

Computational Toxicology–Objective 3: Applications of Computational Toxicology in Quantitative Risk Assessment

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The Computational Toxicology Program develops approaches derived from modern computational methods, molecular biology, and systems biology to improve risk assessments. Emerging technologies, commonly referred as “Omics technologies,” are based on biochemical and molecular characterization of an organism, tissue, or cell type by global analyses of their gene, protein, and metabolite components. Application of data obtained using new technologies to quantitative risk assessment is a key component of the Computational Toxicology Program. Evaluation of risk posed by exposure to a specific chemical involves the analysis of research data, generation of qualitative and quantitative assessments of dose and response, and determination of a concentration/dose that would not be harmful to the general population. Data from human (epidemiological studies) or, more frequently, animal studies are used to determine potential links between exposure to a chemical and development of an adverse effect indicative of toxicity. The next step in the assessment process is to make extrapolations of dose-response relationships observed in animal studies to humans. Successful application of computational toxicology methods to quantitative risk assessment will require interaction between scientists with expertise in Omics technologies generating laboratory data and those knowledgeable in applying research data to risk assessment. Current EPA research on the common mode of action of conazoles, which are a class of toxicants that can affect multiple organs and produce different types of toxicity, could lead to new approaches in risk assessment. Scientific data suggest that these toxicants might exert their key effects through the modulation of compound-metabolizing enzymes (P450s and related xenobiotic-modulating enzymes or XMEs) present in different target tissues including the liver, thyroid, and reproductive system. Experiments using rodents are in progress to determine the toxic effects of a series of structurally related conazoles in different target organs and to assess patterns of gene and protein expression using Omics technologies that will serve to identify key events involved in their common mode of action. This group of projects will be used as examples to explore the implication of a deeper understanding of mode of action and the dose-response relationship on risk assessment. Omics technologies promise to be useful to NCEA by expanding our knowledge on mode/mechanism of action, allowing the agency to use better informed risk assessments and by generating improved products to support program office regulatory actions.