Systems Biology & Toxicity Testing in the 21st Century

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Contributing Organizations: ORD: NHEERL, NCCT, NCEA;

B·O·S·C HUMAN HEALTH PROGRAM REVIEW

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RESEARCH & DEVELOPMENT

LTG 1 Poster 11

Science Questions

- How do we measure, model, and predict the key attributes of the mode of action (MOA) that could impact risk assessment?
- How do we get better and more detailed understanding of MOA at various scales and reduce the associated uncertainty in a shorter time frame than traditional methods have allowed?
- How do we incorporate in vitro data into future toxicity testing in a way that will support risk assessment?
- How can 'omics' approaches be used in the context of quantitative risk assessments?

Research Goals

- To identify toxicity pathways underlying adverse outcomes relevant to risk assessment
- To develop *in vitro* assays to measure perturbations of toxicity pathways by environmental stressors
- To elucidate the quantitative relationship between *in vitro* toxicity pathway assays and adverse outcomes in humans
- To create computational models of human tissues, organs, and systems to enable quantitative risk assessment based on toxicity pathway information
- Evaluation of toxicity pathway based models for quantitative risk assessment in humans

Findings and Conclusions

This represents a proposal for future research and does not have specific findings and conclusions at this stage. However, there are internal and peer reviewed publications outlining components of the strategy.

"Draft U.S. EPA Strategic Plan for Evaluating the Toxicity of Chemicals", Future of Toxicity Testing Workgroup, EPA white paper under review by the Science Policy Council.

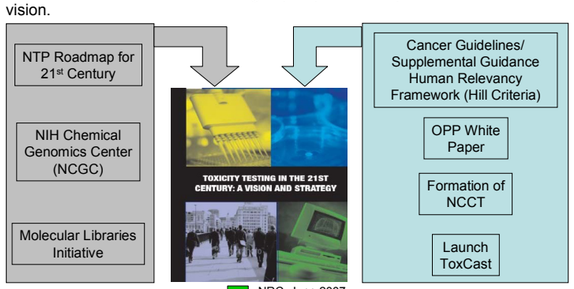
"Transforming Environmental Health Protection", FS Collins, GM Gray, JR Bucher, *Science* **319**: 906-907 (2008).

"Computational Toxicology – A State of the Science Minreview", RJ Kavlock, et al., *Toxicological Sciences* **103**: 14-27 (2008)

"Systems Biology & Mode of Action Based Risk Assessment", SW Edwards, RJ Preston, *Toxicological Sciences,* **106**: 312-318 (2008)

Future of Toxicity Testing (FTT) and Risk Assessment

At EPA's request, the NRC recommended a new strategy for toxicity testing based on in vitro assays for cellular perturbations sufficient to cause adverse outcomes. In response, EPA established external collaborations and an internal workgroup to plan and implement this vision.



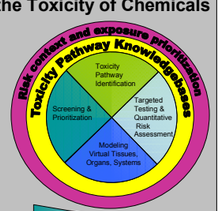
NRC, June 2007

Tox21 Collaboration

Collins, Gray, Bucher, (2008) Science, 319:906

EPA's Strategic Plan for Evaluating the Toxicity of Chemicals

1. Toxicity Pathway Identification And Chemical Screening And Prioritization
   - Goal 1: Toxicity Pathway Identification And Assay Development
   - Goal 2: Chemical Prioritization
2. Toxicity Pathway-based Risk Assessment
   - Goal 3: Toxicity Pathway Knowledgebases
   - Goal 4: Virtual Tissues, Organs, And Systems: Linking Exposure, Dosimetry, And Response
   - Goal 5: Human Evaluation And Quantitative Risk Assessment

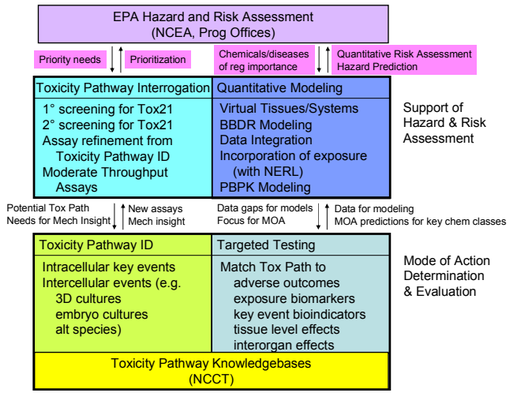


Sponsored by the Science Policy Council
Co-Chairs: Michael Firestone, Robert Kavlock, Hal Zenick
Participants: ORD (NCCT, NHEERL, NERL, NCEA), OCHPEE, OSA, Region 10, OCFO, OGC, OPPTS, OAR, OPEI, OEI, OW, OSWER

