Appendix A: Background Information for Pyrethroids

Pyrethroids are manufactured insecticides that are similar in chemical structure to pyrethrins, naturally occurring chemicals found in certain chrysanthemum flowers (ATSDR 2003a). The pyrethroids are more photostable than pyrethrins and are widely used in agriculture and in medical and veterinary products (EPA 2011a). In the 1990s, permethrin was the most frequently used pyrethroid in U.S. agricultural crop production, representing about 40% of the amount of pyrethroids applied to U.S. crops in this period (about 2.5 million pounds total pyrethroids per year; ATSDR 2003a). It has been estimated that pyrethroids account for about 25% of the recent global insecticide market (Costa 2008; Soderlund et al. 2002).

A.1 Toxicokinetics

Based on studies in humans and animals, pyrethroids are expected to be absorbed via the oral, inhalation, and dermal routes of exposure (ATSDR 2003a). Following absorption, pyrethroids are rapidly and widely distributed to tissues, including central and peripheral nerve tissues (ATSDR 2003a). Biotransformation of pyrethroids involves the hydrolytic cleavage of the central ester bond catalyzed by carboxylesterases to yield carboxylic acid derivatives and phenoxybenzoic acid derivatives and oxidation of alcohol groups by CYP oxygenases (ATSDR 2003a; Costa 2008). For most pyrethroids, hydrolytic and oxidative metabolic transformations represent detoxification processes. Inhibitors of CYP and carboxylesterases enhance the toxicity of pyrethroids, and piperonyl butoxide (a CYP inhibitor) consequently is a component of many commercial pyrethroid formulations (Costa 2008). Results from animal studies indicate that pyrethroids are eliminated from the body within 4–12 days following oral exposure via urinary excretion of metabolites and fecal excretion of parent compounds and metabolites (ATSDR 2003a). A human PBPK model for simulating toxicokinetics of exposures to mixtures of deltamethrin, permethrin, cypermethrin, and cyfluthrin was used to reconstruct exposures from biomonitoring (Quindroit et al. 2019, 2021).

A.2 Health Effects

Neurological effects are the principal effects associated with exposure to pyrethroids (ATSDR 2003a; EPA 2011a). Pyrethroid insecticides act by interfering with the function of voltage-gated sodium channels (VGSCs) in nerve cells, producing whole-body tremors associated with coma or seizures and death in mammals with acute exposure to high doses (ATSDR 2003a; EPA 2011a). Modification of the kinetics of VGSC activation and inactivation are thought to underlie acute clinical signs of pyrethroid

neurotoxicity (EPA 2011a, 2011b). At nonlethal doses of pyrethroids, acute- and intermediate-duration studies with animals have reported signs of neurological impairment including increased excitability and aggressiveness, decreased grip strength and motor activity, and altered gait in rats given single doses of pyrethroids or repeatedly exposed to permethrin in the diet, and diarrhea in dogs given cyhalothrin in gelatin capsules daily for 26 weeks (ATSDR 2003a). Two types of pyrethroids are recognized based on syndromes of toxic signs observed in acutely exposed rats (ATSDR 2003a; EPA 2011a; Ray and Fry 2006; Soderlund et al. 2002). Both types have an acid and an alcohol structural moiety. Type II pyrethroids typically have a cyano substituent attached to the alpha carbon of the alcohol moiety, Type I pyrethroids do not (EPA 2011a). Type I pyrethroids (also known as "T" pyrethroids; e.g., bifenthrin, permethrin, resmethrin) produce marked behavioral arousal, aggressive sparring, increased startle response, and tremors progressing from fine to whole-body tremors and prostration (ATSDR 2003a; EPA 2011a; Ray and Fry 2006; Soderlund et al. 2002). Type II pyrethroids (also known as "CS" pyrethroids; e.g., cyfluthrin, cyhalothrin, cypermethrin, fenvalerate, fluvalinate, tralomethrin) produce salivation and coarse tremors progressing to choreoathetosis and clonic seizures. Some pyrethroids (cyphenothrin, flucythrinate, esfenvalerate, and fenpropathrin) produce a mixture of the signs assigned to the two syndromes (ATSDR 2003a; EPA 2011a; Ray and Fry 2006; Soderlund et al. 2002).

Standard developmental toxicity and reproductive toxicity tests in animals orally exposed to pyrethroids have found no consistent evidence for developmental toxicity or reproductive toxicity (ATSDR 2003a; EPA 2011a). EPA (2011a) reported the absence of prenatal sensitivity in 76 guideline studies submitted to EPA for 24 pyrethroids. ATSDR (2003a) evaluated developmental toxicity tests with permethrin and resmethrin and reproductive toxicity tests with cyhalothrin, cypermethrin, and resmethrin. Neurodevelopmental effects have not been consistently associated with oral exposure of rodents orally exposed to pyrethroids (bioallethrin or deltamethrin) during neonatal stages of development (ATSDR 2003a; Costa 2008). However, in its cumulative risk assessment for pyrethroids (see next paragraph), EPA (2011a, 2011c) used a 3X safety factor for childhood exposures from birth to <6 years of age based on: (1) rat PBPK model predictions of a 3-fold increase in pyrethroid concentrations in juvenile brains, compared with adult brains; (2) similar *in vivo* and *in vitro* pharmacodynamic responses to pyrethroids in juvenile and adult rats; and (3) evidence that rat VGSCs are more sensitive to pyrethroids than homologous human isoforms.

The EPA (2011a) OPP conducted a cumulative risk assessment for 16 pyrethrin/pyrethroid insecticides. The assessment used:

1. 24-hour exposure estimates for the general human population to 13–15 pyrethroids by three exposure pathways (food, water, and residential use);

2. a relative potency approach using neurobehavioral data in rats exposed to multiple gavage dose levels of each of 16 pyrethroids (including deltamethrin, the index chemical) to estimate doses expected to be without risk for acute neurobehavioral effects in humans;

3. a margin-of-exposure (MOE) analysis using a target MOE of 100 for adults (10 each for inter- and intra-species variability) and 300 for children (3 for a FQPA safety factor and 10 each for inter- and intra-species variability) and a POD for deltamethrin of 11 mg/kg/day.

The POD was the $BMDL_{20}$ for incidence of rats with a composite score for acute clinical signs of neurological impairment based on measures of body temperature, tremors, clonic convulsions, salivation, and mobility. The EPA (2011a, 2011c) determined that the 10X FQPA safety factor would be reduced to 1X for all populations >6 years of age, including women of child-bearing age, based on the absence of pre-natal sensitivity in 76 guideline studies submitted to EPA for 24 pyrethroids. EPA retained a 3X safety factor for exposures from birth to <6 years of age, based on the reasons described in the previous paragraph.

Relative potencies derived by EPA (2011a) for pyrethroids are listed in Table A-1. Deltamethrin was selected as the index chemical, because it had one of the most robust databases of guideline and literature toxicity studies among the evaluated pyrethroids, and it was tested with three dose levels in the principal studies (EPA 2011a; Weiner et al. 2009), compared with two dose levels for the other candidate index chemical, permethrin (EPA 2011a). For food and water dietary exposure to deltamethrin equivalents, the MOE for the general population was 4,700, indicating no risk of concern. Analyses for age-related subgroups indicated that the MOE of highest concern, 2,000, was for infants <1 year old, but this value is also indicative of no risk of concern. For residential use of pyrethroid insecticides involving dermal and inhalation exposure, MOEs ranged for 3,000 to 240,000 for dermal exposures and from 130,000 to 10,000,000 for inhalation exposures.

The EPA IRIS files (IRIS 2013) present abbreviated summaries of results from unpublished animal toxicity tests and derived oral RfDs for 10 pyrethroids, but these files do not reflect the updated toxicity assessment conducted by the U.S. EPA OPP (EPA 2011a).

Table A-1. Relative Potency Estimates for Pyrethroids Included in the EPA (2011a) Screening-Level Cumulative Risk Assessment

Pyrethroid	Oral BMD_{20}	Oral RPF[b,c]
Allethrin	135	0.11
Bifenthrin	14.3	1.01
Cyfluthrin	12.6	1.15
Lambda-cyhalothrin	8.9	1.63
Cyphenothrin	100[a]	0.15
Cypermethrin	76.3	0.19
Deltamethrin[d]	**14.5**	**1.0**
Esfenvalerate	40.5	0.36
Fenpropathrin	29	0.50
Tau-fluvalinate	14.5	1.0
Imiprothrin	750[a]	0.02
Permethrin	156	0.09
Prallethrin	150[a]	0.1
Pyrethrins	800[a]	0.02
Resmethrin	291	0.05

[a]Values estimated from studies other than the principal study. All other BMD_{20} values were estimated using benchmark dose (BMD) analyses of incidence data from the principal study of gavage-exposed rats. The incidences were for composite scores >4 on a 4–12 composite score based on measures of body temperature, tremors, clonic convulsions, salivation, and mobility.
[b]RPF = BMD_{20} of index chemical (deltamethrin) / BMD_{20} of subject chemical. For example, allethrin RPF = 14.5/135 = 0.11.
[c]RPFs for dermal and inhalation exposures were based on oral BMDs. Five percent absorption values were applied to dermal assessments, and no adjustments were made when assessing inhalation exposures.
[d]Chosen as the index chemical because it had the best dose-response data among candidate pyrethroids with robust databases. The point of departure (POD) in the cumulative risk assessment was the $BMDL_{20}$ value of 11 mg/kg/day for deltamethrin.

A.3 Mechanisms of Action

Neurotoxicity. Although mammals have been estimated to be about 3 orders of magnitude less sensitive to pyrethroids than insects (due to faster metabolism, higher body temperatures, and lower sensitivity of mammal, compared with insect, ion channel sites), the mode of action for pyrethroid neurotoxicity is expected to be the same in insects and mammals (O'Reilly et al. 2014; Ray and Fry 2006). Pyrethroids reversibly slow the closing of sodium channel gates in nerve cells and microglia during the depolarizing phase of an action potential (ATSDR 2003a; Costa 2008; Hossain et al. 2017). This ability of pyrethroids has been proposed to involve pyrethroid stimulation of protein phosphorylation (Ray and Fry 2006).

Other molecular target sites have been identified that may play roles in pyrethroid neurotoxicity including voltage-gated chloride channels, voltage-gated calcium channels; GABA-gated chloride channels, noradrenaline release, and voltage-gated calcium channels (Meijer et al. 2014, 2015; Ray and Fry 2006; Soderlund et al. 2002), but sodium channels appear to be the major target (Ray and Fry 2006). The neuropotency of pyrethroids is influenced by the presence or absence of a cyano group in the alpha position of the central ester bond (Type II pyrethroids contain a cyano group) and stereochemical orientation (e.g., the 1R conformation is more potent than the 1S conformation in Type I pyrethroids) (ATSDR 2003a; Costa 2008; EPA 2011a, 2011b). Type I ("T") and II ("CS") pyrethroids have different effects on the kinetics of the sodium channel opening and closing; these differences have been proposed to be the basis of the differences observed in the "T" and "CS" syndromes of toxic signs (Ray and Fry 2006). Type II pyrethroids cause a prolonged open state of the sodium channel, compared with Type I pyrethroids (EPA 2011a, 2011b).

The identification of multiple molecular target sites for various pyrethroids and different effects on VGSCs by Type I and II pyrethroids has led to uncertainty about whether pyrethroids represent a common mechanism group of chemicals (Ray and Fry 2006; Soderlund et al. 2002). However, all tested pyrethroids have been shown to affect the function of VGSCs (EPA 2011a, 2011b), and results from studies of motor activity in rats (Wolansky et al. 2009) and sodium influx in cultured cerebrocortical neurons (Cao et al. 2011) showed that actions of a mixture of 11 pyrethroids (that included both Type I and II pyrethroids) were consistent with a statistical model of dose additivity. Demonstration of dose additivity is consistent with a common mechanism of action. Based on these and other findings, EPA (2011a, 2011b) concluded that all pyrethroids represent a common mechanism group of structurally related chemicals that modify the kinetics of VGSCs leading to altered neuronal excitability and two syndromes of clinical signs of neurotoxicity.

For most pyrethroids, metabolic transformations represent detoxification processes; inhibition of CYP- and carboxylesterase-mediated metabolism is expected to enhance the toxicity of pyrethroids (Costa 2008). Evidence for a few pyrethroids indicates that neurotoxic action in mammals may involve metabolites, but this evidence appears to be presently equivocal and in need of further confirmation (Ray and Fry 2006). Neonatal rats have been reported to be 4–17 times more sensitive than adult rats to the acute neurotoxicity of permethrin or cypermethrin (Ray and Fry 2006). Potential explanations for this age-related susceptibility include lesser metabolic capacities in neonates and the existence of a specific type of sodium channel in neonatal rats showing a higher binding affinity for saxitoxin (Ray and Fry

2006). EPA (2011a, 2011c) concluded that the increased sensitivity of neonates to pyrethroids was attributable to increased pyrethroid concentrations in juvenile brains, compared with adult brains.

