

## Testing the Dose Addition Hypothesis

### The Impact of Pyrethroid Insecticide Mixtures on Neurons

Pyrethroid insecticides are used extensively in agriculture and in homes to control fleas, cockroaches, bedbugs, and other insects. In a new *in vitro* study researchers tested the hypothesis that mixtures of pyrethroids have a dose-additive effect—that is, that pyrethroids as a chemical group produce toxicity in mammals via a common mode of action and that the combined toxicity of a pyrethroid mixture reflects the sum of its constituents' toxicities [*EHP* 119(9):1239–1246; Cao et al.]. Using increased sodium ion influx as a specific functional measure of toxicity, the researchers found that effects of a mixture of commonly used pyrethroids were consistent with a dose-additive effect on mammalian neurons.

Pyrethroids act on the nervous system by disrupting the normal function of voltage-gated sodium channels (VGSCs), which control the influx of sodium ions into neurons to transmit nerve signals. When VGSCs open, the influx of sodium generates the nerve signal; when they close, the electrical signal halts abruptly. Pyrethroids bind to VGSCs and delay their closing, which causes repetitive nerve stimulation that can lead to muscle tremors as well as interfere with the ability of the channels to respond to stimulation.

Previous research demonstrated that a mixture of 11 pyrethroids had a dose-additive effect on the rat nervous system, decreasing the animals' motor activity at doses below the threshold dose of each constituent compound. The authors of the current study exposed neurons cultured from the cerebral cortices of embryonic mice to the same 11 pyrethroids, then examined how VGSCs responded. To measure sodium influx without disrupting cell function, neurons were treated with a sodium-sensitive dye that fluoresced when VGSCs were open.

Seven of the pyrethroids tested increased sodium influx in a dose-dependent manner (from highest to lowest potency: deltamethrin, *S*-bioallethrin,  $\beta$ -cyfluthrin,  $\lambda$ -cyhalothrin, esfenvalerate, telfluthrin, fenpropathrin). Cypermethrin and bifenthrin had only a marginal effect on sodium influx, whereas permethrin and resmethrin had no effect. Despite these variations in activity, the results when neurons were exposed to all 11 compounds together were consistent with a cumulative, dose-additive effect on neuronal sodium influx.

People are commonly exposed to low doses of pyrethroid mixtures, which tend to persist as residues on treated surfaces and in household dust. Currently the U.S. Environmental Protection Agency is determining whether a cumulative dose-additive model is appropriate to evaluate potential human health effects of pyrethroid mixtures. This model shows that simultaneous exposure to multiple compounds will produce an effect that is consistent with additivity at the VGSC molecular target.

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## Thirdhand Smoke in Review

### Research Needs and Recommendations

Studies over the last half-century have clearly demonstrated that cigarette smoking is associated with adverse health effects both for smokers and for individuals exposed to secondhand smoke (SHS). Now a new level of exposure has been identified: thirdhand smoke (THS), or residual tobacco smoke pollutants that remain on surfaces and in dust and that are reemitted in the gas phase and interact with other compounds. In a new review, researchers offer a descriptive analysis of THS constituents and dynamics and argue for the establishment of a programmatic research agenda to close gaps in our understanding of the nature and effects of THS [*EHP* 119(9):1218–1226; Matt et al.].

THS exposure is the result of inhalation, ingestion, or dermal uptake of THS pollutants in the air, in dust, and on surfaces. The authors point out that THS and SHS are closely related, and in fact coexist as THS is first formed and in settings where smoking recurs regularly. But whereas SHS is removed by ventilation, THS pollutants may persist in environments for several hours or days after tobacco has been smoked.

THS components—such as nicotine and carcinogenic polycyclic aromatic hydrocarbons, including benzo[*a*]pyrene—are sorbed and reemitted from indoor surfaces over varying periods

of time after tobacco sources have been extinguished. Some THS components react with other environmental compounds to produce secondary pollutants. For instance, chemical reactions between nicotine and nitrous acid lead to the formation of additional tobacco-specific nitrosamines, and ozone can react with certain volatile organic compounds to form formaldehyde, acetaldehyde, and benzaldehyde.

THS constituents have been measured in indoor spaces months after smoking last occurred. Given the U.S. Surgeon General's conclusion that there appears to be no risk-free level of exposure to SHS, this raises the possibility that THS could lead to potentially harmful exposures, particularly for vulnerable populations such as children. The investigators recommend that future studies further define the chemistry and toxicology of THS, which will aid in establishing, enhancing, and enforcing public policies and personal practices that limit tobacco smoke exposure.

The authors note that voluntary public and private policies enacted over the last decade—including an increase in smoke-free workplaces, public areas, and lodging—have effectively addressed THS exposure in some settings. They argue that stronger public health policies can be developed through an interdisciplinary research agenda that combines basic and applied risk assessment research with studies on tobacco use and cessation.

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Thirdhand smoke lingers after secondhand smoke has cleared from the room.