A Systems Approach to Assessing Risk: The Role of Metabolism Research in Describing and Predicting Exposure

John F. Kenneke[1], Christopher S. Mazur[1], A. Wayne Garrison[1], Candice K. Cunningham[1], Rebecca D. Miller[2],

[1]U.S. EPA-NERL; [2]Student Services Authority

An important component of assessing risk is defining the exposure of a chemical stressor to a target organism. Often the chemical stressor is assumed to be a single compound even when it is comprised of different stereoisomers (e.g., pyrethroids and 1,2,4-triazole fungicides), which possess different physical, chemical and toxicological properties. Additional uncertainties in exposure assessment arise when the chemical undergoes transformation inside the organism, especially when the transformation is organ, species, and/or gender specific. Thus, a "simple" exposure scenario of a single chemical may ultimately involve multiple stressors (i.e., stereoisomers and metabolites) resulting in multiple internal exposures.

Our research focuses on defining the internal exposure of chemical stressors in organisms. We utilize in vitro and in vivo metabolism assays, specific enzyme inhibitors, purified enzymes, and molecular docking to elucidate the kinetics and mechanisms of xenobiotic metabolism to deconvolute "simple" exposure scenarios. For example, we have shown that the exposure of triadimefon to liver microsomes from eight vertebrate species resulted in the formation of triadimenol in all cases; however, the exposure scenario is actually more complex. Triadimefon metabolism occurs via the reduction of a prochiral carbonyl that yields a unique set of four triadimenol stereoisomers for each species. The stereoisomers have different toxicities and degrees of binding with endogenous receptors (e.g., enzymes involved in steroidogenesis and nuclear receptors), which could impact the mode-of-action of triadimefon. The implications of this for risk assessment are worth considering because triadimefon exposure to human liver microsomes produces a significantly higher percentage of the more toxic stereoisomers than rat (i.e., rat results extrapolated to human may underpredict risk). Examples of the (1) stereoselective and gender specific metabolism of 1,2,4-traizole fungicides, (2) organ and species specific metabolism of bisphenol A, and (3) stereoselective metabolism of pyrethroids for use in exposure reconstruction will also be presented.