Neurodevelopmental Toxicity. Possible associations between oral exposure to pyrethroids and neurodevelopmental effects are not clearly established. One group of investigators reported that oral exposure of mice to bioallethrin or deltamethrin during early postnatal exposure (postnatal days [PNDs] 6–10) caused increases in spontaneous activity behavior at 4 months of age with doses in the range of 0.21–0.7 mg/kg, and decreased spontaneous activity at 4 months of age with a neonatal exposure to a higher dose level of 42 mg/kg; however, other investigators could not duplicate the findings of the first group of investigators (ATSDR 2003a). Shafer et al. (2005) concluded that current evidence is inadequate to establish neurodevelopmental toxicity as a possible human hazard associated with exposure to pyrethroids (Shafer et al. 2005). Similarly, Ray and Fry (2006) concluded that observations of developmental neurotoxic effects in animals repeatedly exposed to pyrethroids during neonatal periods need confirmation. However, EPA (2011a, 2011c) concluded, in its cumulative risk assessment for pyrethroids, that there was sufficient evidence of increased juvenile sensitivity (due to pharmacokinetic differences leading to increased brain concentrations in juveniles compared with adults) to warrant using a safety factor of 3 for children <6 years old.

Other Effects. Mode-of-action information on other effects found in studies of individual pyrethroids (e.g., decreased body weight, diarrhea, and decreased pup survival; see ATSDR 2003a) was not located. Some of these effects (e.g., decreased body weight, diarrhea) may be related to the actions of pyrethroids on the sodium channels of nerve cells; the mode of action for decreased pup survival and liver hypertrophy is unknown.

A.4 Health Guidelines

For oral exposure, ATSDR (2003a) derived acute-duration MRLs for *permethrin, cypermethrin,* and *cyhalothrin* and intermediate-duration MRLs for *permethrin* and *cyhalothrin*. No chronic-duration oral MRLs were derived for any pyrethroids, but, because no clinical signs of neurotoxicity were observed in a 2-year study of rats exposed to 1,000 ppm *permethrin* in the diet (at estimated doses of 40 mg/kg/day), ATSDR (2003a) expected that the intermediate-duration oral MRL for permethrin would be protective for a chronic duration of exposure.

ATSDR (2003a) derived an MRL of 0.1 mg/kg/day for acute-duration oral exposure to *permethrin* based on a no-observed-adverse-effect level (NOAEL) of 25 mg/kg and a lowest-observed-adverse-effect level (LOAEL) of 75 mg/kg for neurological impairment in rats given single doses of the chemical (increased excitability and aggressiveness, abnormal motor movement, and decreased grip strength and motor activity). This derivation used an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ATSDR (2003a) derived an MRL of 0.02 mg/kg/day for acute-duration oral exposure to *cypermethrin* based on a LOAEL of 20 mg/kg for neurological impairment in rats given single doses of the chemical (altered gait and decreased motor activity). This derivation used an uncertainty factor of 1,000 (10 for the lack of a NOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

ATSDR (2003a) derived an MRL of 0.01 mg/kg/day for acute-duration oral exposure to *cyhalothrin* based on a NOAEL of 1 mg/kg/day and a LOAEL of 2.5 mg/kg/day for diarrhea in dogs given the chemical daily in gelatin capsules for 26 weeks. This derivation used an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ATSDR (2003a) derived an MRL of 0.2 mg/kg/day for intermediate-duration oral exposure to *permethrin* based on a NOAEL of 15.5 mg/kg/day and a LOAEL of 91.5 mg/kg/day for neurological impairment (hindlimb splay) in rats given permethrin in the diet for 13 weeks. This derivation used an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ATSDR (2003a) derived an MRL of 0.01 mg/kg/day for intermediate-duration oral exposure to *cyhalothrin* based on a NOAEL of 1 mg/kg/day and a LOAEL of 2.5 mg/kg/day for diarrhea in dogs given the chemical daily in gelatin capsules for 26 weeks. As with the acute-duration MRL for cyhalothrin, this derivation used an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

In a cumulative risk assessment for pyrethroid insecticides, the U.S. EPA OPP (EPA 2011a) selected deltamethrin as the index chemical in a relative potency approach that derived relative potency factors for 14 additional pyrethroids and a $BMDL_{20}$ POD of 11 mg/kg/day for deltamethrin. The RPF values (listed in Table A-1) were derived using benchmark dose (BMD) analyses of incidence data from the principal studies of gavage exposed rats (EPA 2011d; Weiner et al. 2009). The incidences were for composite scores >4 on a 4–12 scale, based on measures of body temperature, tremors, clonic convulsions,

salivation, and mobility. RfDs for 10 pyrethroids are still listed on EPA IRIS (IRIS 2013), and more recent pyrethroid assessments are reported in EPA (2011a). The 2011 EPA relative potency assessment has the advantage of being predominantly based on data collected from a single laboratory, obviating the uncertainty from interlaboratory variability associated with subjectivity in behavioral assessments and pharmacokinetic differences from different gavage vehicles and volumes.

The International Agency for Research on Cancer (IARC 2012) classified deltamethrin, fenvalerate, and permethrin in Cancer Group 3—*Not classifiable as to its carcinogenicity to humans*. IARC (2012) has not evaluated the carcinogenic potential of other pyrethroids. The National Toxicology Program (NTP 2011), the EPA OPP (EPA 2011a), and the EPA IRIS program (IRIS 2013) have not formally evaluated the evidence for the human carcinogenic potential of pyrethroid insecticides.

A.5 Derivation of Target-Organ Toxicity Dose (TTD) Values

The most clearly established end points of concern for pyrethroids are neurological effects mediated via the slowing of sodium channels in nerve cells during action potentials (ATSDR 2003a; EPA 2011a, 2011b). In the absence of mode-of-action data to indicate otherwise, other effects (which are the critical effects for ATSDR MRLs or EPA RfDs listed on IRIS, such as diarrhea, decreased body weight gain, decreased pup survival, and increased liver weight) are assumed to occur via the same mode of action. Thus, TTD values for other effects were not derived for the pyrethroid pesticides of concern. Neurodevelopmental TTD values for pyrethroids were not developed due the equivocal nature of evidence for associations between pyrethroids and neurodevelopmental effects. Results from standard developmental toxicity and reproductive toxicity tests with animals orally exposed to the 10 pyrethroids listed on EPA's IRIS do not identify reproductive effects (e.g., effects on fertility) or standard developmental effects (e.g., developmental delays, malformations) as health hazards of concern from exposure to most pyrethroids, with the possible exception of resmethrin. More recently, EPA's OPP reported that no prenatal sensitivity was observed in 76 guideline studies submitted for 24 pyrethroids (EPA 2011a).

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Appendix B: Background Information for Organophosphorus Insecticides

Organophosphorus compounds have been synthesized and developed as insecticides beginning in the 1940s and continuing to the present time (Costa 2008). Hundreds of organophosphorus compounds have been synthesized and commercialized as insecticides, and more than half of insecticides used are organophosphorus compounds (Costa 2008).

B.1 Toxicokinetics

Most organophosphorus insecticides are expected to be absorbed following inhalation, oral, or dermal exposures, distributed by the blood to various tissues including nervous system tissues, rapidly metabolized, and eliminated as metabolites in the urine (the principal route of elimination) and feces without significant accumulation in tissues (ATSDR 1995, 1997a, 1997b, 1997c, 2000, 2001, 2003b, 2008a, 2008b). Many organophosphorus insecticides are metabolized, via CYP enzymes, to metabolites more potent than the parent compound in inhibiting ChE, the principal mode of action by which these compounds cause neurological effects: diazinon to diazoxon (ATSDR 2008a); guthion to gutoxon (ATSDR 2008b); ethion to monoxon (ATSDR 2000); methyl parathion to methyl paraoxon (ATSDR 2001); malathion to malaoxon (ATSDR 2003b); disulfoton to disulfoton sulfoxide, disulfoton sulfone, demeton S-sulfoxide, or demeton S-sulfone (ATSDR 1995); and chlorpyrifos to chlorpyrifos-oxon (ATSDR 1997b). For these organophosphorus insecticides, further metabolism of the potent ChE-inhibiting initial metabolites to other, often more polar, metabolites represent detoxification processes. Examples of detoxification processes include CYP-mediated dealkylation or dearylation of the parent compound, hydrolysis of oxon intermediates by A-esterases, and hydrolysis via reaction with B-esterases, such as carboxylesterases and butyrylcholinesterase (Costa 2008). Thus, the balance between the kinetics of bioactivation and detoxification is critical in the expression of the neurotoxicity of these chemicals. For direct-acting organophosphorus insecticides, metabolism represents a detoxification process. Examples of direct acting organophosphorus insecticides include chlorfenvinphos, which is metabolized by CYP monooxygenases, esterases, and glutathione S-transferases (ATSDR 1997a), and dichlorvos, which is metabolized by esterases and glutathione S-transferases (ATSDR 1997c). The extent of potential reactivation of organophosphate-inhibited acetylcholinesterase decreases with time, a phenomenon called aging. Aging is due to dealkylation of the alkoxyl group of the residue bound to the enzyme. The rate of ageing is proportional to the electron-donating capacity of the alkyl group (ATSDR 2008a, 2008b, 2003b).

B.2 Health Effects

The critical and most well-studied effect of organophosphorus insecticides is the inhibition of ChE, which results in accumulation of acetylcholine at acetylcholine receptors and overstimulation of nerve junctions in the peripheral and central nervous systems (ATSDR 1995, 1997a, 1997b, 1997c, 2000, 2001, 2003b, 2008a, 2008b). Acute exposure to high doses of organophosphorus insecticides causes severe ChE inhibition associated with cholinergic signs and symptoms including lacrimation, perspiration, miosis, diarrhea, nausea, and vomiting, accompanied with cramps or muscle weakness, drowsiness, fatigue, mental confusion, convulsions, or coma. Numerous animal studies and limited controlled-exposure human studies have identified acute and repeated exposure levels (via oral, inhalation, dermal, or parenteral routes) resulting in inhibition of plasma, RBC, and/or brain ChE (ATSDR 1995, 1997a, 1997b, 1997c, 2000, 2001, 2003b, 2008a, 2008b). Inhibition of RBC or brain ChE in the 20–59% range is generally considered to be a "less serious" adverse neurological effect not associated with the gross signs and symptoms of serious neurological dysfunction resulting from high dose levels (ATSDR 1995, 1997a, 1997b, 1997c, 2000, 2001, 2003b, 2008a, 2008b).

The critical nature of ChE inhibition for acute, intermediate, and chronic exposure to organophosphate insecticides is reflected in the critical effects for ATSDR MRLs for organophosphorus insecticides, which are listed in Table B-1. Inhibition of either plasma, RBC, or brain ChE is the critical effect for the majority of ATSDR's inhalation MRLs (9/10) and oral MRLs (21/25) for organophosphorus insecticides (Table B-1). The exceptions include:

- The intermediate inhalation MRL for malathion, which is based on nasal and larynx lesions in rats exposed for 13 weeks at an exposure level (100 mg/m^3) that did not significantly inhibit RBC ChE (ATSDR 2003b; Table B-1). Decreased RBC ChE activity was observed at the next highest exposure level (450 mg/m^3) in the principal study, and decreased RBC or brain ChE was the critical effect for the other MRLs for malathion (acute inhalation, intermediate oral, and chronic oral).

- The intermediate oral MRL for methyl parathion, which is based on nerve function deficits in rat dams given daily gavage doses on gestation days (GDs) 5–15 and extending through PNDs 1–28 (ATSDR 2001; Table B-1).

- The chronic oral MRL for methyl parathion, which is based on decreased hematocrit and RBC counts in rats exposed to methyl parathion in the diet for 2 years at a dose level (0.25 mg/kg/day) that did not significantly decrease RBC or brain ChE (ATSDR 2001; Table B-1). In the principal study, decreased RBC and brain ChE activities were reported in rats exposed to the next highest dose level of methyl parathion (2.5 mg/kg/day, Table B-1).

