

Casida J E. Mixed-function oxidase involvement in the biochemistry of insecticide synergists. *J. Agr. Food Chem.* 18:753-72, 1970.
[Division of Entomology, University of California, Berkeley, CA]

The potency of many organic insecticides is strongly synergized by methylenedioxyphenyl compounds and other inhibitors of oxidative detoxification. These synergists inhibit the microsomal cytochrome P450-dependent mixed-function oxidase system as alternative substrates or by derivatizing at or near the active site. [The SCI® indicates that this paper has been cited in over 140 publications.]

John E. Casida
Pesticide Chemistry and
Toxicology Laboratory
Department of Entomological Sciences
University of California
Berkeley, CA 94720

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In the 1950s and 1960s, while at the University of Wisconsin at Madison and after moving to the University of California at Berkeley, I was interested in the pathways and enzymatic mechanisms of pesticide metabolism and particularly the oxidative reactions that lead to either activation or detoxification.

Piperonyl butoxide, other methylenedioxyphenyl derivatives, and many seemingly unrelated compounds enhance the insecticidal activity of pyrethrum, other pyrethroids, and certain methylcarbamates, organophosphorus compounds, and chlorinated hydrocarbons. A general phenomenon is involved since a variety of synergists increase the toxicity of many types of insecticides. The most important commercial synergized insecticide is the mixture of piperonyl butoxide and pyrethrum extract, with pyrethrin I as the major insecticidal ingredient.

Ernest Hodgson, now at North Carolina State University, initiated our studies on inhibitors of mammalian mixed-function oxidases (MFOs)¹ and he continues to stay at

the forefront of this important and fascinating field.^{2,3} Further insight into the mechanisms of synergist action required an insect oxidase that metabolized the relevant compounds and a variety of radiolabeled insecticides and synergists to clarify their metabolic pathways. I decided on November 22, 1963, to focus on this problem by developing the relevant insect MFO system and radiolabeling pyrethrin I and piperonyl butoxide. The date is firmly set in my mind because this decision was made while driving to a meeting during which time the music on the radio was interrupted by the announcement of President Kennedy's assassination.

Within a few years, Masuhisa Tsukamoto established the housefly MFO system and showed its role in insecticide tolerance and synergist action in his biochemical genetic studies with insecticide-susceptible and resistant insect strains.⁴ The synergists were shown to be MFO substrates as well as inhibitors.⁵ The *trans*-methyl group of the isobutenyl substituent was identified as the most metabolically labile site of pyrethrin I.⁶ Our studies then considered several interrelated phenomena: resistance and selective toxicity conferred by oxidative detoxification; the persistence of synergist inhibition of P450-mediated reactions; and the variety of insecticide substrates for insect MFOs leading to cross-resistance in high oxidase strains.

This review was the first detailed consideration of toxicologically important MFO inhibitors. It discussed the mechanism and genetic control of P450 systems. It pointed out the need for synergists of increased potency and safety and the importance of including tests of MFO inhibition in mammals, along with the usual toxicological parameters, in evaluating risks associated with such compounds. This publication provided the documentation for a lecture I presented in May 1970 at a symposium commemorating my receipt of the first International Award for Research in Pesticide Chemistry, the Burdick and Jackson Award of the American Chemical Society.

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4. Tsukamoto M & Casida J E. Metabolism of methylcarbamate insecticides by the NADPH₂-requiring enzyme system from houseflies. *Nature (London)* 213:49-51, 1967. (Cited 85 times.)
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