentals, vegetables, trees, container stock)	0.97	60 acres	5,200		680	3400	6800		1.6	3.6	4.2	
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.75	60 acres	6,800		870	4400	8700		2	4.6	5.5	
	Tobacco	0.73	80 acres	5,200		680	3400	6800		1.6	3.6	4.2	
	Non-bell pepper	0.5	80 acres	7,600		990	4900	9900		2.3	5.2	6.2	
	Christmas Tree farm	0.48	40 acres	16,000		2,100	10000	21000		4.9	11	13	
	Non-crop areas	0.24	80 acres	16,000		2,100	10000	21000		4.9	11	13	
WSP	Sod	3.99	80 acres	No Data	3,300	No Data			**180**	No Data			**0.51**
	Golf course (fairways, tees, greens)	3.9	40 acres		6,800				370				1
	Golf course (tees and greens only)	3.9	5 acres		54,000				2,900				8.2
	Non-bearing citrus	0.99	40 acres		27,000				1,400				4
	Field crop, typical	0.99	80 acres		13,000				730				2
	Field crop, high-acreage	0.99	200 acres		5,300				**290**				**0.82**
	Field-grown ornamental crops	0.97	40 acres		27,000				1,500				4.2

Table C1. Occupational Handler Exposure and Risk Estimates for the Foliar Uses of Acephate.													
Formulation[1]	**Crop / Target Category[2]**	**Application Rate (lb ai/A unless otherwise noted)[3]**	**Amount Handled / Area Treated[4]**	**Dermal MOE[5] (LOC = 1000)**		**Inhalation MOE (LOC = 300)**				**ARI**			
				SL/G	**EC**	**No-R**	**PF5 R**	**PF10 R**	**EC**	**SL/G + No-R**	**SL/G + PF5 R**	**SL/G + PF10 R**	**EC**
	Nursery (ornamentals, vegetables, trees, container stock)	0.97	60 acres		18,000				990				2.8
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.75	60 acres		23,000				1,300				3.6
	Christmas Tree farm	0.48	40 acres		55,000				3,000				8.5
	Mixer/loaders for Tractor-drawn Spreader (Broadcast) Applications												
G	Golf course (fairways, tees, greens)	4.95	40 acres	7,500	6,100	**41**	**210**	410	840	**0.13**	**0.64**	1.2	1.9
	Golf course (tees and greens only)	4.95	5 acres	60,000	49,000	330	1,600	3,300	6,700	1.1	4.9	9.3	15
	Sod	3	80 acres	6,200	5,000	**34**	**170**	340	690	**0.11**	**0.52**	0.96	1.6
	Field crop, high-acreage	1	200 acres	7,500	6,000	**41**	**200**	410	830	**0.13**	**0.61**	1.2	1.9
	Nursery (ornamentals, vegetables, trees, container stock)	1	60 acres	25,000	20,000	**140**	680	1,400	2,800	**0.46**	2.1	3.9	6.4
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)												
	Mixer/loaders for Tree Injection (Injector) Applications												
L	Landscaping, trees/shrubs/bushes	0.32 lb ai/tree	20	43,000	190,000	9,900	49,000	99,000	26,000	19	34	38	60
	Nursery (ornamentals, vegetables, trees, container stock)												
	Applying Sprays via Aerial Equipment												
Spray (all starting formulations)	Sod	4.77	350 acres	No Data	3,000	No Data			1,700	No Data	No Data	No Data	2
	non-bearing citrus (FL only)	3.99			3,600				2,000	No Data	No Data	No Data	2.3
	Southern Pine tree Orchards	2.99			4,700				2,700	No Data	No Data	No Data	3.1
	Field crop, typical	0.99			14,000				8,100	No Data	No Data	No Data	9.2

