

Using Proteomics to Predict Mode of Action Specific Activity for Chemical Screening and Prioritization

Authors: Calvin Walker, Kimberly Salinas, Michael Hemmer

U.S. EPA/Office of Research and Development (ORD)/National Health and Environmental Effects Research Laboratory (NHEERL)/Gulf Ecology Division (GED)

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A major challenge confronting the U.S. Environmental Protection Agency (U.S. EPA) is a need to evaluate the large number and diversity of chemicals in existing inventories for adverse effects. Many chemicals of regulatory concern lack basic toxicity data, and current testing approaches are costly, time consuming, and use large numbers of animals. Thus, U.S. EPA must have more efficient test methods for screening and prioritizing chemicals for multiple modes of action (MOA). Methods capable of evaluating multiple chemical MOA effects from a single exposure are highly desirable. This has provided the impetus to evolve from extensive hazard testing toward targeted, hypothesis-based approaches for chemical risk assessments. The low abundance and low molecular mass range of the plasma proteome holds great potential as a source of MOA-specific biomarkers. Research to discover and identify such diagnostic biomarkers, develop and optimize exposure protocols and analytical techniques, evaluate the ability of biomarkers to accurately classify chemicals by MOA, and determine cross-species conservation of such biomarkers is ongoing. Plasma or tissue culture media from control and MOA agonist exposed treatments are applied to protein chip arrays, processed, and then analyzed by mass spectrometry to produce protein expression profiles for each sample. Differences in protein expression between control and treatment groups are used to discover protein biomarkers uniquely expressed in the agonist treatment samples. A model to classify samples according to MOA activity is then derived. In addition, fish exposures are being used to link expression of diagnostic protein biomarkers with traditional toxicological endpoints and with expression of homologous proteins in multiple fish species. As proof of concept, research efforts have focused on developing diagnostic models using well characterized estrogen and androgen agonists. We are currently extending the technique to anti-estrogenic and anti-androgenic MOA's. Future efforts will be directed toward a systems approach using development of MOA-specific biomarker libraries predictive of multiple chemical classes capable of causing adverse effects on the reproductive system. Examples of the technique's applications are provided.

Point of Contact:

Calvin Walker
Research Chemist
U.S. EPA/ORD/NHEERL/GED
1 Sabine Island Drive
Gulf Breeze, FL 32561
850-934-9245
walker.calvin@epa.gov