Table B-1. Critical Effects and PODs for ATSDR MRLs for Organophosphorus Insecticides

Chemical	Critical effect	POD		Species and exposure	Other NOAELs (N) and LOAELs (L) for neurological or developmental effects (mg/kg/day or mg/m^3 for N and L)
		NOAEL	LOAEL		
Acute inhalation exposure (mg/m^3)					
Dichlorvos, acute MRL	↓ RBC ChE	1.81 (0.2 ppm)	4.34 (0.48 ppm)	Rats, continuous exposure, 3 days	Fetal body weight and number of live fetuses, mice or rabbits; N=0.44 (7 hours/day, GDs 6–15 or 6–10); L=ND
Disulfoton, acute MRL	↓ RBC ChE	0.5	1.8	Rats, 4 hours/day, 5 days/week, 5 days	
Guthion, acute MRL	↓ RBC ChE	1.24	4.72	Rats, 6 hours/day, 5 days/week, 2 weeks	
Malathion, acute MRL	↓ RBC ChE	65	123	Rabbits, 6 hours	Nasal and eye irritation, volunteers, 2-hour exposure, N=21; L=85; no effect on plasma or RBC ChE
Intermediate inhalation exposure (mg/m^3)					
Dichlorvos, intermediate MRL	↓ RBC ChE	0.27 (0.03 ppm)	1.26 (0.14 ppm)	Rats, 23 hours/day, GDs 1–20	
Diazinon, intermediate MRL	↓ RBC ChE	1.57	11.6	Rats, 6 hours/day, 5 days/week, 3 weeks	
Disulfoton, intermediate MRL	↓ RBC ChE and lethargy	0.02	0.1	Rats, 6 hours/day, 5 days/week, 3 weeks	↓ RBC ChE, rats, 6 hours/day, 5 days/week, 13 weeks, N=0.16; L=1.4
Guthion, intermediate MRL	↓ RBC ChE	1.24	4.72	Rats, 6 hours/day, 5 days/week, 12 weeks	

Table B-1. Critical Effects and PODs for ATSDR MRLs for Organophosphorus Insecticides

Chemical	Critical effect	POD		Species and exposure	Other NOAELs (N) and LOAELs (L) for neurological or developmental effects (mg/kg/day or mg/m^3 for N and L)
		NOAEL	LOAEL		
Malathion, intermediate MRL	Nasal and larynx lesions	NI	100	Rats, 6 hours/day, 5 days/week, 13 weeks	↓ RBC ChE, rats, 6 hours/day, 5 days/week, 13 weeks, N=100; L=450 ↓ RBC ChE, volunteers, 2 hours/day, 42 days, N=85; L=NI
Chronic inhalation exposure (mg/m^3)					
Dichlorvos, chronic MRL	↓ RBC ChE	0.05 (0.006 ppm)	0.54 (0.06 ppm)	Rats, 23 hours/day, 2 years	
Acute oral exposure (mg/kg/day)					
Chlorfenvinphos, acute MRL	↓ RBC ChE	NI	2.4	Rats, in diet for 10 days	↓ brain ChE, rats, single gavage dose, N =1; L=2
Chlorpyrifos, acute MRL	↓ plasma ChE	0.03	0.10	Humans, daily capsules for 9–20 days	↓ RBC ChE, rat dams, gavage on GDs 6–15; N=0.1; L=1
Diazinon, acute MRL	↓ RBC ChE	0.6	1.2	Rats, in diet for 12 days	Deficits in neurobehavioral tests, mouse offspring, gavage GDs 1–18, N=NI; L=0.18
Dichlorvos, acute MRL	↓ brain ChE	NI	4	Rats, gavage, 1time/day for 14 days	Decreased fetal body weight and number of live fetuses, mice or rabbits; N=60 (mouse), 5 (rabbit); L=ND
Disulfoton, acute MRL	↓ RBC ChE	0.1	0.3	Rat dams, gavage GDs 6–15	Delayed ossification, rat fetuses, gavage GDs 6–15, N=0.3; L=1
Ethion, acute MRL	↓ RBC and brain ChE	0.06	0.71	Dogs, in diet for 90 days	Delayed ossification, rat fetuses, gavage GDs 6–15, N=0.6, L=2.5 Fused sterna, rabbit fetuses, gavage GDs 6–18, N=2.4, L=9.6
Guthion, acute MRL	↓ RBC and brain ChE	1	2	Rat dams, gavage GDs 6–15	Misaligned sternebrae, mouse fetuses, gavage GDs 6–15, N=2.5, L=5

Table B-1. Critical Effects and PODs for ATSDR MRLs for Organophosphorus Insecticides

Chemical	Critical effect	POD		Species and exposure	Other NOAELs (N) and LOAELs (L) for neurological or developmental effects (mg/kg/day or mg/m^3 for N and L)
		NOAEL	LOAEL		
Intermediate oral exposure (mg/kg/day)					
Chlorfenvinphos, intermediate MRL	↓ immune responses	NI	1.5	Mice, gavage for 90 days	↓ RBC ChE, rats, in diet for 12 weeks, N=3; L=10
Chlorpyrifos, intermediate MRL	↓ plasma ChE	0.03	0.1	Humans, daily capsules for 9–20 days	↓ RBC ChE, rat dams, gavage on GDs 6–15; N=0.1; L=1
Diazinon, intermediate MRL	↓ RBC ChE	0.18	0.27	Rats, in diet for 42 days	↓ RBC and brain ChE, dogs, in diet for 13 weeks; N=0.75, L=5.6 Deficits in neurobehavioral tests, mouse offspring, gavage GDs 1–18, N=NI, L=0.18
Dichlorvos, intermediate MRL	↓ RBC ChE	0.033	NI	Humans, 3 times/day for 21 days	
Disulfoton, intermediate MRL	↓ brain ChE in F1a pups	0.009	0.03	Rats, in diet for 2 generations	↓ RBC ChE, adult rats, in diet for 6 months, N=0.03, L=0.07
Ethion, intermediate MRL	↓ RBC and brain ChE	0.06	0.71	Dogs, in diet for 90 days	
Guthion, intermediate MRL	↓ RBC ChE	0.15	0.69	Dogs, in diet for 26 weeks	↓ RBC, rats, in diet 14 weeks pre-mating through postpartum day 5 or 28, F0 dams at postpartum day 5 or 28: N=NI; L=0.55; F1 pups at postpartum day 5 or 28: N=1.5, L=4.9 Gross neuromuscular incoordination and decreased fetal survival, rat offspring, gavage GD 6 through postpartum day 21, N=2.5, L=5
Malathion, intermediate MRL	↓ RBC ChE	0.24	0.34	Humans, daily capsules for 32–56 days	↓ brain ChE on PND 21, rat offspring, gavage on GDs 6–13; N=NI; L 138

Table B-1. Critical Effects and PODs for ATSDR MRLs for Organophosphorus Insecticides

Chemical	Critical effect	POD		Species and exposure	Other NOAELs (N) and LOAELs (L) for neurological or developmental effects (mg/kg/day or mg/m^3 for N and L)
		NOAEL	LOAEL		
Methyl parathion, intermediate MRL	Nerve function deficits	NI	0.22	Rats, gavage GDs 5–15 through PND 28 via dams, followed by gavage from weaning through 11–12 weeks of age	Nerve function deficits, rat offspring, gavage GDs 5–15 through PND 28 via dams only, N=0.88, L=NI ↓ RBC and brain ChE, mouse, gavage 28 days, N=1; L=3 ↓ RBC and brain ChE, dogs, in diet 13 weeks, N=0.3; L=3
Chronic oral exposure (mg/kg/day)					
Chlorfenvinphos, chronic MRL	↓ RBC ChE	NI	10	Rats, in diet for 2 years	↓ RBC ChE, dogs, in diet for 2 years, N=2; L=10
Chlorpyrifos, chronic MRL	↓ RBC ChE	0.1	1	Rats, in diet for 2 years	↓ RBC ChE, dogs, in diet for 1 year; N=0.1; L=1
Diazinon, chronic MRL	↓ RBC ChE	0.065	5.5	Rats, in diet for 97 weeks	↓ RBC and brain ChE, dogs, in diet for 52 weeks, N=0.017, L=4.6 Deficits in neurobehavioral tests, mouse offspring, gavage GDs 1–18, N=NI, L=0.18
Dichlorvos, chronic MRL	↓ RBC and brain ChE	0.05	1	Dogs, 1 time/day, 52 weeks	
Disulfoton, chronic MRL	↓ RBC ChE	NI	0.06	Rats, in diet for 1.5–2 years	↓ RBC and brain ChE, dogs, in diet for 2 years, N=0.03, L=0.14
Ethion, chronic MRL	↓ RBC and brain ChE	0.06	0.71	Dogs, in diet for 90 days	↓ RBC or brain ChE, rats or mice, in diet for 2 years, N=2 (rats) or 1.2 (mice), L=NI
Guthion, chronic MRL	↓ RBC and brain ChE	0.15	0.69	Dogs, in diet for 52 weeks	↓ RBC and brain ChE, rats, in diet 2 years, N=0.75, L=2.3
Malathion, chronic MRL	↓ RBC ChE	2 (males) 3 (females)	29 (males) 35 (females)	Rats, in diet for 2 years	

Table B-1. Critical Effects and PODs for ATSDR MRLs for Organophosphorus Insecticides

Chemical	Critical effect	POD		Species and exposure	Other NOAELs (N) and LOAELs (L) for neurological or developmental effects (mg/kg/day or mg/m^3 for N and L)
		NOAEL	LOAEL		
Methyl parathion, chronic MRL	Decreased hematocrit and RBC counts	0.025	0.25	Rats, in diet for 2 years	↓ RBC and brain ChE, rats, in diet 2 years, N=0.25; L=2.5

ATSDR = Agency for Toxic Substances and Disease Registry; ChE = acetylcholinesterase; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NI = not identified; NOAEL = no-observed-adverse-effect level; PND = postnatal day; POD = point of departure; RBC = red blood cell

Sources: ATSDR 1995, 1997a, 1997b, 1997c, 2000, 2001, 2003b, 2008a, 2008b

- The intermediate oral MRL for chlorfenvinphos, which is based on decreased immune response in mice exposed to 1.5 mg/kg/day chlorfenvinphos for 90 days (ATSDR 1997a; Table B-1). Decreased RBC and brain ChE activities were observed in rats exposed to chlorfenvinphos in the diet for 12 weeks at 10 mg/kg/day, but not at 3 mg/kg/day (Table B-1). Decreased RBC ChE activity is the critical effect for the acute and chronic oral MRLs for chlorfenvinphos (Table B-1).

There is concern for the possible neurodevelopmental toxicity of organophosphorus insecticides, but most have not been evaluated for neurodevelopmental effects. As reviewed by EPA (2006), ChE has been suspected to play roles in the development of the neural system involving cell adhesion during neurite growth, but inhibition of the acetylcholine esterase activity by organophosphorus insecticides does not appear to be closely correlated with inhibition of neurite growth—some organophosphate insecticides inhibit neurite outgrowth *in vitro*, but others do not (EPA 2006). Many organophosphorus insecticides have been evaluated in standard developmental toxicity tests, but most have not been evaluated for neurodevelopmental effects. Concern for the neurodevelopmental effects of organophosphorus insecticides in general is raised by positive results found in a few studies that have been conducted. For example, offspring of mice exposed to 0.18 or 9 mg/kg/day diazinon on GDs 1–18 showed developmental delays and abnormal neuromuscular endurance and coordination (Spyker and Avery 1977). Similarly, offspring of rats exposed to 5 mg/kg/day guthion on GD 6 through PND 21 (weaning) showed gross neuromuscular incoordination and reduced survival; these effects were not observed in offspring of rats exposed to 2.5 mg/kg/day (Short et al. 1980). Another example is the finding that male rats showed electrophysiological changes in neural tissues following oral exposure to 0.22 mg/kg/day methyl

parathion during GDs 5–15 (via the dam), lactational days 2–28 (via the dam), and PNDs 23–84, a dose below those inhibiting ChE in adult rats, but when exposure did not include PNDs 23–84, no effects were found, even at a dose level of 0.88 mg/kg/day (Desi et al. 1998).

There is also concern for the possible increased susceptibility of children, compared with adults, to the ChE inhibiting activity of organophosphorus insecticides, but the relative sensitivities of early life and adult stages of development have been assessed only for a few of these chemicals. In its cumulative risk assessment for organophosphorus insecticides, EPA (2006) applied a FQPA 10 safety factor to RPFs to provide protection for the possible susceptibility of infants to prenatal and postnatal toxicity, except for 13 insecticides with appropriate data evaluating ChE inhibition in juvenile and adult rats. These data were used to reduce the FQPA safety factor for 10 of these insecticides (see Section B.4 for more details). In concurrence with this recommendation, Costa (2008) concluded that there is evidence to indicate that young animals are more sensitive to acute toxicity from organophosphorus insecticides and the increased sensitivity appears to be due to lower detoxification abilities of young animals, compared with mature animals. Illustrating this conclusion, Slotkin (2006) cited published evidence that the LD_{50} value for chlorpyrifos in 1-day-old rats was about 10- and 100-fold less than LD_{50} values in 1-week-old and adult rats, respectively.

Exposure to certain organophosphorus insecticides has also been associated with two other neurological conditions that do not appear to involve ChE (Costa 2008). The "intermediate syndrome" has been described in 20–50% of acute organophosphorus poisoning cases with distinguishing features that develop one to several days after poisoning and can often resolve within 15 days (Costa 2008). Distinguishing features include weakness of respiratory, neck, and proximal limb muscles that can lead to mortality due to respiratory paralysis and associated complications. The mechanism of this syndrome is unknown, although it does not appear to involve ChE inhibition (Costa 2008).

