This Week's Citation Classic

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Dorough H W & Casida J E. Nature of certain carbamate metabolites of the insecticide Sevin. *J. Agric. Food Chem.* **12**:294-304, 1964.

In addition to ester hydrolysis, Sevin (1-naphthyl N-methylcarbamate) and other carbamates undego extensive oxidative metabolism in mammals, insects, and plants. Hydroxylations of the ring and NCH_3 moiety yield metabolites containing the intact ester linkage and, unlike the hydrolysis products, may retain anticholinesterase activity. [The *SCI*® indicates that this paper has been cited 124 times since 1964.]

H. Wyman Dorough
Dept. of Entomology and
Graduate Center for Toxicology
University of Kentucky
Lexington, KY 40506

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"I completed my master's degree in the warm December of 1959 at Auburn University (Alabama) and by mid-january found myself, along with my wife and two-year-old son, arriving in Madison in our VW Beetle, containing the total of our possessions, to continue my graduate studies in pesticide toxicology with Professor J. E. Casida of the University of Wisconsin (currently at the University of California, Berkeley) The temperature was well below zero, my son had chicken pox, and our apartment was under a teen bar which "swung" into the wee hours of the morning. After two weeks, I told Casida I was headed back south... this was too much for me! In his typical calm style, he told me to think it over for one week and let's talk about it then. To this date, neither of us has again mentioned the subject.

"What happened during that one week to change my mind? Simply put, I recognized the unique opportunity to participate in pioneering studies to elucidate the chemistry, biochemistry and toxicology of an exciting new group of pesticidal chemicals, namely the carbamates Another of Casida's students, J. G. Krishna, was on the verge of successfully synthesizing radioactive forms of these toxicants which would provide the potential for fully exploring, for the first time, the chemical and biological nature of this family of chemicals.

"The monomethyl carbamates ($X\text{-}CO(O)NHCH_3$) were generally considered highly biodegradable by undergoing simple ester hydrolysis, thereby destroying their anticholinesterase activity. Thus, the disappearance of the parent molecule from treated substrates and the environment was taken as signifying the disappearance of all toxic residues of the compound. Such a situation, if true, was highly desirable. If untrue, serious consequences possibly could result; without evidence to the contrary, efforts were not being made to monitor food products and the environment for toxic metabolites of the carbamates. Ester hydrolysis alone was inconsistent with my meager knowledge of bioalteration and with Casida's vast knowledge of xenobiotic metabolism.

"Our work subsequently did demonstrate that the carbamate pesticides were converted to a variety of oxidative metabolites and that many of these could be toxic. Perhaps the major reason the article has been so frequently cited is that it was the first to document oxidative pathways of bioalteration for the carbamates. Moreover, Sevin (carbaryl) is one of the most widely used pesticides throughout the world and has been the subject of numerous publications over the years. The findings also were applicable to a wide variety of biologically active compounds (insecticides, herbicides, fungicides, drugs, etc.) and were of significance to human health and quality of the environment. Whatever the reasons, it is an honor that the citation frequency of the paper has resulted in it becoming a Citation Classic."