Table C1. Occupational Handler Exposure and Risk Estimates for the Foliar Uses of Acephate.													
Formulation[1]	**Crop / Target Category[2]**	**Application Rate (lb ai/A unless otherwise noted)[3]**	**Amount Handled / Area Treated[4]**	**Dermal MOE[5] (LOC = 1000)**		**Inhalation MOE (LOC = 300)**				**ARI**			
				SL/G	**EC**	**No-R**	**PF5 R**	**PF10 R**	**EC**	**SL/G + No-R**	**SL/G + PF5 R**	**SL/G + PF10 R**	**EC**
	Field crop, high-acreage		1200 acres		4,200				2,400	No Data	No Data	No Data	2.8
	Nursery (ornamentals, vegetables, trees, container stock)	0.97	60 acres		86,000				48,000	No Data	No Data	No Data	56
	Non-bearing citrus	0.73	350 acres		19,000				11,000	No Data	No Data	No Data	13
	Tobacco				19,000				11,000	No Data	No Data	No Data	13
	Non-bell pepper	0.5			28,000				16,000	No Data	No Data	No Data	18
	Christmas Tree farm	0.48			30,000				17,000	No Data	No Data	No Data	20
	Non-crop areas	0.24			59,000				34,000	No Data	No Data	No Data	39
Applying Sprays via Airblast Equipment													
Spray (all starting formulations)	Nursery (ornamentals, vegetables, trees, container stock)	4.4	20 acres	**74**	8,100	**33**	**170**	330	2,300	**0.044**	**0.065**	**0.069**	3.9
	non-bearing citrus (FL only)	3.99	40 acres	**41**	4,400	**18**	**92**	**180**	1,300	**0.024**	**0.036**	**0.038**	2.2
	Southern Pine tree Orchards	2.99		**55**	5,900	**25**	**120**	**250**	1,700	**0.033**	**0.048**	**0.052**	2.9
	Nursery (ornamentals, vegetables, trees, container stock)	0.97	20 acres	**340**	37,000	**150**	750	1,500	10,000	**0.2**	**0.3**	**0.32**	18
	Non-bearing citrus	0.73	40 acres	**220**	24,000	**100**	500	1,000	6,900	**0.13**	**0.19**	**0.21**	12
	Christmas Tree farm	0.48		**340**	37,000	**150**	760	1,500	11,000	**0.2**	**0.3**	**0.32**	18
Applying Sprays via Groundboom Equipment													
Spray (all starting formulations)	Golf course (tees and greens only)	4.77	5 acres	27,000	85,000	1,700	8,500	17,000	13,000	4.7	14	18	29
	Golf course (fairways, tees, greens)		40 acres	3,400	11,000	**210**	1,100	2,100	1,700	**0.58**	1.8	2.3	3.7
	Sod		80 acres	1,700	5,300	**110**	530	1,100	840	**0.3**	**0.87**	1.2	1.8
	non-bearing citrus (FL only)	3.99	40 acres	4,000	13,000	**250**	1,300	2,500	2,000	**0.69**	2.1	2.7	4.4
	Southern Pine tree Orchards	2.99		5,400	17,000	340	1,700	3,400	2,700	0.94	2.8	3.7	5.9
	Tobacco (transplant water)	1.125	20 acres	29,000	90,000	1,800	9,000	18,000	14,000	5	15	20	31
	Field crop, typical	0.99	80 acres	8,100	26,000	510	2,600	5,100	4,000	1.4	4.2	5.5	8.8

