Interaction of Organophosphate Flame Retardants with Efflux Transporters

David Viramontes, Xia Wen, Lauren M. Aleksunes
University of Nevada and Rutgers, The State University of New Jersey

Organophosphate-containing molecules are a diverse group of chemicals that have been used in pesticides and nerve agents and more recently, as flame retardants in clothing, plastics, building materials, electronics, and furniture. As the use of organophosphate flame retardants becomes more widespread, the exposure of humans also increases. Emerging data suggest organophosphate flame retardants are toxic to the reproductive, endocrine, and nervous systems. One mechanism to reduce the toxicity of chemicals is active efflux that prevents accumulation in tissues. Efflux transporters are a class of proteins that excrete substrates from the cell using energy generated from ATP hydrolysis. In this study, we sought to determine whether the flame retardants tricresyl phosphate and triphenyl phosphate are substrates for the efflux transporter multidrug resistance protein 1 (MDR1). To test this hypothesis, the cytotoxicity of both chemicals was tested in HEK293 cells expressing an empty vector or the human MDR1 gene. Cytotoxicity (LC_{50}) was determined using the Alamar Blue assay. The positive control MDR1 substrate doxorubicin exhibited a 5-fold increase in LC_{50} in cells expressing MDR1. By comparison, the cytotoxicity of tricresyl phosphate and triphenyl phosphate were similar between the control and MDR1-expressing cell lines. While additional tests need to be performed, these data suggest that these flame retardants are not substrates for MDR1. Understanding which transporters interact with a chemical enables the prediction of tissues in the human body that may not be protected by efflux transport and are potentially at greater risk of toxicity. Supported by NIH R25ES020721, P30ES005022, and R01ES021800, and the ASPET and SOT Intern Programs.