"Organophosphate-induced delayed polyneuropathy" (OPIDP) is characterized by a progressive set of signs and symptoms associated with axonal degeneration starting with initial tingling of the hands and feet and progressing to sensory loss, muscle weakness of the lower and upper extremities, and ataxia (Costa 2008). Although initial phosphorylation of a nerve tissue esterase (neuropathy target esterase, NTE), followed by an aging reaction, are thought to be key events in the mode of action for OPIDP, events linking these effects on NTE to axonal degeneration have not been characterized. Organophosphorus agents that inhibit NTE, but do not age, do not cause OPIDP (Costa 2008). Commercial organophosphorus insecticides must undergo specific testing ensuring that cholinergic

potency is much higher than potency in producing OPIDP, so this effect is not expected with general public or occupational exposures from the use of most organophosphorus insecticides. Nevertheless, symptoms characteristic of OPIDP have been described in several cases of high level poisoning from certain organophosphorus insecticides including chlorpyrifos, dichlorvos, isofenphos, methamidophos, mipafox, trichlorfon, and trichlornat (Lotti and Moretto 2005).

B.3 Mechanisms of Action

Neurotoxicity. The principal and common mode of action by which organophosphorus insecticides cause neurological effects is through inhibition of ChE. The organophosphorus insecticides, and in some cases their metabolites, form stable phophorylated complexes with the active sites of ChE, preventing the enzymatic catalysis of the hydrolyzation of acetylcholine at nerve endings and nerve junctions and leading to excessive nerve stimulation and receptor desensitization (ATSDR 2008a, 2008b). Muscarinic effects from organophosphorus insecticides involve postganglionic parasympathetic nerve stimulation in end organs (e.g., heart, blood vessels, and secretory glands) and include miosis; excessive salivation, lacrimation, and rhinitis; vomiting; and diarrhea (ATSDR 2008a). Nicotinic effects from acetylcholine accumulation at skeletal muscle junctions and sympathetic preganglionic nerve endings include muscular fasciculations, weakness, tachycardia, and hypertension (ATSDR 2008a). Central nervous system effects from nerve stimulation in the cerebral cortex, hippocampus, and extrapyramidal motor system include respiratory depression, restlessness, mental confusion, drowsiness, ataxia, and coma (ATSDR 2008a).

For organophosphorus insecticides that are metabolized to more potent ChE inhibitors via CYP enzymes (e.g., diazinon is metabolized to diazoxon), coexposure to substances that induce or inhibit CYP enzymes may influence the toxic response to the parent insecticide as determined by the balance of the kinetics of activation and detoxification mechanisms (ATSDR 2008a). Inhibitors of enzymes involved in the metabolism of direct acting organophosphorus insecticides (e.g., dichlorvos and chlorfenvinphos) would be expected to enhance or prolong neurotoxic effects from these chemicals (ATSDR 1997a, 1997c).

Modes of action by which organophosphorus produce non-ChE-mediated neurological effects are poorly characterized. The “intermediate syndrome” of weakness of respiratory, neck, and proximal limb muscles has been hypothesized to result from nicotinic receptor desensitization due to chronic cholinergic stimulation, but molecular mechanisms are unknown (Costa 2008). OPIDP has been clearly associated with high-level exposure to certain organophosphorus agents that phosphorylate and “age” NTE, but events occurring between NTE aging and axonal degeneration are unknown (Costa 2008).

Organophosphorus insecticides have been shown to inhibit voltage-gated calcium channels (Meijer et al. 2014, 2015)

Neurodevelopmental Toxicity. Animal studies involving gestational exposure to some organophosphorus insecticides have noted mild delays in skeletal development at maternally toxic exposure levels, but most organophosphorus insecticides have not been evaluated for neurodevelopmental effects. In a recent review, Costa (2008) concluded that accumulating evidence from rodent studies in recent years indicates that perinatal exposure to organophosphorus insecticides can affect various cellular processes (e.g., neuronal survival, neurite outgrowth) and non-cholinergic pathways (e.g., serotoninergic synaptic functions), and cause various behavioral abnormalities. Slotkin (2006) recently reviewed evidence, predominantly from *in vitro* studies, that chlorpyrifos or its reactive metabolite, chlorpyrifos oxon, can influence neurodevelopment via multiple mechanisms, including: (1) alteration of acetylcholine concentrations leading to overstimulation of cholinergic receptors involved in signaling cascades important in neural development; (2) direct effects on expression and function with serotonin receptors involved in neural developmental signaling cascades; (3) direct effects on expression and function of signaling intermediates, such as adenylyl cyclase, and on expression of nuclear transcription factor; and (4) indirect effects, through generation of oxidative stress, on signaling pathways controlling cell replication, differentiation, growth, or apoptosis.

B.4 Health Guidelines

ATSDR Guidelines Based on Neurotoxicity As discussed in the previous section, decreased RBC or brain ChE activity is the critical effect for the majority of ATSDR MRLs for organophosphorus insecticides. Table B-2 lists the MRLs, PODs, and uncertainty factors used in the derivations. For inhalation exposure scenarios, MRLs ranged from 0.006 to 0.2 mg/m^3 for acute duration and from 0.0002 to 0.01 mg/m^3 for intermediate duration (Table B-2). Only one chronic inhalation MRL was derived (0.0005 mg/m^3 for dichlorvos). For oral exposure scenarios, MRLs ranged from 0.001 to 0.01 mg/kg/day for acute duration, from 0.00009 to 0.02 mg/kg/day for intermediate duration, and from 0.00006 to 0.02 mg/kg/day for chronic duration.

Table B-2. ATSDR MRLs for Organophosphorus Insecticides: PODs and Uncertainty Factors

Chemical	POD		MRL	Uncertainty factor[a]
	NOAEL	LOAEL		
Acute inhalation exposure (mg/m^3)				
Dichlorvos	1.81 (0.2 ppm)	4.34 (0.48 ppm)	0.02	100 (10 AH, 10 HV)
Disulfoton	0.5	1.8	0.006	30 (3 AH, 10 HV); applied to duration-adjusted NOAEL
Guthion	1.24	4.72	0.02	30 (3 AH, 10 HV): applied to NOAEL(HEC), 0.5 mg/m^3
Malathion	65	123	0.2	100 (10 AH, 10 HV); applied to duration-adjusted NOAEL
Intermediate inhalation exposure (mg/m^3)				
Dichlorvos	0.27 (0.03 ppm)	1.26 (0.14 ppm)	0.003	100 (10 AH, 10 HV)
Diazinon	1.57	11.6	0.01	30 (3 AH, 10 HV); applied to duration-adjusted NOAEL
Disulfoton	0.02	0.1	0.0002	30 (3 AH, 10 HV); applied to duration-adjusted NOAEL
Guthion	1.24	4.72	0.01	30 (3 AH, 10 HV); applied to NOAEL(human equivalent concentration), 0.37 mg/m^3
Malathion	NI	100	0.02	1,000 (10 LN, 10 AH, 10 HV); applied to duration-adjusted LOAEL
Chronic inhalation exposure (mg/m^3)				
Dichlorvos	0.05 (0.006 ppm)	0.54 (0.06 ppm)	0.0005	100 (10 AH, 10 HV)
Acute oral exposure (mg/kg/day)				
Chlorfenvinphos	NI	2.4	0.002	1,000 (10 LN, 10 AH, 10 HV)
Chlorpyrifos	0.03	0.10	0.003	10 HV
Diazinon	0.6	1.2	0.006	100 (10 AH, 10 HV)
Dichlorvos	NI	4	0.004	100 (10 AH, 10 HV)
Disulfoton	0.1	0.3	0.001	100 (10 AH, 10 HV)
Ethion	0.06	0.71	0.002	30 (3 AH, 10 HV)
Guthion	1	2	0.01	100 (10 AH,10 HV); applied to BMDL, 1 mg/kg/day
Intermediate oral exposure (mg/kg/day)				
Chlorfenvinphos	NI	1.5	0.002	1,000 (10 LN, 10 AH, 10 HV)
Chlorpyrifos	0.03	0.1	0.003	10 HV
Diazinon	0.18	0.27	0.002	100 (10 AH, 10 HV)
Dichlorvos	0.033	NI[b]	0.003	10 HV
Disulfoton	0.009	0.03	0.00009	100 (10 AH, 10 HV)
Ethion	0.06	0.71	0.002	30 (3 AH, 10 HV)
Guthion	0.15	0.69	0.003	100 (10 AH, 10 HV); applied to BMDL, 0.29 mg/kg/day

Table B-2. ATSDR MRLs for Organophosphorus Insecticides: PODs and Uncertainty Factors

Chemical	POD		MRL	Uncertainty factor[a]
	NOAEL	LOAEL		
Malathion	0.24	0.34	0.02	10 HV
Methyl parathion	NI	0.22	0.0007	300 (3 LN,10 AH, 10 HV)
Chronic oral exposure (mg/kg/day)				
Chlorfenvinphos	NI	10	0.0007	1,000 (10 LN, 10 AH, 10 HV)
Chlorpyrifos	0.1	1	0.001	100 (10 AH, 10HV)
Diazinon	0.065	5.5	0.0007	100 (10 AH,10 HV)
Dichlorvos	0.05	1	0.0005	100 (10 AH, 10 HV)
Disulfoton	NI	0.06	0.00006	1,000 (10 LN, 10 AH, 10 HV)
Ethion	0.06	0.71	0.0004	150 (3 AH,10 HV, 5 for long-term effects and possible susceptibility of children)
Guthion	0.15	0.69	0.003	100 (10 AH, 10 HV); applied to BMDL, 0.30 mg/kg/day
Malathion	2	29	0.02	100 (10 AH, 10 HV)
Methyl parathion	0.025	0.25	0.0003	100 (10 AH, 10 HV)

[a]Uncertainty factor abbreviations: AH for animal to human extrapolation; HV for human variability; LN for LOAEL to NOAEL extrapolation.

ATSDR = Agency for Toxic Substances and Disease Registry; BMDL = benchmark dose limit; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NI=not identified; NOAEL = no-observed-adverse-effect level; POD = point of departure

Sources: ATSDR 1995, 1997a, 1997b, 1997c, 2000, 2001, 2003b, 2008a, 2008b

EPA Guidelines Based on Neurotoxicity. Although EPA lists chronic oral RfDs for 17 organophosphorus insecticides on IRIS (IRIS 2013), these assessments are less up to date than the EPA OPP RPFs used in the cumulative risk assessment for organophosphorus insecticides (EPA 2006). Organophosphorus insecticides were determined to represent a common mechanism group based on similar structural characteristics and shared ability to inhibit ChE at the active site. Methamidophos was selected as the index chemical in a RPF approach that derived RPFs for 33 organophosphorus insecticides, based on adult rat brain ChE inhibition data, submitted to EPA under the pesticide registration program (EPA 2006). Based on an analysis of available data, EPA (2006) concluded that the time to peak ChE inhibition, the persistence of action following acute exposure, and the duration of exposure required to reach a steady-state level of ChE is influenced by a number of toxicokinetic and toxicodynamic factors and that RPFs should be based on rat studies of duration of ≥21 days (when steady-

state levels of ChE inhibition are expected) in order to develop RPFs that are reproducible and applicable to human exposure scenarios of concern.

The RPF values (listed in Table B-3) were derived using BMD analyses of brain ChE activity data for adult female rats (female rats were generally more sensitive than male); the central tendency estimate of the dose of the index chemical resulting in 10% ChE inhibition (e.g., BMD_{10}) was divided by BMD_{10} values for the other chemicals to derive the unadjusted RPFs. For estimating risks for children, the RPFs were adjusted by multiplication by the default FQPA 10 factor or replaced with chemical-specific FQPA factors, when appropriate data were available to compare juvenile and adult susceptibility to ChE inhibition (see Table B-3). Methamidophos was selected as the index chemical because it had the highest quality dose-response data and the most robust database for all three exposure routes of interest (oral, dermal, inhalation) among the evaluated organophosphorus insecticides. Route-specific BMD_{10} values for female rats exposed to the index chemical were selected as the POD for the cumulative risk assessments and are listed (along with $BMDL_{10}$ values) in Table B-4.

EPA (2006) evaluated cumulative risks for various U.S. regions from organophosphorus pesticides in food, residential and recreational use, and drinking water. The residential pathways comprised oral, dermal, and inhalation exposures. In accordance with the 1996 FQPA, the RPF/MOE approach used RPF values, which were adjusted with chemical-specific or default uncertainty factors (FQPA factors) to protect infants and children. Concentrations of organophosphorus residues in appropriate media (e.g., food, drinking water) were multiplied by appropriate FQPA-adjusted RPF values (see Table B-3) and summed to arrive at methamidophos-equivalent concentrations, which were then used in exposure models to estimate methamidophos-equivalent intakes (in units of mg/kg/day) for the various exposure scenarios investigated. The exposure estimates for food were based on residue monitoring data collected by the U.S. Department of Agriculture's Pesticide Data Program supplemented with information from the U.S. Food and Drug Administration's Surveillance Monitoring Programs and Total Diet Study. Drinking water and residential exposures were estimated with probabilistic modeling approaches which were focused on U.S. regions where organophosphorus insecticide use was high and drinking water vulnerability was high. The exposure assessments indicated that exposure to organophosphorus insecticides from foods represents the dominant exposure pathway for the general population.