Table C1. Occupational Handler Exposure and Risk Estimates for the Foliar Uses of Acephate.													
Formulation[1]	**Crop / Target Category[2]**	**Application Rate (lb ai/A unless otherwise noted)[3]**	**Amount Handled / Area Treated[4]**	**Dermal MOE[5] (LOC = 1000)**		**Inhalation MOE (LOC = 300)**				**ARI**			
				SL/G	**EC**	**No-R**	**PF5 R**	**PF10 R**	**EC**	**SL/G + No-R**	**SL/G + PF5 R**	**SL/G + PF10 R**	**EC**
	Field crop, high-acreage		200 acres	3,200	10,000	**210**	1,000	2,100	1,600	**0.57**	1.6	2.2	3.5
	Field-grown ornamental crops	0.97	40 acres	17,000	52,000	1,000	5,200	10,000	8,300	2.8	8.6	11	18
	Nursery (ornamentals, vegetables, trees, container stock)		60 acres	11,000	35,000	700	3,500	7,000	5,500	1.9	5.7	7.5	12
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.75		14,000	45,000	900	4,500	9,000	7,100	2.5	7.2	9.5	16
	Non-bearing citrus	0.73	40 acres	22,000	69,000	1,400	6,900	14,000	11,000	3.9	11	15	24
	Tobacco		80 acres	11,000	35,000	690	3,500	6,900	5,500	1.9	5.7	7.4	12
	Non-bell pepper	0.5		16,000	51,000	1,000	5,100	10,000	8,000	2.8	8.2	11	18
	Christmas Tree farm	0.48	40 acres	33,000	110,000	2,100	11,000	21,000	17,000	5.8	17	22	37
	Non-crop areas	0.24	80 acres	33,000	110,000	2,100	11,000	21,000	17,000	5.8	17	22	37
Applying Granulars via Aerial Equipment													
G	Nursery (ornamentals, vegetables, trees, container stock)	1	60 acres	No Data	100,000	No Data	No Data	No Data	**180**	No Data	No Data	No Data	**0.6**
Applying Granulars via Tractor-drawn spreader Equipment													
G	Golf course (fairways, tees, greens)	4.95	40 acres	7,200	26,000	**58**	**290**	580	320	**0.19**	**0.85**	1.5	1
	Golf course (tees and greens only)		5 acres	58,000	210,000	470	2,300	4,700	2,500	1.5	6.8	12	8
	Sod	3	80 acres	6,000	22,000	**48**	**240**	480	**260**	**0.16**	**0.71**	1.3	**0.83**
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	1	60 acres	24,000	86,000	**190**	960	1,900	1,000	**0.62**	2.8	5	3.2
	Nursery (ornamentals, vegetables, trees, container stock)												
	Field crop, high-acreage		200 acres	7,200	26,000	**57**	**290**	570	310	**0.19**	**0.85**	1.5	0.99
Applying RTU Aerosol Can													

Table C1. Occupational Handler Exposure and Risk Estimates for the Foliar Uses of Acephate.													
Formulation[1]	**Crop / Target Category[2]**	**Application Rate (lb ai/A unless otherwise noted)[3]**	**Amount Handled / Area Treated[4]**	**Dermal MOE[5] (LOC = 1000)**		**Inhalation MOE (LOC = 300)**				**ARI**			
				SL/G	**EC**	**No-R**	**PF5 R**	**PF10 R**	**EC**	**SL/G + No-R**	**SL/G + PF5 R**	**SL/G + PF10 R**	**EC**
RTU (PL)	Food handling establishment (Broadcast application)	0.011 lb ai/can	10	1,200	No Data	**97**	480	970	No Data	**0.25**	**0.69**	**0.88**	No Data
	Food handling establishment (crack/crevice application)												
	Warehouse (Broadcast application)												
	Warehouse (crack/crevice application)												
	Childcare center/schools/institutions (Broadcast application)												
	Childcare center/schools/institutions (crack/crevice application)												
Applying RTU Fogger													
RTU (PL)	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.045 lb ai/can	NA	Negligible exposure									
Flagging for Aerial Spray Applications													
Spray (all starting formulations)	non-bearing citrus (FL only)	3.99	350 acres	**620**	No Data	**28**	**140**	**280**	No Data	**0.081**	**0.27**	**0.37**	No Data
	Southern Pine tree Orchards	2.99		**820**	No Data	**38**	**190**	380	No Data	**0.11**	**0.36**	**0.5**	No Data
	Field crop, high-acreage	0.99		2,500	No Data	**110**	570	1,100	No Data	**0.32**	1.1	1.5	No Data
	Nursery (ornamentals, vegetables, trees, container stock)	0.97	60 acres	15,000	No Data	680	3,400	6,800	No Data	2	6.5	9	No Data
	Non-bearing citrus	0.73	350 acres	3,400	No Data	**150**	770	1,500	No Data	**0.44**	1.5	2	No Data

