3. Recommendation for Exposure-Based Assessment of Joint Toxic Action of the Mixture

To conduct exposure-based assessments of possible neurologic health hazards from oral exposures to mixtures of members of all three insecticide classes (pyrethroid, organophosphorus, and carbamate insecticides), ATSDR recommends the use of a component-based approach, because there are no direct data available to characterize health hazards (and dose-response relationships) from exposure. In addition, "interaction" PBPK/PD models have not yet been developed that would predict appropriate target doses of the components.

Recommendations focus on oral exposure because it is the predominant route of exposure for the general population to these insecticide classes. In the EPA cumulative risk assessments for organophosphorus insecticides (EPA 2006), carbamate insecticides (EPA 2007b), and pyrethroids (EPA 2011a), analysis of exposure estimates from food, water, and residential use (the latter pathway involved oral, dermal, and inhalation exposures) indicated that exposures through the food pathway were greater than the residential use and drinking water pathways for the general population. For carbamates, food exposure estimates were greater than the residential pathway estimates (which were dominated by dermal exposures from lawn uses of carbaryl), which were greater than exposures through drinking water (EPA 2007b). For organophosphorus insecticides, exposure estimates from the food pathway were substantially greater than exposure estimates from drinking water, which were substantially greater than exposure estimates from residential use pathways (EPA 2006). Similarly, the general population's exposure to pyrethroid insecticides is expected to be primarily from food sources, especially fruits and vegetables (ATSDR 2003a; EPA 2011a).

As discussed by ATSDR (1992, 2004a), the exposure-based assessment of potential health hazard is a screening approach, to be used in conjunction with evaluation of community-specific health outcome data, consideration of community health concerns, and biomedical judgment, to assess the degree of public health hazard presented by mixtures of substances released into the environment. In a component-based approach for noncancer health effects: (1) joint additive actions of the components on shared targets of toxicity are assumed; (2) oral intakes are calculated based on measured concentrations of the components in media of concern; (3) intakes are divided by MRLs or TTDs; and (4) resulting HQs are summed to arrive at a HI.

TTDs are developed for an end point of concern when the critical effect levels for those effects are higher than those associated with the most sensitive end point. When the most sensitive end point is the effect of concern, the MRL is used as the reference toxicity benchmark for estimating the effect-specific HI (ATSDR 2004a). For this assessment, TTDs were not developed for any of the insecticide classes because neurological effects from short-term exposures are the most clearly established health effect of concern for each class, and other end points are not clearly established as shared toxicity targets by most members of each class (see Appendices A–C).

ATSDR recognizes that EPA's RPFs for organophosphorus insecticides (EPA 2006), carbamate insecticides (EPA 2007b), and pyrethroids (EPA 2011a) represent alternative approaches for assessing neurological hazards from these insecticide classes and mixtures, compared with single chemical ATSDR MRLs or EPA RfDs. RPFs for 33 organophosphorus insecticides were developed versus intermediate oral ATSDR MRLs for 9 members of this class (see Appendix B). RPFs for 15 pyrethroids were developed versus acute oral MRLs for 3 pyrethroids and intermediate oral MRLs for 2 pyrethroids (see Appendix A). RPFs for 13 carbamates were developed versus no ATSDR MRLs for any carbamates (see Appendix C). As described herein, ATSDR recommends the use of provisional oral MRLs for the index chemicals (methamidophos for organophosphorus insecticides, deltamethrin for pyrethroids, and oxamyl for the carbamates) and apply RPFs to exposure concentrations for other members of each class to assess neurological effects from organophosphorus, pyrethroid, and carbamate insecticides.

