Title: The Role of Integrative, Whole Organism Testing in Monitoring Applications: Back to the Future

Authors: Joseph E. Tietge, Daniel L. Villeneuve, Gerald T. Ankley

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Abstract:

The biological effects of chemicals released to surface waters continue to be an area of uncertainty in risk assessment and risk management. Based on conventional risk assessment considerations, adequate exposure and effects information are required to reach a scientifically sound assessment. Analytical chemistry, as a measure of exposure, is a viable monitoring approach for those chemicals with sufficient toxicological data to establish criteria or benchmark concentrations. However, most individual chemicals lack such information, as do the variable chemical mixtures that inevitably exist in aquatic systems. Furthermore, analytical chemistry approaches to monitoring are limited by several factors, including: lack of appropriate analytical methods, insufficient detection limits, inability to aggregate effects of chemicals in mixtures, and the requirement to identify, *a priori*, the chemical(s) of interest. Historically, biological monitoring of wastewater effluents with *in vivo* tests was introduced because chemical monitoring programs were unable to predict effluent toxicity. The premise of organismal testing is that the toxicological responses of the organisms will report the integrated toxicological effects of complex mixtures. While valuable as an indicator of effects, this approach by itself is unable to provide information on the chemical composition of the mixtures and, thus, cannot determine which chemicals are related to an observed effect. This deficiency in organismal testing was addressed by the introduction of the Toxicity Identification Evaluations (TIE) approach. TIE methods employ a variety of physico-chemical manipulations of samples to produce simplified fractions of the original effluent that are then tested in a biological system for a relevant response. Fractions that are active in the biological system are further manipulated to the extent feasible, depending on the nature of the sample, which ultimately could lead to identification of the chemical(s) eliciting the biological effect. Recent advances in biological and toxicological sciences have enhanced our ability to use organismal testing and TIE methods to address the uncertainties associated with chemicals released to aquatic systems. Increasing knowledge of biological systems has led to the development of the concept of the Adverse Outcome Pathway (AOP), which is a simplified pathway that links chemical interaction at the molecular level to outcomes relevant to risk assessment. AOPs provide the linkages across the continuum of biological complexity, molecular to organismal, which allows sub-organismal information to inform the pathway. Thus, AOPs establish the framework to interpret post-genomic information (transcriptomics, metabolomics, proteomics, etc.) in both supervised and unsupervised contexts. Effects-based monitoring is now poised to take advantage these developments through a combination of organismal testing with enhanced sub-organismal endpoints, *in vitro* testing of surface water samples for pathway-specific information, and improved analytical chemistry. This triad of approaches, using lessons from the past, represents a modernized approach to monitoring surface waters for chemical toxicity.