# 4. Conclusions

ATSDR recommends a component-based HI approach that assumes dose-additive joint toxic action for preliminary assessment of possible neurological health hazards from oral exposure to mixtures of pyrethroid, organophosphorus, and carbamate insecticides. No studies were located that examined neurological end points following exposure to any mixtures of members of all three of these insecticide classes, thereby precluding the derivation of any "whole mixture" MRLs. Acute neurological effects are expected from all three classes of insecticides albeit through different mechanisms of action: (1) alteration of VGSCs by pyrethroids, predominantly via parent compounds; (2) irreversible ChE inhibition by organophosphorus insecticides or their metabolites; and (3) reversible ChE inhibition by carbamate insecticides, predominantly via parent compounds. The common general toxicity target shared by all members of each of these insecticide classes supports the use of a component-based HI approach as a reasonable and practical strategy for addressing public health concerns.

On the basis of the existing data presented in Section 2.2 and summarized and evaluated in the BINWOE tables presented in Section 2.3, ATSDR recommends that the default assumption of dose-additive action at shared targets of toxicity (i.e., effects on neurological end points) be used for screening-level assessments of the potential adverse neurological outcomes from concurrent oral exposures to mixtures of pyrethroid, organophosphorus and carbamate insecticides. Dose-additive action is the default assumption for several reasons. The *in vivo* and *in vitro* research studies reviewed in the Framework for Assessing Health Impacts of Multiple Chemicals and Other Stressors (ATSDR 2018) provide support that: (1) dose additivity often provided adequate descriptions of responses to defined mixtures of various classes of chemicals; (2) positive and negative deviations from dose additivity were small from a risk assessment perspective (generally <5-fold); and (3) observed responses to mixtures of chemicals were often below values predicted by dose addition, but higher than values predicted by response addition.

For each insecticide class, ATSDR recommends a RPF approach using RPFs derived by the EPA OPP (EPA 2006, 2007b, 2011b) and provisional oral MRLs for index chemicals of each class (Section 3). The HI for neurological effects would be calculated as the sum of class-specific HQs of estimated intakes of index chemical divided by provisional oral MRLs for the index chemical. When the screening assessment indicates a potential hazard (concern increases as the HI increases beyond a value of 1), further evaluation is needed, including: (1) further refined cumulative risk assessment methods; (2) use of biomedical judgment; (3) community-specific health outcome data; and (4) taking into account community health concerns.

ATSDR recommends that screening-level assessments of neurological hazard using the HI approach be accompanied by qualitative descriptions of weight-of-evidence evaluations of available interaction data:

5. greater-than-additive action on neurological end points is possible between certain pyrethroid and organophosphorus insecticides;

6. the available data are inadequate to assess the possible direction of interactions between pyrethroids and carbamates;

7. limitations in evidence for greater-than-additive interactions support assumption of dose additivity of carbamate and organophosphorus insecticides on neurological end points; and

8. BINWOEs include scoring categories that address uncertainty in the data.

Overall, the evidence is not compelling to move from a dose-additive approach. The evaluations indicate that greater-than-additive interactions between certain pyrethroid and organophosphorus insecticides are possible, 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.

## Table 10. Interactions/Mixtures Terminology

| | |
|---|---|
| Interaction | When the effect of a mixture is different from the expectation of additivity based on the dose-response relationships of the individual components. |
| Additivity | When the effect of the mixture can be estimated from the sum of the exposure levels (weighted for potency in dose or concentration additivity) or the probabilities of effect (response additivity) of the individual components. |
| No apparent influence | When a component that is not toxic to a particular biological system does not influence the toxicity of a second component on that system. |
| Synergism | When the effect of a mixture is greater than that estimated by additivity. Synergism is defined in the context of the definition of no interaction, which is usually dose additivity or response additivity. The use of “greater-than-additive” is preferred over the use of the term synergism. |
| Potentiation | When a component that is not toxic to a particular biological system increases the effect of a second chemical on that system. |
| Antagonism | When the effect of a mixture is less than that estimated by additivity. Antagonism is defined in the context of the definition of no interaction, which is usually dose additivity or response additivity. The use of “less-than-additive” is preferred over the use of the term antagonism. |
| Inhibition | When a component that does not have a toxic effect on a particular biological system decreases the apparent effect of a second chemical on that organ system. |
| Masking | When the components produce opposite or functionally competing effects on the same biological system, and diminish the effects of each other, or one overrides the effect of the other. |