1. Introduction

The primary purpose of this Interaction Profile for Mixtures of Insecticides: Pyrethroids, Organophosphorus Compounds, and Carbamates is to evaluate data on the toxicology of the "whole" mixture and the joint toxic action of the chemicals in the mixture in order to recommend approaches for assessing the potential hazard of mixtures of these insecticide classes to public health. To this end, the profile evaluates the whole mixture data (if available), focusing on the identification of health effects of concern (i.e., neurological effects), adequacy of the data as the basis for a mixture health guidance value, and adequacy and relevance of physiologically-based pharmacokinetic/pharmacodynamic models for the mixture. The profile also evaluates the evidence for joint toxic action—additivity and interactions—among the mixture components. A weight-of-evidence approach is commonly used in these profiles to evaluate the influence of interactions in the overall toxicity of the mixture. The weight-of-evidence evaluations are qualitative in nature, although the Agency for Toxic Substances and Disease Registry (ATSDR) recognizes that observations of toxicological interactions depend greatly on exposure doses and that some interactions appear to have thresholds. Thus, the interactions are evaluated in a qualitative manner to provide a sense of what influence the interactions may have when they do occur. The profile provides environmental health scientists with ATSDR Division of Toxicology and Human Health Sciences (DTHHS) recommended approaches for the incorporation of the whole mixture data or the concerns for additivity and interactions into an assessment of the potential hazard of this mixture to public health. These approaches can then be used with specific exposure data from hazardous waste sites or other exposure scenarios.

Interactions between pyrethroid, organophosphorus, and carbamate insecticides are of interest to ATSDR because members of these chemical classes are the most widely used insecticides, and the general population is expected to be exposed to mixtures of members of these insecticide classes from eating food or drinking water with insecticide residues and from the use of insecticides in the home and workplace. The U.S. Environmental Protection Agency (EPA) estimated that the world-wide and U.S. expenditure for insecticides in the year 2012 was U.S. $ 16,023 million (or 25% of the market for all pesticides) and $ 2,184 million (or 25% of the market for all pesticides), respectively, at the producer level (EPA 2007a). Because of the widespread use, these insecticides also end-up at hazardous waste sites. The occurrence of the insecticides at hazardous waste sites based on the ATSDR's database is provided in Appendix E. Exposures at the sites may be higher than those encountered by the general population. In addition, all three routes of exposure may be of concern.

This profile concentrates on neurological effects, as these are the principal and most well-studied toxic effects associated with exposure to individual members of each of these insecticide classes. Appendices A–C to this profile provide background information on the toxicokinetics, health effects, and mechanisms of action of pyrethroid insecticides (Appendix A), organophosphorus insecticides (Appendix B), and carbamate insecticides (Appendix C). Also included in the appendices are descriptions of current ATSDR and EPA health guidelines for members of each insecticide class. As discussed in the appendices, cancer is not an expected health end point of concern for most members of each of these insecticide classes. Likewise, results from standard developmental toxicity and reproductive toxicity tests in animals do not identify developmental toxicity or reproductive toxicity as critical health effects for most members of each class (Appendices A–C). There is a concern for possible neurodevelopmental effects from organophosphorus insecticides based on positive results in a few *in vivo* studies and *in vitro* mechanistic studies (see Appendix B). Available studies that tested these end points, did not clearly establish neurodevelopmental effects as health effects of concern for pyrethroid or carbamate insecticides (see Appendices A and C).

Mechanistic information indicates that pyrethroids induce neurological effects by interfering with voltage-gated sodium channels (VGSC) in nerve cells (see Appendix A), whereas organophosphorus and carbamate insecticides induce neurological effects via inhibition of the enzyme, acetylcholinesterase (ChE), leading to accumulation of acetylcholine at acetylcholine receptors and overstimulation of junctions in central and peripheral nerves (see Appendices B and C). Pyrethroids are manufactured insecticides that are similar in chemical structure to pyrethrins, naturally occurring chemicals found in certain chrysanthemum flowers (Appendix A; ATSDR 2003a). Hundreds of organophosphorus compounds have been synthesized and many commercialized as insecticides, and more than half of insecticides used are organophosphorus compounds (Costa 2008). Carbamate insecticides are structurally diverse derivatives of carbamic acid or N-methyl carbamic acid (Costa 2008). The carbamate insecticides discussed in this profile are all N-methyl carbamate derivatives.