For the assessment of organophosphorus insecticides, concentrations of organophosphorus residues in the media of concern should be converted to methamidophos equivalents via multiplication by the pertinent RPF (see Table B-4 in Appendix B) and summed to arrive at exposure levels that can be converted to oral intakes (in units of mg/kg/day). The estimated intake is then divided by the provisional oral MRL for methamidophos to arrive at a HQ for exposure to methamidophos equivalents. To derive a provisional oral MRL for methamidophos, the $BMDL_{10}$ value for 10% inhibition of brain ChE in rats in the principal study, 0.07 mg/kg/day (see Table B-5 in Appendix B), is selected as the POD and divided by a total uncertainty factor of 100 (10 to account for extrapolation from rats to humans and 10 for human variability) as follows:

$$\text{Provisional oral MRL for methamidophos} = \text{POD} \div \text{uncertainty factor} = 0.07 \text{ mg/kg/day} \div 100 = 0.0007 \text{ mg/kg/day}$$

For the assessment of carbamate insecticides, concentrations of carbamate residues in the media of concern should be converted to oxamyl equivalents via multiplication by the pertinent RPF (the

unadjusted "Oral RPF" values in Table C-2 in Appendix C) and summed to arrive at exposure levels that can be converted to oral intakes (in units of mg/kg/day). The estimated intake is then divided by the provisional oral MRL for oxamyl to arrive at a HQ for exposure to oxamyl equivalents. To derive a provisional oral MRL for oxamyl, the $BMDL_{10}$ value for 10% inhibition of brain ChE in rats in the principal study, 0.18 mg/kg/day, is selected as the POD (see Table C-3 in Appendix C) and divided by a total uncertainty factor of 100 (10 to account for extrapolation from rats to humans and 10 for human variability) as follows:

Provisional oral MRL for oxamyl = POD ÷ uncertainty factor =
0.18 mg/kg/day ÷ 100 = 0.0018 mg/kg/day

In the EPA (2007b) carbamate cumulative risk assessment, EPA developed chemical-specific "interspecies factors" for aldicarb (factor = 2), aldicarb sulfone (factor = 2), aldicarb sulfoxide (factor = 2), methomyl (factor = 5), and oxamyl (factor = 3) to replace the default interspecies uncertainty factor of 10 (see Table C-1 in Appendix C). These factors were calculated as ratios of rat and human BMD_{10} values for ChE inhibition, when they were available. Since this type of data is not available for all 13 carbamates assessed by EPA (2007b), and the provisional MRL for oxamyl will be used to assess a cumulative HQ for all carbamates with RPFs, the default uncertainty factor of 10 for extrapolation from animals to humans was used in the derivation of the provisional oral MRL for oxamyl.

For the assessment of pyrethroid insecticides, concentrations of pyrethroid residues in the media of concern should be converted to deltamethrin equivalents via multiplication by the pertinent RPF (see Table A-1 in Appendix A) and summed to arrive at exposure levels that can be converted to oral intakes (in units of mg/kg/day). The estimated intake is then divided by the provisional oral MRL for deltamethrin to arrive at a HQ for exposure to deltamethrin equivalents. To derive a provisional oral MRL for deltamethrins, the $BMDL_{20}$ value for 20% increase in incidence for scores >4 on a composite neurological score of body temperature, tremors, clonic convulsions, salivation, and altered mobility, 11 mg/kg/day (Table A-1 in Appendix A), is selected as the POD and divided by a total uncertainty factor of 100 (10 to account for extrapolation from rats to humans and 10 for human variability) as follows:

Provisional oral MRL for deltamethrin = POD ÷ uncertainty factor =
11 mg/kg/day ÷ 100 = 0.11 mg/kg/day

As specified by the FQPA, EPA (2006, 2007b, 2011a) used additional FQPA factors to provide additional protection of infants and children in its cumulative risk assessments for organophosphorus, carbamate,

and pyrethroid insecticides. The default FQPA factor of 10 was replaced with chemical-specific FQPA factors for 9 of the 13 carbamates assessed (see Table C-2 in Appendix C) and for 10 of the 33 organophosphorus insecticides assessed (see Table B-4 in Appendix B). For pyrethroids, the default 10 safety factor was replaced with a 3 safety factor for children from birth to <6 years of age (see Appendix A.2). Therefore, to provide additional protection for infants and children, the concentrations of the individual carbamates, organophosphorus, or pyrethroid insecticides in the media of concern could be multiplied by the chemical-specific RPF values and appropriate FQPA factors before summing and converting to intakes of index chemical equivalents.