Table B-3. EPA RPFs for Oral, Dermal and Inhalation Exposures to Organophosphorus Insecticides, Based on Data for Brain ChE Inhibition in Female Rats and FQPA Factors used to Adjust the RPFs in Cumulative Risk Assessments

Chemical	Oral RPF	Dermal RPF	Inhalation RPF	FQPA factor[a]
Acephate	0.08	0.0025	0.208	1
Azinphos-methyl	0.1	ND[1]	ND	4.5
Bensulide	0.003	0.0015	ND	10
Chlorethoxyfos	0.13	ND	ND	10
Chlorpyrifos	0.06	ND	ND	1
Chlorpyrifos-methyl	0.005	ND	ND	10
Diazinon	0.01	ND	ND	10
DDVP (dichlorvos)	0.03	ND	0.677	1
Dicrotophos	1.91	ND	ND	1.7
Dimethoate	0.32	ND	ND	1
Disulfoton	1.26	0.47	6.596	2.2
Ethoprop	0.06	ND	ND	10
Fenamiphos	0.04	1.5	0.315	10
Fenthion	0.33	0.015	ND	10
Fosthiazate	0.07	ND	ND	2.6
Malathion	0.0003	0.015	0.003	10
Methamidophos	1	1	1	2
Methidathion	0.32	ND	ND	10
Methyl-parathion	0.12	ND	ND	10
Mevinphos	0.76	ND	ND	10
Naled	0.08	0.075	0.82	10
Omethoate	0.93	ND	ND	10
Oxydemeton-methyl	0.86	ND	ND	1
Phorate	0.39	ND	ND	10
Phosalone	0.01	ND	ND	10
Phosmet	0.02	ND	ND	10
Phosteburpirim	0.22	ND	ND	10
Pirimiphos-methyl	0.04	ND	ND	10
Profenofos	0.004	ND	ND	10
Terbufos	0.85	ND	ND	6.5
Tetrachlorvinphos	0.001	0.00075	ND	10
Tribufos	0.02	ND	ND	10
Trichlorfon	0.003	0.0075	0.087	10

[a]The default FQPA 10 factor was replaced with chemical-specific FQPA factors, when appropriate data were available to compare juvenile and adult susceptibility to ChE inhibition. In the EPA cumulative risk assessments, route-specific RPFs were adjusted by multiplying by the appropriate FQPA factor.
[b]ND = not determined due to lack of pertinent data.

ChE = acetylcholinesterase; EPA = U.S. Environmental Protection Agency; FQPA = U.S. Food Quality and Protection Act; RPF = relative potency factor

Source: EPA 2006

Table B-4. Oral, Dermal, and Inhalation BMD_{10} and $BMDL_{10}$ Values for Adult Female Rat Brain ChE Inhibition by Methamidophos, the Index Chemical for the EPA Cumulative Risk Assessment for Organophosphorus Insecticides

End point	Oral (mg/kg/day)	Dermal (mg/kg/day)	Inhalation (mg/kg/day)
BMD_{10}	0.08	2.12	0.39
$BMDL_{10}$	0.07	1.77	0.21

BMD = benchmark dose; BMDL = benchmark dose limit; ChE = acetylcholinesterase EPA = U.S. Environmental Protection Agency

Source: EPA 2006

MOE values for the various age group and exposure scenario combinations were calculated by dividing the appropriate methamidophos POD (e.g., BMD_{10} = 0.08 mg/kg/day for oral exposure, see Table 5) by the appropriate methamidophos-equivalent intake estimate. The target MOE for the cumulative risk assessment was 100 to account for uncertainty in extrapolating from rats to humans (10) and uncertainty related to human variability in susceptibility to organophosphorus insecticides (10). EPA (2006) evaluated the available toxicity studies with human subjects and determined that none provided appropriate data to adjust the default inter-species or intra-species uncertainty factors. MOE values <100 were taken as values requiring some mitigation action; those >100 were assessed to be without the need for mitigation. The combined analysis of cumulative risk for three expected pathways (food + water + residential use) indicated combined MOEs at the 99.9th percentile (of exposure) that were approximately >100 for all populations using 21-day average results. In this analysis, the food pathway dominated the combined MOEs. MOE values calculated for 95, 99th and 99.9th percentiles of 21-day average food intakes for children and adults are listed in Table B-5.

Table B-5. MOE Values for 95th, 99th, and 99.9% Percentiles of Cumulative 21-Day Average Intakes of Organophosphorus Insecticides in Food for U.S. Children and Adults

Age group	95th percentile	99th percentile	99.9th percentile
Children, 1–2 years old	550	250	110
Children, 3–5 years old	670	300	99
Adults, 20–49 years old	820	610	280

MOE = margin of exposure

Source: EPA 2006

Cancer Guidelines. Most organophosphorus insecticides have not been evaluated for cancer. Among the 17 organophosphorus insecticides assessed on the EPA IRIS (IRIS 2013), only three have been assessed for carcinogenicity: acephate was classified in Cancer Group C—*possible human carcinogen*; dichlorvos was classified in Cancer Group B2—*probable human carcinogen*; and methidathion was classified in Cancer Group C—*possible human carcinogen*. Oral cancer slope factors were developed for acephate (0.0087 per mg/kg/day) and dichlorvos (0.29 per mg/kg/day). No oral slope factor was developed for methidathion.

NTP (2011) has not assessed any organophosphorus insecticides for carcinogenicity.

IARC (2012) has assessed the possible carcinogenicity of five organophosphorus insecticides. Dichlorvos was classified in Cancer Group 2B—*possibly carcinogenic to humans*. Parathion, malathion, methyl parathion, and tetrachlorvinphos were classified in Cancer Group 3—*not classifiable as to its carcinogenicity to humans*.

B.5 Derivation of Target-Organ Toxicity Dose (TTD) Values

The most clearly established end points of concern for organophosphorus insecticides are neurological effects mediated via the inhibition of ChE. Inhibition of plasma, RBC, or brain ChE is the critical effect for the majority of ATSDR's inhalation MRLs (9/10) and oral MRLs (23/25), regardless of duration of exposure. Based on results from *in vivo* animal tests for a few organophosphorus agents and *in vitro* mechanistic studies, there is concern for the possible neurodevelopmental toxicity of organophosphorus insecticides, but there are inadequate data to describe possible dose-response relationships for neurodevelopmental toxicity of most organophosphorus insecticides (Costa 2008; EPA 2006). Due to the lack of appropriate dose-response data for effects other than ChE inhibition for most organophosphorus insecticides, TTDs were not developed.

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Appendix C: Background Information for Carbamates

Carbamate insecticides are structurally diverse derivatives of carbamic acid or N-methyl carbamic acid, which display a range of potencies in inducing toxic effects in mammals (Costa 2008). The carbamate insecticides discussed in this document (aldicarb, carbaryl, carbofuran, methomyl, oxamyl, and propoxur) are derivatives of N-methyl carbamic acid (EPA 2007b). Like organophosphorus insecticides, their principal and most well-studied effect in insects and mammals is neurological dysfunction mediated through inhibition of ChE (Baron 1991; Costa 2008). The differences in potencies of carbamate insecticides in producing toxic effects in mammals have been associated to a limited degree with structural differences influencing water solubility (Costa 2008). For example, aldicarb, with a water solubility of 6 g/L, is much more potent than carbaryl and carbofuran, with water solubilities of about 0.7 g/L; acute oral LD_{50} values for rats are 0.8, 10, and 400 mg/kg for aldicarb, carbaryl, and carbofuran, respectively (Costa 2008).

C.1 Toxicokinetics

Carbamate insecticides are expected to be absorbed following inhalation, oral, and dermal exposures, and skin penetration is increased by organic solvents and emulsifiers present in commercial preparations (Costa 2008). Results from animal studies indicate that, after absorption, carbamates are rapidly distributed by the blood to tissues and organs, metabolized to water soluble products, and rapidly excreted, predominantly in urine with no bioaccumulation in tissues (Baron 1991). Carbamate insecticides inhibit ChE directly, and most metabolites of carbamate insecticides from pathways involving oxidation and hydrolysis do not inhibit ChE (Costa 2008). Aldicarb is an example of a carbamate, however, with metabolites (sulfoxide and sulfone derivatives) that are potent ChE inhibitors (Costa 2008).

C.2 Health Effects

The principal and most well-studied effect of carbamate insecticides is neurological effects mediated by the inhibition of ChE (Costa 2008). EPA (2007b) determined that the N-methyl carbamate pesticides represent a common mechanism group based on similar structural characteristics and shared ability to inhibit ChE at the active enzymatic site.

The signs and symptoms of acute high-level exposure to carbamate insecticides are similar to those induced by organophosphorus insecticides: miosis, urination, lacrimation, diarrhea, muscle fasciculation, and central nervous system effects such as dizziness, mental confusion, depression of respiratory centers, and coma (Costa 2008). However, the carbamylated ChE is transiently inhibited, rapidly reversible, and

does not undergo the irreversible aging reaction, which happens with organophosphorylated ChE (Costa 2008). Thus, cholinergic signs and symptoms of acute carbamate intoxication are generally resolved within a few hours (Costa 2008). Results from subchronic and chronic animal toxicity studies with carbamate insecticides have identified a number of effects including signs of ChE inhibition, kidney, liver or spleen effects, and decreased body weight gain, but ChE inhibition is a sensitive effect for all studied carbamate insecticides (EPA 2007b).

Results from developmental toxicity, developmental neurotoxicity, and reproductive toxicity studies with several carbamates (aldicarb, carbofuran, methoymyl, oxamyl, and baygon) provide no evidence for effects on reproductive performance from these chemicals and show that fetotoxic effects, such as decreased fetal body weight or delayed ossification of sternebrae, only occurred at doses equal to or greater than those inducing maternal toxicity (see Section C.4). EPA (2007b) compared NOAELs and LOAELs and BMDs from developmental neurotoxicity studies and ChE inhibition studies in animals and reported that, for three carbamates with appropriate data (aldicarb, carbaryl, and carbofuran), ChE inhibition was 10–100-fold more sensitive than developmental neurotoxic effects. As a result, in its cumulative risk assessment for N-methyl carbamates (see Section C.4), EPA (2007b) used ChE inhibition as the end point of concern, as well as the end point of concern for evaluating the FQPA 10X safety factor for infants and children.

C.3 Mechanisms of Action

Neurotoxicity. The principal and common mode of action by which carbamates induce neurological effects in insects and mammals is inhibition of ChE (Baron 1991; Costa 2008). Carbamates rapidly bind to the active site of ChE, but the inhibition of enzyme function is transient and reversible because the reactivation of the carbamylated enzyme is rapid and no “aging” of the active site occurs, such as that which occurs with organophosphorus insecticides (Baron 1991; Costa 2008). EPA (2007b) determined that the N-methyl carbamate pesticides represent a common mechanism group based on similar structural characteristics and shared ability to inhibit ChE by carbamylation of the serine hydroxyl group located in the active site of the enzyme.

Even though some carbamates have been shown to inhibit NTE, they are not expected to cause delayed peripheral neuropathy such as that caused by organophosphorus insecticides, because the carbamylated enzyme does not age (Costa 2008).

Other Effects. Results from chronic exposure animal studies with a few carbamate insecticides have identified a few effects that occur at chronic administered dose levels similar to or slightly lower than those associated with ChE inhibition. The mechanism(s) by which these carbamate insecticides induce effects other than ChE inhibition is unknown.

C.4 Health Guidelines

ATSDR has not prepared toxicological profile for any of the carbamate insecticides discussed in this document.

The EPA IRIS (IRIS 2013) lists chronic oral RfDs for aldicarb, carbaryl, carbofuran, methomyl, oxamyl, and baygon (also known as propoxur), and a more recent cumulative risk assessment for N-methyl carbamates is reported in EPA (2007b).

EPA (2007b) determined that N-methyl carbamate insecticides represent a common mechanism group based on similar structural characteristics and shared ability to inhibit ChE at the active enzymatic site. A multi-chemical, multi-pathway PBPK/PD model could not be developed for the cumulative risk assessment because appropriate pharmacokinetic data for model development were only available for one carbamate insecticide, carbaryl (EPA 2007b). Based on an analysis of available data, including data collected by EPA and data submitted for registration, EPA (2007b) concluded that acute ChE inhibition, measured at the peak time of effect, was the most sensitive effect from exposure to carbamates and thus, the pertinent effect of concern. A component-based RPF approach, assuming dose additivity, was used in the cumulative risk assessment. RPFs for 10 carbamates (and several carbamate metabolites—aldicarb sulfone, aldicarb sulfoxide, and 3- and 5-hydroxy carbofuran) were developed based on brain ChE inhibition data for adult rats (Table C-1). The rat brain ChE inhibition data were modeled with a dose-time response model to estimate BMD_{10} values (doses at which ChE was inhibited by 10%), and the RPF values were calculated by dividing the BMD_{10} value for the subject carbamate by the BMD_{10} value for the index carbamate, oxamyl (EPA 2007b). Oxamyl was chosen as the index chemical, because oxamyl, compared with the other nine carbamates, had the most robust database for all three pertinent routes of exposure (oral, dermal, inhalation).