EPA (2006, 2007b) determined that the organophosphorus insecticides and the N-methyl carbamate pesticides represent separate common mechanism of toxicity groups (see Appendices B and C). Although the signs and symptoms of acute high-level exposure to carbamate insecticides are similar to those induced by organophosphorus insecticides, the carbamylated ChE is transiently inhibited, rapidly reversible, and does not undergo the irreversible aging reaction that happens with organophosphorylated ChE (Costa 2008). Thus, cholinergic signs and symptoms of acute carbamate intoxication are generally resolved within a few hours, whereas acute organophosphorus intoxication takes longer to resolve (Costa

2008). To conduct cumulative risk assessments for these two classes of insecticides, EPA's Office of Pesticide Programs (OPP) derived relative potency factors (RPFs) for 33 organophosphorus insecticides based on relative ability to inhibit brain ChE in adult rats exposed for 21 days, compared with the index chemical, methamidophos (EPA 2006; see Appendix B), and RPFs for 10 carbamates based on the ability to inhibit brain ChE in acutely exposed adult rats, compared with the index chemical, oxamyl (EPA 2007b; see Appendix C).

Pyrethroids represent a class of chemicals that rapidly modify the function of nerve cells predominantly by modifying the kinetics of VGSCs, but other diverse targets have been identified, including voltage-gated chloride channels, gamma-aminobutyric acid (GABA)-gated chloride channels, and noradrenaline release and voltage-gated calcium channels (Appendix A; Ray and Fry 2006; Soderlund et al. 2002). EPA (2011b) concluded that pyrethroids share the same mechanism of action, namely interacting with VGSCs in nerve cells. Although different pyrethroids have been demonstrated to interact differentially with different VGSC subunits, all tested pyrethroids alter the kinetics of VGSCs in nerve cells (EPA 2011a, 2011b). In addition, EPA (2011a, 2011b) determined that the weight of evidence supporting mechanisms of action at other channels was "not compelling", relative to action on sodium channels. For a cumulative risk assessment, EPA (2011a) derived RPFs for 15 pyrethroids, based on scores for changing several clinical end points related to alterations in VGSCs in acutely exposed rats, compared with the index pyrethroid, deltamethrin (see Appendix A).

Although members of all of these chemical classes have been detected in air samples and some residential exposure scenarios are expected to involve oral, dermal, and inhalation exposures, the major source of exposure to these classes of insecticides in the general human population is likely to be as residues in food (Appendices A–C). Information regarding mixtures of these chemicals at hazardous waste sites can be found in Appendix E.

Information to prepare this profile was obtained via searches of the literature (conducted in February–July 2009 and updated in February 2013) with a focus on information for members of each insecticide class listed in Table 1. These insecticides were selected because they were either the subject of an ATSDR Toxicological Profile, had a reference dose (RfD) on the EPA Integrated Risk Information System (IRIS 2013), or were included in the EPA OPP cumulative risk assessments for these classes of insecticides (EPA 2006, 2007b, 2011a). Searches were not restricted with regard to toxic end point (even though this profile is focused on neurological end points) or route of exposure.

Table 1. List of Pyrethroid, Organophosphorus, and Carbamate Insecticides That are the Focus of the Literature Search for This Profile

