ORD Research Integration:
Applying New Chemical Assessment Approaches in Human Health Risk Assessment

Introduction

The goal of this integration effort is to advance data and methods to enhance the throughput, reduce costs, and improve accuracy of human health risk assessment. This effort will support decisions across different risk contexts regarding new and existing chemicals in commerce and inform the design of chemical products and processes. It holds promise for improved communication and coordination across ORD concerning the generation and application of data and models to support Agency decision-making.

Integration

Integration of the CSS and HHRA research programs is essential to meet these goals and can provide value to both programs. Specific topic areas of integration include:

- Ongoing work to develop databases and bioinformatics tools to aid characterization of the numerous chemicals lacking comprehensive toxicological data and/or human health risk assessments;
- Ongoing exploration of how molecular and systems biology data and tools can be applied in human health risk assessments, including in hazard identification, mode of action analyses, dose-response evaluation, and characterization of variability in sensitivity (including based on life stage);
- Planned exploration of methodologies to speed screening and priority-setting; and
- Expanded implementation of tools and guidance for "greener" chemical production to improve environmental sustainability and life cycle analyses.

Management Approach

The integration research will be lead by the HHRA program. The work will be coordinated across programs by a transdisciplinary workgroup, comprising expertise in computational methods, bioinformatics, hazard identification, and dose-response analyses pertinent to human health risk assessment. The workgroup will meet regularly to share information about planned research and priorities and to foster opportunities for collaboration across labs and centers. Collaboration with academic scientists supported by EPA grants and fellowships will be sought to address scientific capacity needs on specific projects.

Challenges

A key anticipated challenge to implementation is that both programs are already supporting multiple high-priority ORD activities needed to address a diversity of EPA Program Office needs. Thus, some realignment of staff and resources will be needed so that appropriate effort can be devoted to the integration research activities.

Strengths

The HHRA program will benefit from opportunities to apply state-of-the-science data streams and methods (*e.g.*, *in vitro* toxicity testing results, gene expression profiling data, bioinformatics and QSAR modeling) in specific processes and products. The CSS research program will also benefit from improved

relevancy due to alignment of CSS research with EPA's human health risk assessment priorities. The effort will also enhance the understanding, use and acceptance of novel data streams and methods by risk assessors and managers, an advantage to both programs. Additionally, HHRA and CSS scientists will gain knowledge informative of current and future strategic planning. Thus, integration will afford opportunities for both programs to be anticipatory, CSS regarding data needs of the HHRA program, and HHRA regarding planned data and product development from CSS with relevance for hazard identification and dose-response assessments.

Another key strength is the anticipated value of the outputs. Outputs in the CSS and HHRA research programs, as identified in the Strategic Research Action Plans and summarized in the table below, include data and bioinformatics tools to support human health risk assessments and comprehensive environmental assessment methodologies for application to nanomaterials and other chemicals. This includes NexGen risk assessments, defined as incorporating recent progress in molecular and systems biology. The integration effort will also provide inputs for cumulative and community risk evaluations. The outputs comprise a range of CSS-generated data and bioinformatics tools to support efficiency and accuracy of specific HHRA products and workflows.

Program	Output
CSS	4.2.2 Data, case studies and guidance to support EPA NexGen assessments for Integrated Risk Information System (IRIS), Provisional Peer-reviewed Toxicity Value (PPRTV) and Integrated Science Assessment programs
CSS	7.1.1 Process to gather scientific information that EPA risk assessors need to make environmental decisions
CSS	7.1.4 Initial prototype dashboards for PPRTV and NexGen risk assessments (HHRA21)
CSS	8.2.2 Identification of best practices for future projects and potential future impacts of CSS program products, particularly NexGen risk assessments and CEA
HHRA	Integration of CSS Dashboards, CSS and HHRA Toolboxes, and HERO Systems into a standard HHRA Informatics Platform

As a specific example, one current project aims to predict risks for chemicals currently lacking toxicity values using existing and emerging data streams. The effort is assembling a data matrix of the nearly 2,000 chemicals with derived US human health toxicity values, integrated with existing animal in vivo (*i.e*., rat LD50) and emerging in vitro (ToxCast, Tox21, *etc*.). Computational models are using chemical and/or biological data streams for chemicals with existing toxicity values. A user-friendly interface will enable end-users to input chemical compound(s) of interest, receive available information (*e.g*., chemical properties, toxicity values, toxicity data, *etc*.) and generate quantitative predictions (*i.e*., conditional toxicity values) and associated model performance metrics. The effort will be useful for speeding chemical ranking, grouping, and prioritization for additional study and evaluation. Additionally, the conditional toxicity values can support end-user decision-making for chemicals lacking comprehensive toxicological data and/or human health risk assessments. This collaborative project draws expertise from academic and EPA scientists as well as human health risk assessors working in state and national settings. Outreach and training to end-users at the state, federal and international levels are planned. Thus, this project provides an example integrative approach to computational methodology development for addressing Agency and regional priorities, including the need to generate toxicity values for health risk assessment and sustainability applications.