Table C1. Occupational Handler Exposure and Risk Estimates for the Foliar Uses of Acephate.													
Formulation[1]	**Crop / Target Category[2]**	**Application Rate (lb ai/A unless otherwise noted)[3]**	**Amount Handled / Area Treated[4]**	**Dermal MOE[5] (LOC = 1000)**		**Inhalation MOE (LOC = 300)**				**ARI**			
				SL/G	**EC**	**No-R**	**PF5 R**	**PF10 R**	**EC**	**SL/G + No-R**	**SL/G + PF5 R**	**SL/G + PF10 R**	**EC**
	Christmas Tree farm	0.48		5,100	No Data	**230**	1,200	2,300	No Data	**0.67**	2.2	3.1	No Data
Flagging for Aerial Granular Applications													
G	Nursery (ornamentals, vegetables, trees, container stock)	1	60 acres	63,000	No Data	1,500	7,700	15,000	No Data	4.6	18	28	No Data
Mixing/loading/applying via Backpack													
DF/WDG	Foundations/perimeter	0.075lb ai/gallon	40	**420**	No Data	1,800	8,900	18,000	No Data	**0.39**	**0.41**	**0.42**	No Data
	Landscaping, turf (lawns, athletic fields, parks, etc.) (spot treatment)	0.06 lb ai/gallon		**520**		2,200	11,000	22,000		**0.49**	**0.51**	**0.52**	
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.01 lb ai/gallon		2,300		**250**	1,200	2,500		**0.61**	1.5	1.8	
	Landscaping, trees/shrubs/bushes	0.01 lb ai/gallon		**850**		500	2,500	5,000		**0.56**	**0.77**	**0.81**	
	Landscaping, plants/flowers												
	Nursery (ornamentals, vegetables, trees, container stock)	0.007 lb ai/gallon		1,200		710	3,600	7,100		**0.8**	1.1	1.1	
	Christmas Tree farm	0.005 lb ai/gallon		1,700		1,000	5,000	10,000		1.1	1.5	1.6	
L	Landscaping, trees/shrubs/bushes	0.012 lb ai/gallon		**710**		420	2,100	4,200		**0.47**	**0.64**	**0.68**	
	Landscaping, plants/flowers												
WSP	Landscaping, turf (lawns, athletic fields, parks, etc.) (spot treatment)	0.09 lb ai/gallon		**350**		1,500	7,400	15,000		**0.33**	**0.35**	**0.35**	
	Foundations/perimeter	0.075 lb ai/gallon		**420**		1,800	8,900	18,000		**0.39**	**0.41**	**0.42**	