Chemical	CAS Number	RfD on IRIS	ATSDR MRL	OPP RPF
Pyrethroid insecticides				
Allethrin	584-79-2	No	No	Yes
Bifenthrin	82657-04-3	Yes	No	Yes
Cyfluthrin (Baythroid)	68359-37-5	Yes	No	Yes
Cyhalothrin	68085-85-8 or 91465-08-6 (lambda)	Yes	Oral	Yes
Cypermethrin	52315-07-8	Yes	Oral	Yes
Cyphenothrin	39515-40-7	No	No	Yes
Deltamethrin	52918-63-5	No	No	Yes
Esfenvalerate	66230-04-4	No	No	Yes
Fenpropathrin (Danitol)	39515-41-8	Yes	No	Yes
Fenvalerate (Pydrin)	51630-58-1	Yes	No	No
Fluvalinate	69409-94-5	Yes	No	No
Imiprothrin	72963-72-5	No	No	Yes
Permethrin	52645-53-1	Yes	Oral	Yes
Resmethrin	10453-86-8	Yes	No	Yes
Tau-fluvalinate	102851-06-9	No	No	Yes
Tralomethrin	66841-25-6	Yes	No	No
Organophosphorus insecticides				
Acephate	30560-19-1	Yes	No	Yes
Azinphos-methyl (guthion)	86-50-0	No	Inhalation, oral	Yes
Bensulide	741-58-2	No	No	Yes
Chlorethoxyfos	54593-83-8	No	No	Yes
Chlorfenvinphos	470-90-6	No	Oral	No
Chlorpyrifos	2921-88-2	Yes	Oral	Yes
Diazinon	333-41-5	No	Inhalation, oral	Yes
Dichlorvos (DDVP)	62-73-7	Yes	Inhalation, oral	Yes
Dicrotophos (bidrin)	141-66-2	Yes	No	Yes
Dimethoate	60-51-5	Yes	No	Yes
Disulfoton	298-04-4	Yes	Inhalation, oral	Yes
Ethion	563-12-2	Yes	Oral	No
Ethoprop	13194-48-4	No	No	Yes
Fenamiphos	22224-92-6	Yes	No	Yes
Fenthion	55-38-9	No	No	Yes
Fosthiazate	98886-44-3	No	No	Yes
Malathion	121-75-5	Yes	Inhalation, oral	Yes
Methamidophos	10265-92-6	Yes	No	Yes
Methidathion	950-37-8	Yes	No	Yes
Methyl-parathion	298-00-0	Yes	Oral	Yes

Table 1. List of Pyrethroid, Organophosphorus, and Carbamate Insecticides That are the Focus of the Literature Search for This Profile

Chemical	CAS Number	RfD on IRIS	ATSDR MRL	OPP RPF
Mevinphos	7786-34-7	No	No	Yes
Naled	300-76-5	Yes	No	Yes
Omethoate	1113-02-6	No	No	Yes
Oxydemeton-methyl	301-12-2	No	No	Yes
Phorate	298-02-2	No	No	Yes
Phosalone	2310-17-0	Yes	No	Yes
Phosmet	732-11-6	Yes	No	Yes
Phostebupirim	96182-53-5	No	No	Yes
Pirimiphos-methyl	29232-93-7	Yes	No	Yes
Profenofos	41198-08-7	No	No	Yes
Terbufos	13071-79-9	No	No	Yes
Tetrachlorvinphos	961-11-5, 22248-79-9	Yes	No	Yes
Tribufos (merphos oxide)	78-48-8	Yes	No	Yes
Trichlorfon	52-68-6	No	No	Yes
Carbamate insecticides				
Aldicarb	116-06-3	Yes	No	Yes
Aldicarb sulfone	1646-88-4	No	No	Yes
Aldicarb sulfoxide	1646-87-3	No	No	Yes
Carbaryl	63-25-2	Yes	No	Yes
Carbofuran	1563-66-2	Yes	No	Yes
Formetanate hydrochloride	23422-53-9	No	No	Yes
3-Hydroxycarbofuran	16655-82-6	No	No	Yes
5-Hydroxycarbofuran	Not on CHEMIDplus	No	No	Yes
Methiocarb	2032-65-7	No	No	Yes
Methomyl	16752-77-5	Yes	No	Yes
Oxamyl	23135-22-0	Yes	No	Yes
Pirimicarb	23103-98-2	No	No	Yes
Propoxur (Baygon)	114-26-1	Yes	No	Yes
Thiodicarb	59669-26-0	No	No	Yes

ATSDR = Agency for Toxic Substances and Disease Registry; CAS = Chemical Abstracts Service; EPA = U.S. Environmental Protection Agency; IRIS = Integrated Risk Information System; MRL = Minimal Risk Level; OPP = U.S. EPA Office of Pesticide Programs; RfD = reference dose; RPF = relative potency factor