Application of Metabolomics for Improving Ecological Exposure and Risk Assessments

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Metabolomics involves the application of advanced analytical and statistical tools to profile changes in levels of endogenous metabolites in tissues and biofluids resulting from disease onset, stress, or chemical exposure. This approach has proven useful in mammalian systems for distinguishing between sites and mechanisms of toxicity for tissue-specific toxins. Metabolomics has been characterized as the true measure of metabolic outcomes suggested by changes in gene and protein expression; as such, metabolomics provides a connection between these molecular endpoints and whole organism responses. Although used mostly in mammalian studies, metabolomics is now finding utility in a wide variety of other organisms including aquatic species.

We have developed a research program in metabolomics that involves numerous partners across the U.S. Environmental Protection Agency (U.S. EPA), other federal labs, academia, and the private sector. A primary goal is to develop metabolite-based markers that can be used by U.S. EPA in ecological exposure and risk assessments. We are focusing this program on ecologically relevant species, in particular, small fish toxicological models.

For example, to better understand the impact of endocrine-disrupting chemicals (EDCs) in small fish (fathead minnow, zebrafish), we are conducting metabolomic analyses with multiple tissues (brain, blood, liver, and gonad) and urine. We are developing hypotheses about which tissue- and biofluid-specific metabolite changes will be definitively related to exposure, based on the current understanding of modes-of-action for these chemicals. Results will allow testing of these hypotheses to refine understanding of activity, and will help ensure that molecular markers of EDC exposure are meaningful. While certain metabolites are being specifically targeted in these studies, we will also discern changes in the complete metabolic profile using nuclear magnetic resonance (NMR) and mass spectroscopy (MS) spectroscopic data with statistical approaches that allow capturing subtle changes in less-abundant metabolites. These data are being integrated with genomic, proteomic, and whole organism data from untreated fish and those exposed to known EDCs. Ultimately, these data are used in integrated systems biology models that link chemical exposures and toxic modes-of-action to ecologically-relevant outcomes.

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