Table C1. Occupational Handler Exposure and Risk Estimates for the Foliar Uses of Acephate.													
Formulation[1]	**Crop / Target Category[2]**	**Application Rate (lb ai/A unless otherwise noted)[3]**	**Amount Handled / Area Treated[4]**	**Dermal MOE[5] (LOC = 1000)**		**Inhalation MOE (LOC = 300)**				**ARI**			
				SL/G	**EC**	**No-R**	**PF5 R**	**PF10 R**	**EC**	**SL/G + No-R**	**SL/G + PF5 R**	**SL/G + PF10 R**	**EC**
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.01 lb ai/gallon		2,300		**250**	1,200	2,500		**0.61**	1.5	1.8	
	Landscaping, trees/shrubs/bushes	0.01 lb ai/gallon		**850**		500	2,500	5,000		**0.56**	**0.77**	**0.81**	
	Landscaping, plants/flowers												
	Nursery (ornamentals, vegetables, trees, container stock)	0.007 lb ai/gallon		1,200		710	3,600	7,100		**0.8**	1.1	1.1	
	Christmas Tree farm	0.005 lb ai/gallon		1,700		1,000	5,000	10,000		1.1	1.5	1.6	
Mixing/loading/applying via Manually-pressurized Handwand													
DF/WDG	Indoors/Food handling establishment (crack/crevice application)	0.085 lb ai/gallon	40	**350**	No Data	**3.7**	**19**	**37**	No Data	**0.012**	**0.054**	**0.091**	No Data
	Indoors/Warehouse (crack/crevice application)												
	Indoors/Childcare center/schools/institutions (crack/crevice application)												
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.01 lb ai/gallon		60,000		1,100	5,700	11,000		3.5	14	23	
	Landscaping, trees/shrubs/bushes												
	Landscaping, plants/flowers												
	Nursery (ornamentals, vegetables, trees, container stock)	0.007 lb ai/gallon		86,000		1,600	8,200	16,000		5	21	33	

Table C1. Occupational Handler Exposure and Risk Estimates for the Foliar Uses of Acephate.													
Formulation[1]	**Crop / Target Category[2]**	**Application Rate (lb ai/A unless otherwise noted)[3]**	**Amount Handled / Area Treated[4]**	**Dermal MOE[5] (LOC = 1000)**		**Inhalation MOE (LOC = 300)**				**ARI**			
				SL/G	**EC**	**No-R**	**PF5 R**	**PF10 R**	**EC**	**SL/G + No-R**	**SL/G + PF5 R**	**SL/G + PF10 R**	**EC**
L	Landscaping, trees/shrubs/bushes	0.012 lb ai/gallon		50,000		960	4,800	9,600		3	12	20	
	Landscaping, plants/flowers												
WSP	Indoors/Food handling establishment (crack/crevice application)	0.085 lb ai/gallon		**350**		**3.7**	**19**	**37**		**0.012**	**0.054**	**0.091**	
	Indoors/Warehouse (crack/crevice application)												
	Indoors/Childcare center/schools/institutions (crack/crevice application)												
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.01 lb ai/gallon		60,000		1,100	5,700	11,000		3.5	14	23	
	Landscaping, plants/flowers												
	Landscaping, trees/shrubs/bushes												
	Mounds/nests (spot treatment)	0.009 lb ai/gallon		67,000		1,300	6,400	13,000		4.1	16	26	
	Nursery (ornamentals, vegetables, trees, container stock)	0.007 lb ai/gallon		86,000		1,600	8,200	16,000		5	21	33	
	Christmas Tree farm	0.005 lb ai/gallon		120,000		2,300	11,000	23,000		7.2	28	47	
Mixing/loading/applying via Mechanically-pressurized Handwand													
DF/WDG	Golf course (tees and greens only)	4.77	5 acres	**310**	No Data	**14**	**69**	**140**	No Data	**0.041**	**0.13**	**0.19**	No Data
	Golf course (fairways, tees, greens)												
	Christmas Tree farm	0.005 lb ai/gallon	1000	1,000		320	1,600	3,200		**0.52**	**0.84**	**0.91**	

