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MEETING ABSTRACTS

CHRONIC ILLNESS FROM ORGANOPHOSPHORUS TOXICANT EXPOSURE

Oksana Lockridge* and Lawrence M. Schopfer
* Presenting author, Oksana Lockridge

Eppley Institute, University of Nebraska Medical Center, Omaha, NE, 68198-5900 USA olockrid@unmc.edu

The mechanism of toxicity from acute exposure to organophosphorus toxicants (OP) is understood. Thousands of publications have confirmed that AChE inhibition results in muscle weakness and respiratory failure. AChE activity returns to normal levels within one month, but symptoms can persist for a lifetime. For example, people exposed to sarin in the 1995 Tokyo subway attack still have adverse symptoms 23 years later. Farmers and sheep dippers exposed to OP pesticides have an elevated risk of psychiatric disorders and suicidal behavior. Epidemiology studies show an association between OP exposure and Alzheimer's disease and Parkinson's disease. We propose a mechanism to rationalize these observations independent of cholinesterase inhibition. Mass spectrometry analysis of OP-treated proteins shows that OP make stable adducts on tyrosine and lysine. Furthermore, we have mass spectrometry evidence that OP-lysines promote crosslinks between proteins. The crosslinked proteins are visualized as protein aggregates on SDS gels and Western blots. Mass spectrometry has identified γ-glutamyl-ε-lysine and aspartyl-ε-lysine isopeptide bonds between crosslinked peptides. We propose, but have not yet proven, that isopeptide crosslinked proteins form stable, insoluble aggregates in the brain, similar to the protein aggregates found in Alzheimer's, Parkinson's, and prion diseases. In summary, we propose that chronic neurotoxicity from OP exposure is initiated by OP-lysine formation followed by protein aggregation. Our proposed mechanism could apply to a variety of compounds and lead to an understanding of neurotoxicity induced by many chemicals.

Keywords: crosslinking; protein aggregates; mass spectrometry