Table C-1. EPA RPFs for Oral, Dermal, and Inhalation Exposure to Carbamate Insecticides Based on Rat Brain ChE Inhibition

Chemical	Oral RPF	Dermal RPF	Inhalation RPF
Aldicarb	4	ND	ND
Aldicarb sulfone[a]	3.44	ND	ND
Aldicarb sulfoxide[a]	3.68	ND	ND
Carbaryl	0.15	0.71	0.51
Carbofuran	2.4	ND	ND
3- and 5-hydroxycarbofuran	2.4	ND	ND
Formetanate HCL	2.18	ND	ND
Methiocarb	0.18	0.09	0.62
Methomyl	0.67	ND	ND
Oxamyl	1	1	1
Primicarb	0.02	ND	ND
Propoxur	0.11	0.03	0.18
Thiodicarb	0.89	ND	ND

[a]Values for aldicarb sulfone and aldicarb sulfoxide were calculated based on molecular weight conversions from aldicarb assuming equipotency to aldicarb. 3- and 5-Hydroxycarbofuran were assumed to be equipotent to carbofuran.

ChE = acetylcholinesterase; EPA = U.S. Environmental Protection Agency; ND = not derived due to lack of data; RPF = relative potency factor

Source: EPA 2007b

EPA (2007b) incorporated uncertainty and extrapolation factors into the cumulative risk assessment for carbamate insecticides in two ways:

1. Adjustment of the RPF: Chemical-specific information was evaluated, when available, to determine chemical-specific inter-species uncertainty factors (animal to human extrapolation) and FQPA factors to arrive at adjusted RPF values for children and adults (Table C-2). Chemical-specific FQPA factors were calculated, when appropriate data were available, by dividing the adult BMD_{10} by the pup BMD_{10} for ChE inhibition; in the absence of appropriate data, the default value of 10 was used. Chemical-specific interspecies uncertainty factors were calculated similarly when appropriate data were available to compare human BMD_{10} values for ChE inhibition with rat BMD_{10} values.

2. Incorporation into the Target MOE: A default uncertainty factor of 10 for intrahuman variability was taken as the target MOE for each of the carbamate insecticides. The PODs, used in the

cumulative risk assessments to compare against exposure estimates, were the route-specific rat $BMDL_{10}$ values for brain ChE inhibition shown in Table C-3.

Table C-2. EPA Adjusted Oral RPFs for Children and Adults Based on Inter-Species and FQPA Factors

Chemical	Oral RPF	Interspecies factor	FQPA factor for children	Adjusted RPF children	Adjusted RPF adult
Aldicarb	4	2	2	16	8
Aldicarb sulfone	3.44	2	2	13.8	6.9
Aldicarb sulfoxide	3.68	2	2	14.7	7.4
Carbaryl	0.15	10	1.8	2.7	1.5
Carbofuran	2.4	10	2.75	66	24
3- and 5-hydroxycarbofuran	2.4	10	2.75	66	24
Formetanate HCL	2.18	10	2.03	44	22
Methiocarb	0.18	10	10	18	1.8
Methomyl	0.67	5	3.05	10	3.3
Oxamyl	1	3	3.48	10	3
Primicarb	0.02	10	10	2	0.2
Propoxur	0.11	10	10	11	1.1
Thiodicarb	0.89	10	10	89	8.9

EPA = U.S. Environmental Protection Agency; FQPA = U.S. Food Quality and Protection Act; RPF = relative potency factors

Source: EPA 2007b

Table C-3. Oral, Dermal, and Inhalation BMD_{10} and $BMDL_{10}$ Values for Rat Brain ChE Inhibition by Oxamyl, the Index Chemical for the EPA Cumulative Risk Assessment for N-Methyl Carbamates

End point	Oral	Dermal	Inhalation
BMD_{10}	0.24 mg/kg	34.91 mg/kg	0.0047 mg/L
$BMDL_{10}$	0.18 mg/kg	17.05 mg/kg	0.0038 mg/L (converted to 0.66 mg/kg)

BMD = benchmark dose; BMDL = benchmark dose limit; ChE = acetylcholinesterase; EPA = U.S. Environmental Protection Agency

Source: EPA 2007b

EPA (2007b) conducted route-specific cumulative risk assessments for adult and child exposures to N-methyl carbamate insecticides by incorporating the RPF values into a MOE approach applied to food, water, and residential exposure pathways. The residential pathways comprised oral, dermal, and inhalation exposures. Concentrations of carbamate residues in appropriate media (e.g., food, drinking

water) were multiplied by appropriate interspecies- and FQPA-adjusted RPF values (Table C-2) and summed to arrive at oxamyl-equivalent concentrations, which were then used in exposure models to estimate oxamyl equivalent intakes (in units of mg/kg) for the various exposure scenarios investigated. MOE values were calculated by dividing the appropriate oxamyl POD (e.g., the oral rat $BMDL_{10}$—Table C-3—for oral exposure scenarios) by the estimated oxamyl equivalent intake. MOE values <10 were taken as values requiring some mitigation action; those >10 were assessed to be without the need for mitigation. EPA also determined total MOE values for combined estimates of food, water, and residential exposure scenarios, showing that the food pathway was the dominant exposure pathway for the general population.

EPA (IRIS 2013) classified aldicarb in Cancer Group D—*not classifiable as to human carcinogenicity*, based on no human carcinogenicity data and inadequate carcinogenicity data in animal studies. EPA (2007b) reviewed studies that found no statistically significant increases in tumor incidence in mice or rats in 2-year feeding studies or in mice in a skin painting study. EPA (IRIS 2013) noted that there were significant trends in pituitary tumors in female rats and fibrosarcomas in male mice in the feeding studies.

EPA (IRIS 2013) concluded that the assays were inadequate to assess the carcinogenicity of aldicarb, because maximum tolerated doses were not included in the assays. EPA (IRIS 2013) has not formally assessed the carcinogenicity of any other carbamate insecticide.

NTP (2011) has not assessed the possible carcinogenicity of carbamate insecticides.

IARC (2012) classified aldicarb and carbaryl in cancer Group 3—n*ot classifiable as to carcinogenicity to humans*, but has not assessed other carbamates for possible carcinogenicity.

C.5 Derivation of Target-Organ Toxicity Dose (TTD) Values

The most clearly established end points of concern for carbamate insecticides are neurological effects mediated via the inhibition of ChE. ATSDR has not derived MRLs for any of the carbamate insecticides, but EPA (2007b) concluded that acute ChE inhibition, measured at the peak time of effect, was the most sensitive effect from exposure to carbamates and thus, the pertinent effect of concern in its cumulative risk assessment for N-methyl carbamates. Due to the lack of appropriate and readily available dose-response data for effects other than ChE inhibition for most carbamate insecticides, TTDs were not developed.

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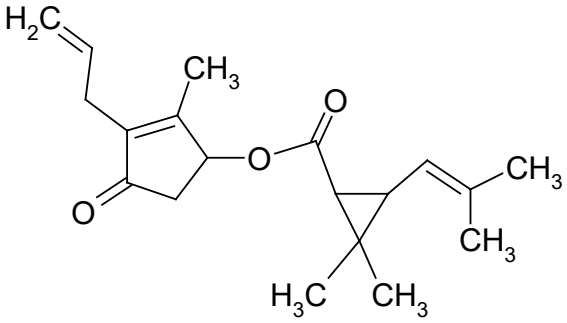
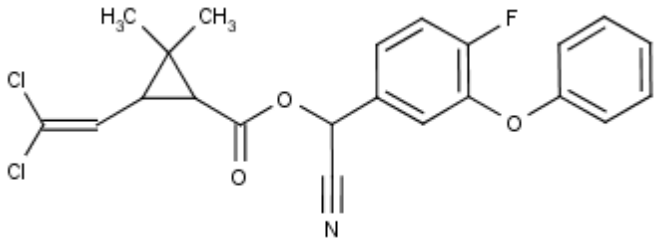
Appendix D: Chemical Structures of Mixture Components

Pyrethroid Insecticides

Allethrin



Cyfluthrin (Baythroid)



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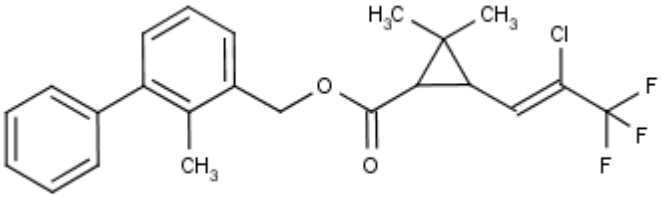

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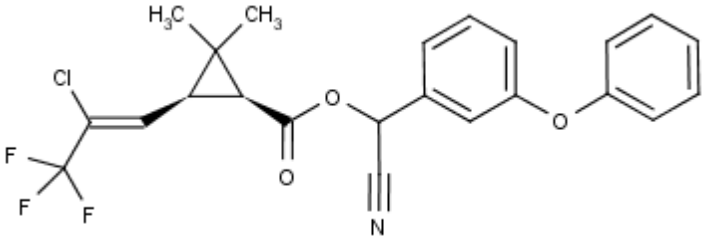
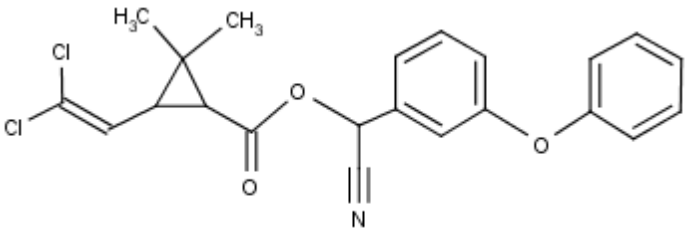


Cypermethrin



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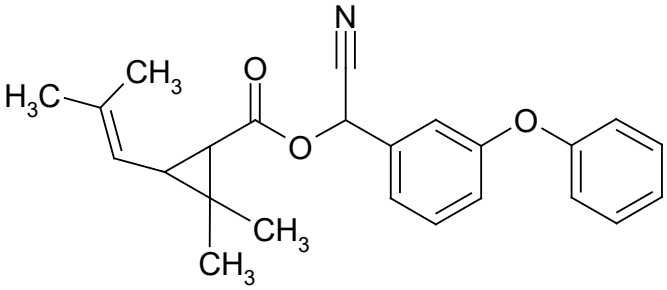
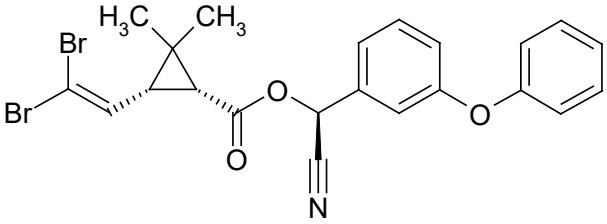
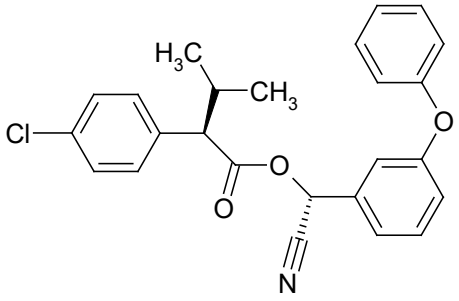


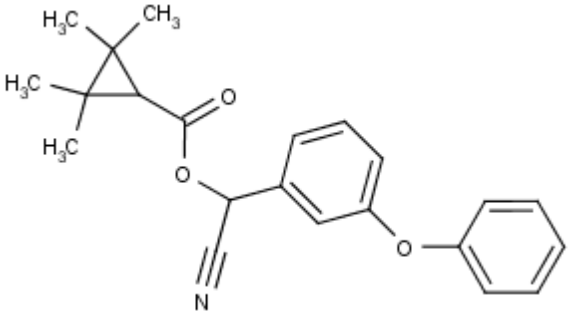
Deltamethrin



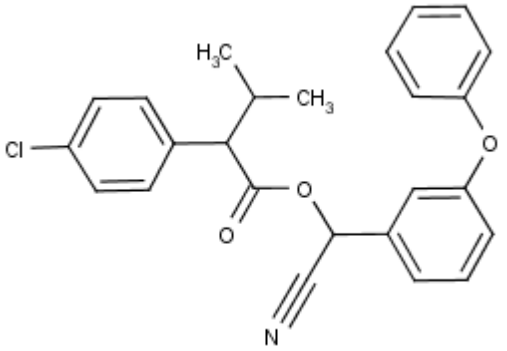
Esfenvalerate



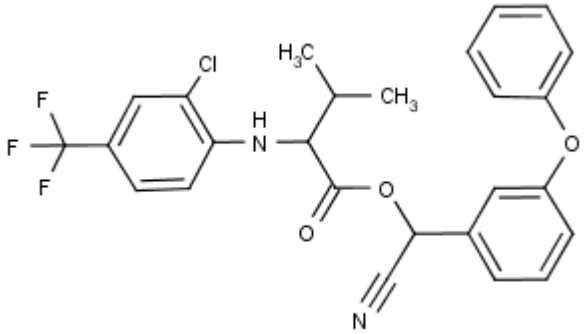
Fenpropathrin (Danitol)