Table C1. Occupational Handler Exposure and Risk Estimates for the Foliar Uses of Acephate.													
Formulation[1]	**Crop / Target Category[2]**	**Application Rate (lb ai/A unless otherwise noted)[3]**	**Amount Handled / Area Treated[4]**	**Dermal MOE[5] (LOC = 1000)**		**Inhalation MOE (LOC = 300)**				**ARI**			
				SL/G	**EC**	**No-R**	**PF5 R**	**PF10 R**	**EC**	**SL/G + No-R**	**SL/G + PF5 R**	**SL/G + PF10 R**	**EC**
	Warehouse	0.085 lb ai/gallon		**190**		**2.1**	**10**	**21**		**0.0068**	**0.028**	**0.051**	
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.01 lb ai/gallon		**410**		**11**	**57**	**110**		**0.034**	**0.13**	**0.19**	
	Landscaping, trees/shrubs/bushes	0.01 lb ai/gallon		**510**		**160**	790	1,600		**0.26**	**0.43**	**0.47**	
	Nursery (ornamentals, vegetables, trees, container stock)	0.007 lb ai/gallon		**720**		**230**	1,100	2,300		**0.37**	**0.6**	**0.66**	
L	Landscaping, trees/shrubs/bushes	0.012 lb ai/gallon		**420**		**130**	660	1,300		**0.21**	**0.35**	**0.38**	
WSP	Golf course (tees and greens only)	4.77	5 acres	**510**		**32**	**160**	320		**0.088**	**0.26**	**0.35**	
	Golf course (fairways, tees, greens)												
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	0.01 lb ai/gallon	1000	**410**		**11**	**57**	**110**		**0.034**	**0.13**	**0.19**	
	Landscaping, trees/shrubs/bushes	0.01 lb ai/gallon		**510**		**160**	790	1,600		**0.26**	**0.43**	**0.47**	
	Nursery (ornamentals, vegetables, trees, container stock)	0.007 lb ai/gallon		**720**		**230**	1,100	2,300		**0.37**	**0.6**	**0.66**	
	Christmas Tree farm	0.005 lb ai/gallon		1,000		320	1,600	3,200		**0.52**	**0.84**	**0.91**	
Loading/applying via Belly Grinder													
G	Landscaping, trees/shrubs/bushes	17.51	1 acre	**64**	No Data	**13**	**64**	**130**	No Data	**0.026**	**0.049**	**0.056**	No Data
	Landscaping, plants/flowers												
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	1		1,100		**220**	1,100	2,200		**0.44**	**0.85**	0.96	

Table C1. Occupational Handler Exposure and Risk Estimates for the Foliar Uses of Acephate.													
Formulation[1]	**Crop / Target Category[2]**	**Application Rate (lb ai/A unless otherwise noted)[3]**	**Amount Handled / Area Treated[4]**	**Dermal MOE[5] (LOC = 1000)**		**Inhalation MOE (LOC = 300)**				**ARI**			
				SL/G	**EC**	**No-R**	**PF5 R**	**PF10 R**	**EC**	**SL/G + No-R**	**SL/G + PF5 R**	**SL/G + PF10 R**	**EC**
	Nursery (ornamentals, vegetables, trees, container stock)												
Loading/applying via Cup													
G	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	1	0.5 acre	1,800,000	No Data	2,200	11,000	22,000	No Data	7.3	36	70	No Data
	Nursery (ornamentals, vegetables, trees, container stock)												
	Mounds/nests	0.009 lb ai/mound	20	5,100,000		6,100	31,000	61,000		20	100	200	
Loading/applying via Rotary Spreader													
G	Golf course (tees and greens only)	4.95	5 acres	1,700	No Data	**56**	**280**	560	No Data	**0.17**	**0.6**	**0.89**	No Data
	Golf course (fairways, tees, greens)												
	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	1		8,600		**280**	1,400	2,800		**0.84**	3	4.5	
Loading/applying via spoon													
G	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	1	0.5 acre	6,800	No Data	**230**	1,100	2,300	No Data	**0.69**	2.4	3.6	No Data
	Nursery (ornamentals, vegetables, trees, container stock)												
	Mounds/nests	0.009 lb ai/mound	20	19,000		630	3,200	6,300		1.9	6.8	10	
Loading/applying via paintbrush													
Paint/stain	Tree treatment	14 lb ai/gallon	0.25	**120**	No Data	**14**	**70**	**140**	No Data	**0.034**	**0.079**	**0.095**	No Data