ATSDR recommends the calculation of a screening-level HI for assessing neurological effects from oral exposures to mixtures of pyrethroid, organophosphorus, and carbamate insecticides under the assumption of dose additivity. The HI for neurological effects from oral exposure to a mixture of pyrethroid, organophosphorus, and carbamate insecticides would be calculated as follows:

$$HI_{Neurologic} = \frac{E_{oxamyl\ equiv}}{MRL_{oxamyl}} + \frac{E_{methamidophos\ equiv}}{MRL_{methamidophos}} + \frac{E_{deltamethrin\ equiv}}{MRL_{deltamethrin}}$$

where E = estimated oral intake in units of mg/kg/day. Modification of the intakes with FQPA factors can provide HIs providing additional protection for infants and children.

Preliminary evidence that the exposure to the mixture may constitute a hazard is provided when the HI exceeds 1. In practice, concern for the possibility of a health hazard increases with increasing value of the HI above 1.

The addition of HQs assumes that less-than-additive (e.g., antagonistic or inhibitory) or greater-than-additive (e.g., synergistic or potentiating) interactions do not occur among the components of the mixture. As discussed in Sections 2.2 and 2.3, greater-than-additive action on neurological end points is possible between certain pyrethroid and organophosphorus insecticides (Tables 3 and 4), the available data are inadequate to assess the possible direction of interactions between pyrethroids and carbamates (Tables 5 and 6), and available data support dose additivity of carbamate and organophosphorus insecticides on neurological end points (Tables 7 and 8). Overall, the evidence is not compelling to move from a dose-additive approach. ATSDR recommends that screening-level assessments of neurological hazard using the HI approach be accompanied by qualitative descriptions of these evaluations of the available interaction data. The evaluations indicate that evidence is available for greater-than-additive interactions

between certain pyrethroid and organophosphorus insecticides, but key findings come from a study of potentiation of fenvalerate lethality in rats pretreated with certain organophosphorus insecticides (Gaughan et al. 1980). The relevance of these findings to relatively low (nonlethal) environmental concurrent exposure to pyrethroid and organophosphorus insecticides is not well understood. No evidence of a toxicokinetic interaction was found in a study of elimination kinetics of pyrethroid metabolites in volunteers exposed to a mixture of low doses (0.01 mg/kg) of deltamethrin and chlorpyrifos-methyl (Sams and Jones 2011). These findings reflect the uncertainty that greater-than-additive joint actions between pyrethroid and organophosphorus insecticides may occur in humans exposed to levels of these insecticides in food.

Data Needs for Assessing Joint Toxic Actions of Pyrethroid, Organophosphorus, and Carbamate Insecticides. Although there are PBPK models for some individual chemicals within these three classes of insecticides, there are no "interaction" PBPK models like those that exist for benzene, toluene, ethylbenzene, and xylene (BTEX) and certain other volatile organic chemicals (e.g., see ATSDR Interaction Profile for BTEX; ATSDR 2004b). Before such models can be developed, pharmacokinetic or pharmacodynamic points of interactions between members of the subject classes must first be identified. To date, no common points of pharmacokinetic or pharmacodynamic interaction have been clearly identified, other than ChE inhibition for carbamate and organophosphorus insecticides. Possible points of interaction including various steps in biotransformation, but the understanding of the complexity of biotransformations for these insecticide classes is too limited to identify key interaction events. With the identification of a common point of pharmacokinetic or pharmacodynamic interaction, it would be possible to design the additional studies needed to develop an "interaction" PBPK model for members of these insecticide classes. Following identification of common points of pharmacokinetic interaction, *in vivo* studies could be conducted to examine the kinetics of internal concentrations of the parent chemicals of concern and their metabolites following co-exposure, comparing results to exposure to each component alone.

Neurodevelopmental effects from exposure to insecticides is of concern to public health because of the likelihood of exposure to mixtures of insecticides in food, but adequate research to establish these types of neurological effects as hazards is not available for most members of each of the subject classes of insecticides (see Appendices A–C). With the possible future identification of neurodevelopment effects as hazards from several members in each class, additional research on possible interactions of these insecticides and the impact of the interactions on neurodevelopmental end points would help to decrease uncertainties in the current approach to assessing only short-term neurological human health hazards.