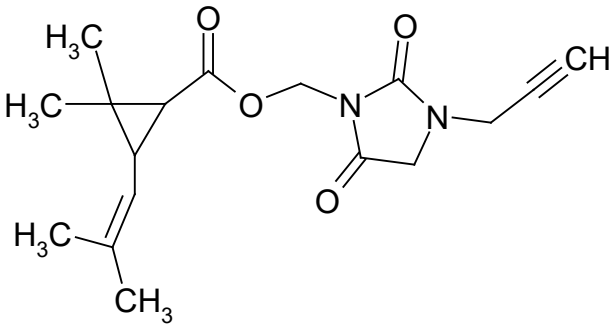
Fenvalerate (Pydrin)



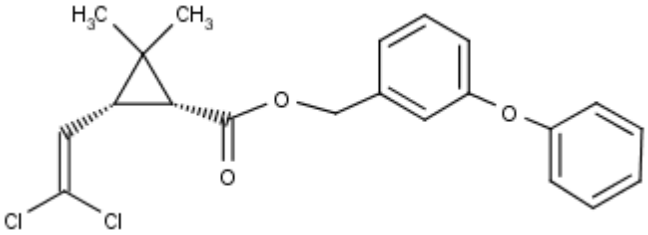
Fluvalinate



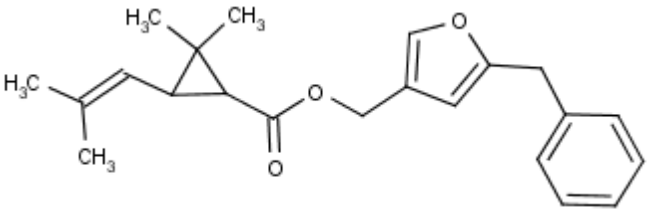
Imiprothrin



Permethrin



Resmethrin



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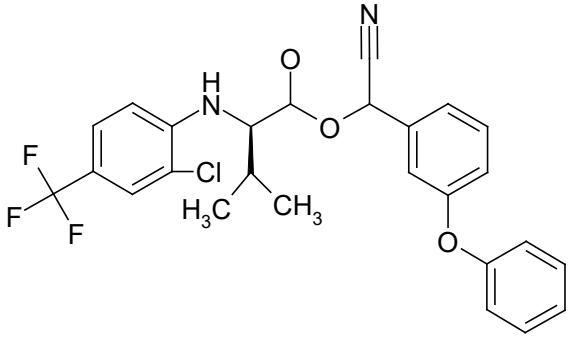
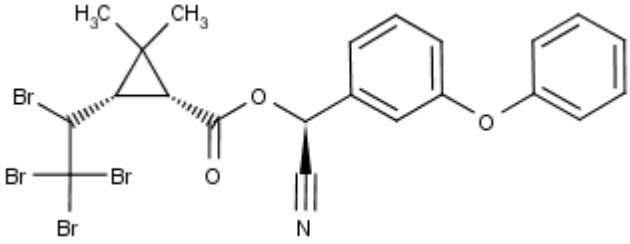
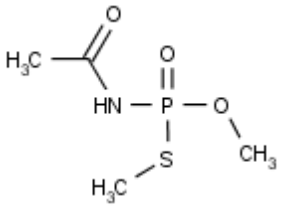


Tralomethrin

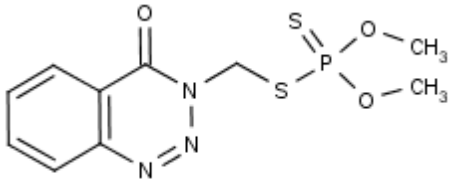


Organophosphorus insecticides

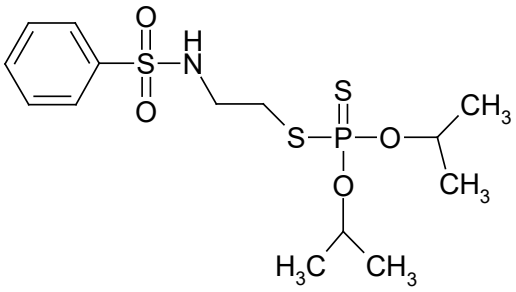
Acephate



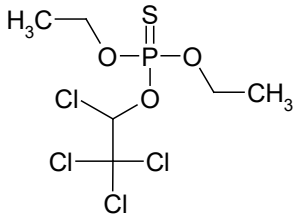
Azinphos-methyl



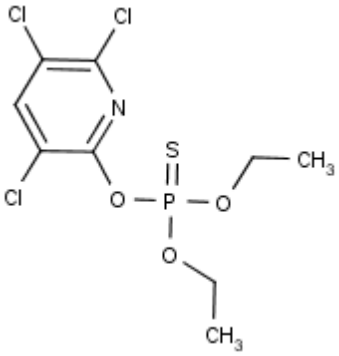
Bensulide



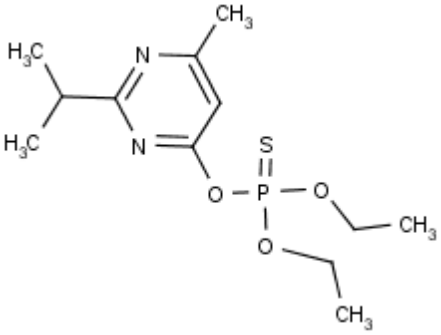
Chlorethoxyfos



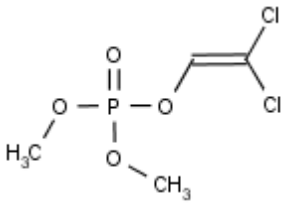
Chlorpyrifos



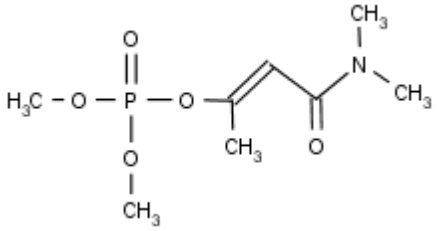
Diazinon



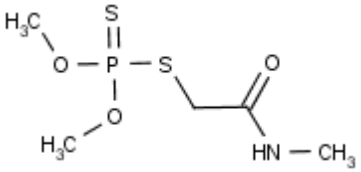
Dichlorvos



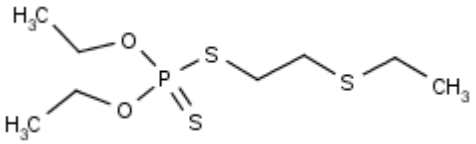
Dicrotophos



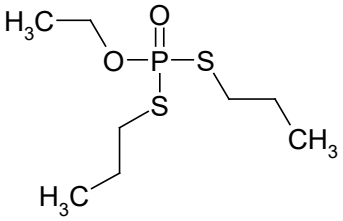
Dimethoate



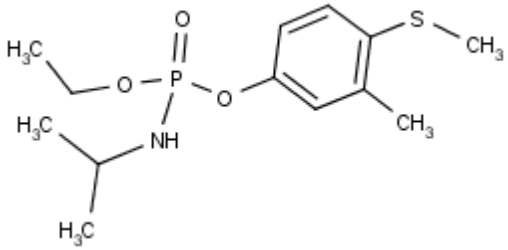
Disulfoton



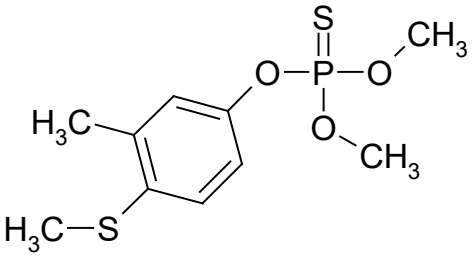
Ethoprop



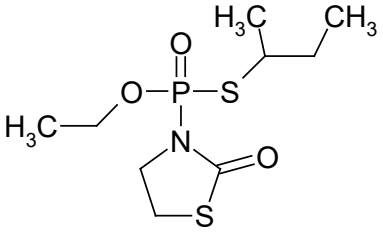
Fenamiphos



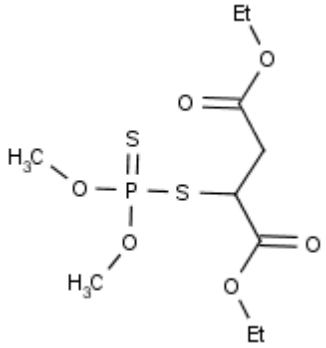
Fenthion



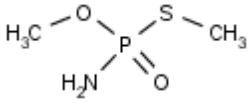
Fosthiazate



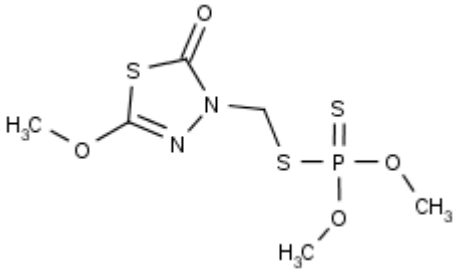
Malathion



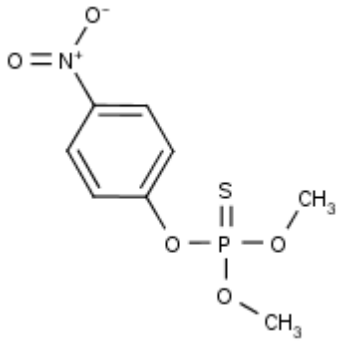
Methamidophos



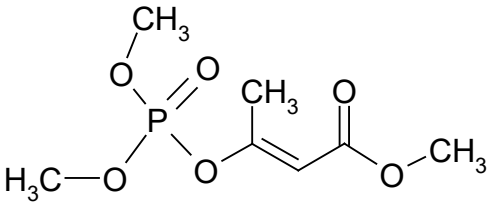
Methidathion



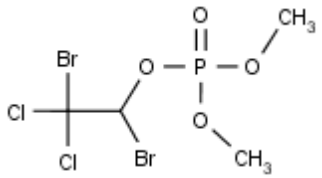
Methyl-parathion



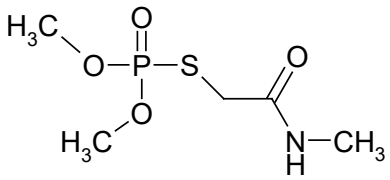
Mevinphos



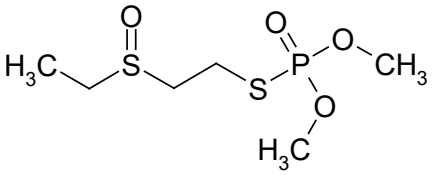
Naled



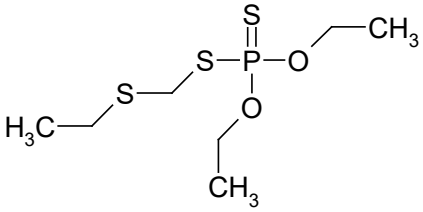
Omethoate



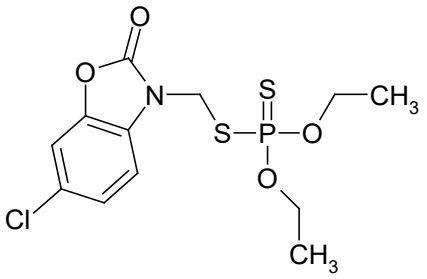
Oxydemeton-methyl



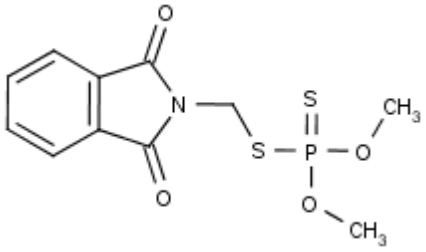
Phorate



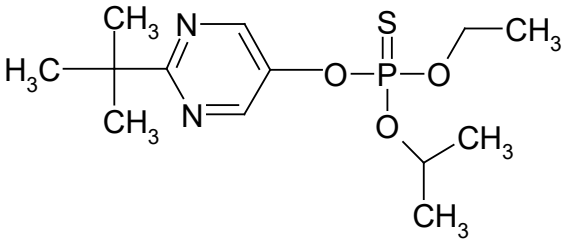
Phosalone



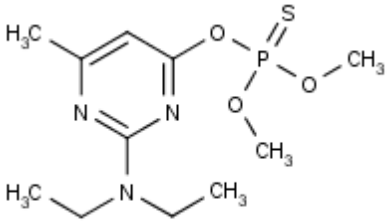
Phosmet



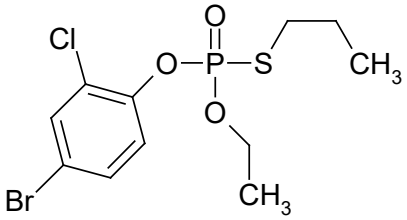
Phostebupirim



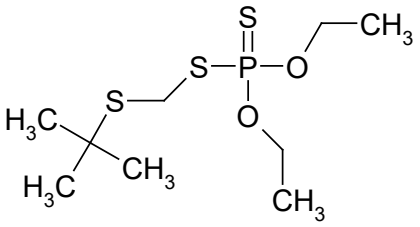
Pirimiphos-methyl



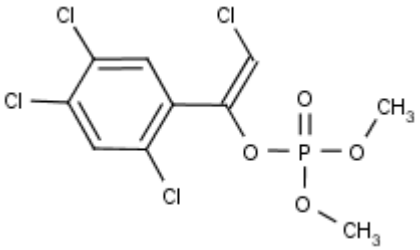
Profenofos



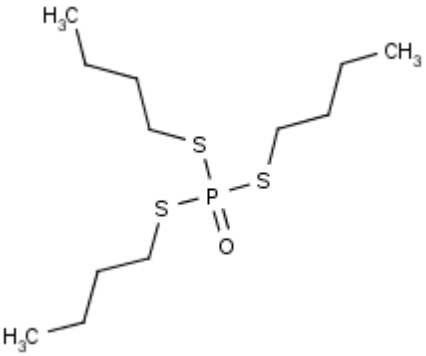
Terbufos



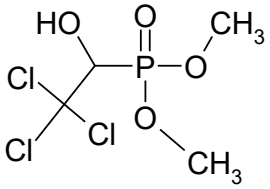
Tetrachlorvinphos



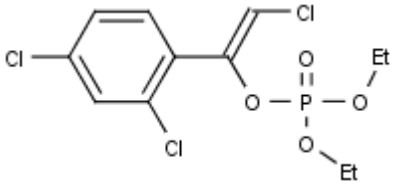
Tribufos (merphos oxide)