Table C1. Occupational Handler Exposure and Risk Estimates for the Foliar Uses of Acephate.													
Formulation[1]	Crop / Target Category[2]	Application Rate (lb ai/A unless otherwise noted)[3]	Amount Handled / Area Treated[4]	Dermal MOE[5] (LOC = 1000)		Inhalation MOE (LOC = 300)				ARI			
				SL/G	EC	No-R	PF5 R	PF10 R	EC	SL/G + No-R	SL/G + PF5 R	SL/G + PF10 R	EC
	Structural (e.g., warehouses, FHE, home bathrooms)	0.085 lb ai/gallon	2	2,500		**290**	1,400	2,900		**0.7**	1.6	2	

Shaded column = current PPE required on labels. Bold MOE values indicate the LOC has been exceeded with label-recommended and/or additional PPE.

1. Formulations: DF/WDG = dry flowable/water dispersible granular; DF/WDG (pellets) = pelleted form of a dry flowable formulation; DF/WDG (prills) = prill form of a dry flowable formulation; G = granular; WSP = water soluble packet; L = liquid; RTU(PL) = ready-to-use pressurized liquid.
2. Typical field crops include beans, bell peppers, Brussels sprouts, celery, cranberries, lettuce, mint, pepper, and tobacco. High acreage field crops included cotton, peanuts, and soybeans.
3. Based on registered labels.
4. Exposure Science Advisory Council Policy #9.1 and HED assumptions.
5. Dermal MOE = (Dermal POD, 150 mg/kg/day) ÷ (Dermal Dose, mg/kg/day), where Dermal dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) ÷ BW (69 kg). Dermal unit exposures based mostly on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (September 2015). For DF (pellets) and DF (prills) chemical-specific unit exposure data were available; MRID 45597001 and MRID 46827101, respectively. Level of mitigation: SL/G = Single layer clothing, gloves; EC = Engineering Controls.
6. Inhalation MOE = (Inhalation POD, 0.2 mg/kg/day) ÷ (Inhalation Dose, 0.2 mg/kg/day), where Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) ÷ BW (69 kg). Inhalation unit exposures based mostly on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (September 2015). For DF (pellets) and DF (prills) chemical-specific unit exposure data were available; MRID 45597001 and MRID 46827101, respectively. Level of mitigation: No-R = no respirator; PF5 R = PF5 respirator; PF10 R = PF10 respirator; EC = Engineering Controls.
7. ARI = Aggregate Risk Index = 1÷ [(Dermal LOC ÷ Dermal MOE) + (Inhalation LOC ÷ Inhalation MOE)].