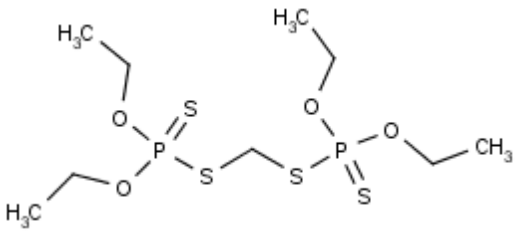
Trichlorfon



Chlorfenvinphos

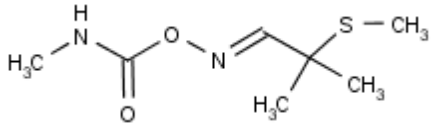


Ethion

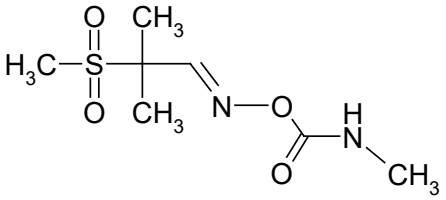


Carbamate insecticides

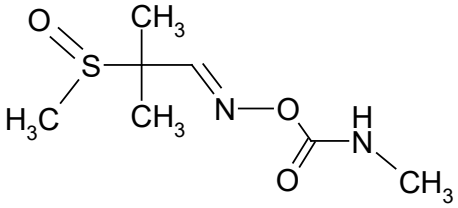
Aldicarb



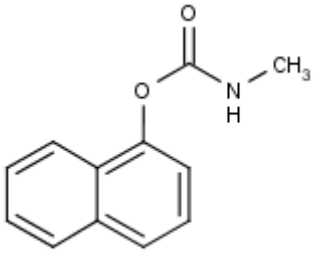
Alidcarb sulfone



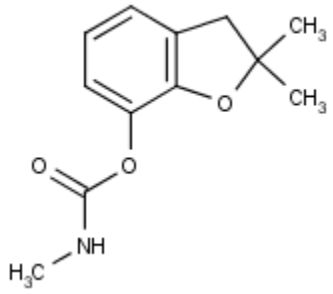
Aldicarb sulfoxide



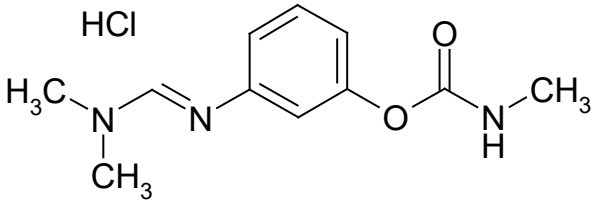
Carbaryl



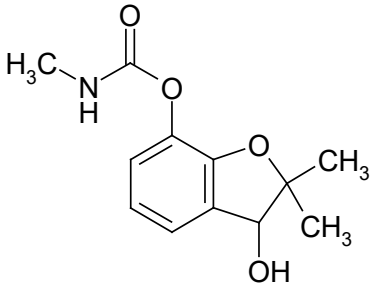
Carbofuran



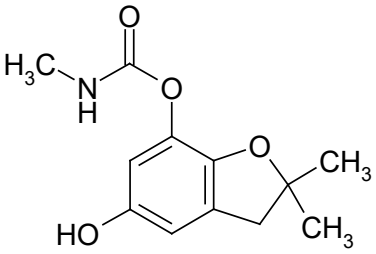
Formetanate hydrochloride



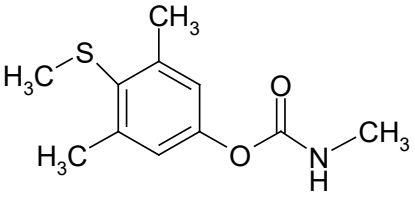
3-Hydroxycarbofuran



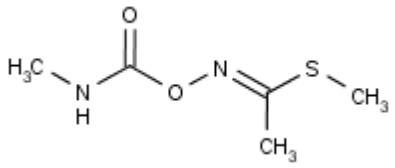
5-Hydroxycarbofuran



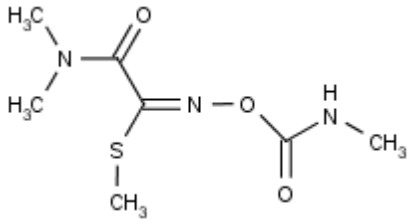
Methiocarb



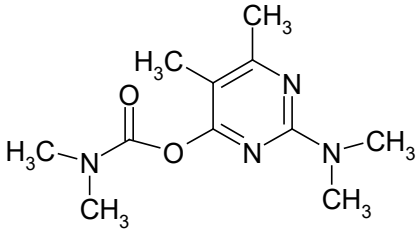
Methomyl



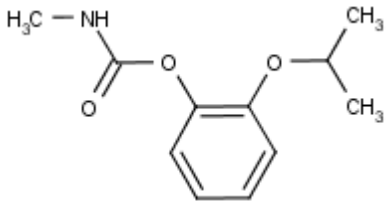
Oxamyl



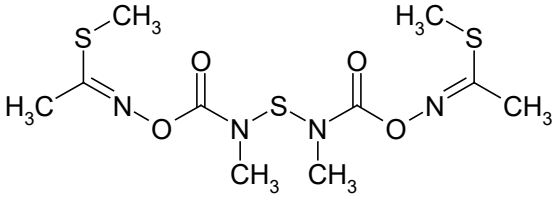
Pirimicarb



Propoxur (Baygon)



Thiodicarb



Appendix E: Mixtures of Insecticides at Hazardous Waste Sites

Table E-1. Sites with Two of the Types of Pesticides[a]

Site event key[b]	Type	Contaminant	CAS number
AZR000041764	Organophosphorus	Chlorpyrifos	2921-88-2
	Pyrethroid	Permethrin	52645-53-1
CAD000629998	Carbamate	Carbaryl	63-25-2
		Carbofuran	1563-66-2
	Organophosphorus	Diazinon	333-41-5
		Dimethoate	60-51-5
		Disulfoton	298-04-4
		Ethion	563-12-2
		Guthion	86-50-0
		Malathion	121-75-5
		Methyl parathion	298-00-0
		Naled	300-76-5
		S,S,S-Tributyl phosphorotrithioate	78-48-8
CAD071530380	Carbamate	Carbaryl	63-25-2
		Methomyl	16752-77-5
		Propoxur	114-26-1
	Organophosphorus	Diazinon	333-41-5
		Disulfoton	298-04-4
CAXCR9P200000004	Carbamate	Carbaryl	63-25-2
		Carbofuran	1563-66-2
	Organophosphorus	Chlorpyrifos	2921-88-2
		Diazinon	333-41-5
		Disulfoton	298-04-4
		Malathion	121-75-5
GAD033478389	Carbamate	Carbofuran	1563-66-2
	Organophosphorus	Methamidophos	10265-92-6
		Methyl parathion	298-00-0
GAD991275686	Carbamate	Carbaryl	63-25-2
	Organophosphorus	Methyl parathion	298-00-0
MAXCR1#MA0000047	Carbamate	Carbaryl	63-25-2
	Organophosphorus	Chlorpyrifos	2921-88-2
MD2210020036	Carbamate	Carbaryl	63-25-2
		Propoxur	114-26-1
	Organophosphorus	Chlorpyrifos	2921-88-2
MN8570024275	Carbamate	Propoxur	114-26-1
	Organophosphorus	Diazinon	333-41-5
		Malathion	121-75-5

Table E-1. Sites with Two of the Types of Pesticides[a]

Site event key[b]	Type	Contaminant	CAS number
MOD000830554	Carbamate	Carbaryl	63-25-2
	Organophosphorus	Diazinon	333-41-5
		Disulfoton	298-04-4
NCD980557656	Carbamate	Carbaryl	63-25-2
		Carbofuran	1563-66-2
	Organophosphorus	Malathion	121-75-5
NVXCRA7220000001	Carbamate	Carbofuran	1563-66-2
	Organophosphorus	Chlorpyrifos	2921-88-2
		Diazinon	333-41-5
		Malathion	121-75-5
TXD007349863	Carbamate	Carbaryl	63-25-2
		Propoxur	114-26-1
	Organophosphorus	Chlorpyrifos	2921-88-2
		Diazinon	333-41-5
		Dichlorvos	62-73-7
		Dimethoate	60-51-5
		Malathion	121-75-5
		Methyl parathion	298-00-0
TXN000605514	Carbamate	Carbaryl	63-25-2
	Organophosphorus	Diazinon	333-41-5
TXXCR6#TX0000006	Carbamate	Carbaryl	63-25-2
	Organophosphorus	Acephate	30560-19-1
TXXCR6#TX0000012	Carbamate	Propoxur	114-26-1
	Organophosphorus	Acephate	30560-19-1
WAD000643577	Carbamate	Carbaryl	63-25-2
	Organophosphorus	Diazinon	333-41-5
		Ethion	563-12-2
		Malathion	121-75-5
		Methyl parathion	298-00-0

[a]Information from the ATSDR HazDat and Sequoia database (through FY2007).
[b]Site IDs that are 12 characters long are for sites (usually defined by EPA). Site IDs that are 16 characters long are for events (like emergency events; always defined by ATSDR).

Table E-2. Sites with All Three Types of Pesticides[a]

Site event key[b]	Type	Substance	CAS number
AZD980735666	Carbamate	Carbaryl	63-25-2
		Methomyl	16752-77-5
	Organophosphorus	Diazinon	333-41-5
		Dimethoate	60-51-5
		Guthion	86-50-0
		Malathion	121-75-5
		Methyl parathion	298-00-0
	Pyrethroid	Permethrin	52645-53-1
CO5210020769	Carbamate	Methomyl	16752-77-5
	Organophosphorus	Chlorfenvinphos	470-90-6
		Dichlorvos	62-73-7
		Dicrotophos	141-66-2
		Malathion	121-75-5
		Methyl parathion	298-00-0
		Naled	300-76-5
		Stirofos	22248-79-9
	Pyrethroid	Fenvalerate	51630-58-1
LAD981057706	Carbamate	Aldicarb	116-06-3
		Carbofuran	1563-66-2
		Oxamyl	23135-22-0
	Organophosphorus	Chlorpyrifos	2921-88-2
		Diazinon	333-41-5
		Dimethoate	60-51-5
		Disulfoton	298-04-4
		Guthion	86-50-0
		Malathion	121-75-5
		Methyl parathion	298-00-0
		Naled	300-76-5
	Pyrethroid	Permethrin	52645-53-1
NVXCRA7220000002	Carbamate	Carbaryl	63-25-2
		Propoxur	114-26-1
	Organophosphorus	Chlorpyrifos	2921-88-2
		Diazinon	333-41-5
		Malathion	121-75-5
		Methyl parathion	298-00-0
	Pyrethroid	Cyfluthrin	68359-37-5
		Cypermethrin	52315-07-8
		Permethrin	52645-53-1

Table E-2. Sites with All Three Types of Pesticides[a]

Site event key[b]	Type	Substance	CAS number
NVXCRA7220000004	Carbamate	Carbaryl	63-25-2
		Propoxur	114-26-1
	Organophosphorus	Chlorpyrifos	2921-88-2
		Diazinon	333-41-5
		Malathion	121-75-5
		Methyl parathion	298-00-0
	Pyrethroid	Cyfluthrin	68359-37-5
		Cypermethrin	52315-07-8
		Permethrin	52645-53-1

[a]Information from the ATSDR HazDat database (through FY2007).
[b]Site IDs that are 12 characters long are for sites (usually defined by EPA). Site IDs that are 16 characters long are for events (like emergency events; always defined by ATSDR).