Table C.2. Occupational Handler Exposure and Risk Estimates for the Seed Treatment Uses of Acephate.								
Exposure Scenario	Crop	Unit Exposures (ug/lb ai)[1]		Application Rate[2]	Amount Handled / Planted[3]	Dermal MOE[4] (LOC = 1000)	Inhalation MOE (LOC=300)[5]	ARI[6]
		Dermal	Inhalation					
Commercial Seed Treatment								
Mixer/loader of Water Soluble Packets	Cotton	EC: 9.8	EC: 0.24	0.004 lb ai/lb seed	125,000 lb seed treated per day	2,100	**110**	EC: **0.31**
Mixer/loader of DF		SL/G: 51.6 EC: 9.8	No-R: 8.96 PF5: 1.792 EC: 0.12			**400** 2,100	**3.1** **15** **110**	SL/G + PF5: **0.044** EC: **0.31**
Mixer/loader of DF (pellets)		SL/G: 16.3	No-R: 0.061 PF5: 0.012			1,300	450 2,300	SL/G + No-R: **0.7** SL/G + PF5: 1.1
Mixer/loader of DF (prills)		SL/G: 34	No-R: 0.35 PF5: 0.07			**610**	**79** 390	SL/G + No-R: **0.18** SL/G + PF5: **0.42**
Sewer		SL/no G: 6.2	No-R: 0.23 PF5: 0.046			3,300	**120** 600	SL/noG + No-R: **0.36** SL/no G + PF5: 1.2
Bagger		SL/no G: 9.1	No-R: 0.16 PF5: 0.032			2,300	**170** 860	SL/noG + No-R: **0.45** SL/no G + PF5: 1.3
Multiple Activities		SL/G: 42	No-R: 1.6 PF5: 0.32			490	**17** **86**	SL/G + No-R: **0.051** SL/G + PF5: **0.18**
Mixer/loader of Water Soluble Packets	Peanuts	EC: 9.8	EC: 0.24	0.002 lb ai/lb seed	126,000 lb seed treated per day	4,200	**110**	EC: **0.31**
Sewer		SL/no G: 6.2	No-R: 0.23 PF5: 0.046			6,600	**120** 600	SL/noG + No-R: **0.71** SL/no G + PF5: 2.5
Bagger		SL/no G: 9.1	No-R: 0.16 PF5: 0.032			4,500	**170** 860	SL/noG + No-R: **0.91** SL/no G + PF5: 2.5
Multiple Activities		SL/G: 42	No-R: 1.6 PF5: 0.32			**970**	**17** **86**	SL/G + No-R: **0.1** SL/G + PF5: **0.36**
Seed Planters								
Planter	Cotton	SL/G: 250	No-R: 1.2 PF5: 0.32	0.004 lb ai/lb seed	3,778 lb seed planted per day	2,700	760 3,800	SL/G + No-R: 1.3 SL/G + PF5: 2.2
	Peanuts			0.002 lb ai/lb seed	45,652 lb seed planted per day	**450**	**130** 630	SL/G + No-R: **0.22** SL/G + PF5: **0.37**
On-Farm Seed Treatment (using chemical-specific unit exposure data from MRID 46634103)								

Table C.2. Occupational Handler Exposure and Risk Estimates for the Seed Treatment Uses of Acephate.								
Exposure Scenario	Crop	Unit Exposures (ug/lb ai)[1]		Application Rate[2]	Amount Handled / Planted[3]	Dermal MOE[4] (LOC = 1000)	Inhalation MOE (LOC=300)[5]	ARI[6]
		Dermal	Inhalation					
On-Farm treatment	Cotton	SL/G: 4894	No-R: 541 PF5: 108.2	0.004 lb ai/lb seed	3,778 lb seed handled per day	**56**	**0.68** **3.4**	SL/G + No-R: **0.0022** SL/G + PF5: **0.0094**
	Peanuts			0.002 lb ai/lb seed	45,652 lb seed handled per day	**23**	**0.28** **1.4**	SL/G + No-R: **0.0009** SL/G + PF5: **0.0039**

1. Based on ExpoSAC Policy #14 and the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (September 2015).
2. Based on registered labels.
3. The amount of seed treated commercially is based on a survey[17] submitted by the Agricultural Handler Exposure Task Force (AHETF). The amount of seed planted per day is based on HED ExpoSAC Policy 15, HED ExpoSAC Policy SOP 15.1, and the BEAD memo: "Acres Planted per Day and Seeding Rates of Crops Grown in the United States."
4. Dermal MOE = (Dermal POD, 150 mg/kg/day) ÷ (Dermal Dose, mg/kg/day), where Dermal dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × application rate (lb ai/lb seed) × amount treated (lb seed/day) ÷ BW (69 kg).
5. Inhalation MOE = (Inhalation POD, 0.2 mg/kg/day) ÷ (Inhalation Dose, 0.2 mg/kg/day), where Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × application rate (lb ai/lb seed) × amount treated (lb seed/day) ÷ BW (69 kg)..
6. ARI = Aggregate Risk Index = 1÷ [(Dermal LOC ÷ Dermal MOE) + (Inhalation LOC ÷ Inhalation MOE)].

[17] Thompson, R and Rosenheck, L. Survey Results of Commercial and Downstream Seed Treating Facilities. Study Number AHE149. July 23, 2013.