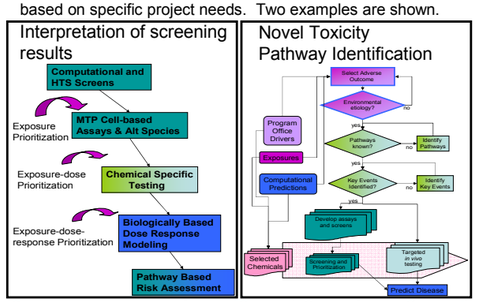
Methods/Approach

Comp Tox & Human Health Research To Support FTT and Risk Assessment

Most ongoing Computational Toxicology efforts at the agency directly support this transformation but funding for laboratory research is limited. A complementary Human Health initiative would provide the experimental resources for this program to be a success. This research would be focused on identifying toxicity pathways, developing *in vitro assays* for those pathways and linking the *in vitro* assays quantitatively to *in vivo* effects.

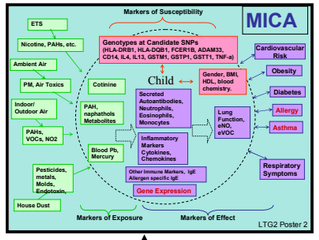


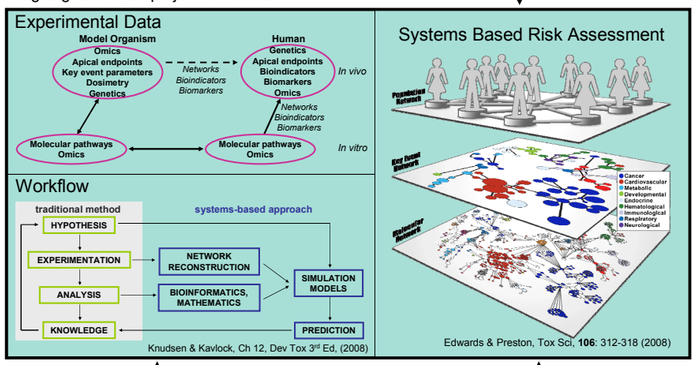
Different implementations of the overall approach are envisioned based on specific project needs. Two examples are shown.

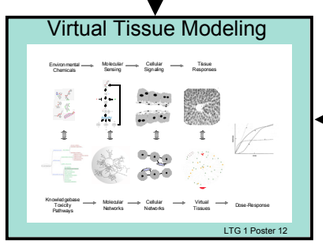


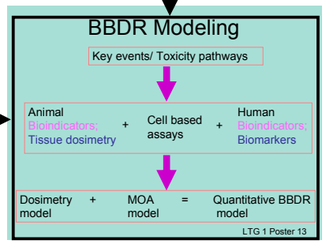
Systems Biology To Support FTT and Risk Assessment

The figure below illustrates the application of systems biology to MOA based risk assessment. The first critical component is an integration of traditional toxicological measurements with global biology ("omics") measurements as well as *in vitro* measurements of molecular pathway perturbations. These data are then modeled mathematically to derive both molecular level networks as well as higher level key event networks. The molecular network provides information on the modularity of the system which can then be modeled via simulation models at the key event level to make quantitative predictions for human populations. Application of this approach in ongoing and future projects is shown.









Impact and Outcomes

- This research effort will integrate computational modeling and data generation to support the development of quantitative models for use in risk assessment.
- New toxicity pathways linked to key events in the mode of action for selected environmental chemicals will be identified. The assays associated with these pathways would then be available for use in ToxCast and Tox21 screening.
- Predictions from ToxCast and Tox21 screening will be evaluated in follow up studies using orthogonal *in vitro* assays as well as *in vivo* animal studies and human clinical and epidemiology studies.
- An implementation plan for toxicity pathway based risk assessment within ORD will be developed in collaboration with NCEA and work initiated under that plan.

Future Key Products

- New toxicity pathway assays for Tox21 chemical screening and prioritization (short term)
- Data to support the use of toxicity pathway data in risk assessment via weight of evidence (mid term)
- Computational models linking toxicity pathway data to adverse outcomes in humans (long term)
- Data to support the use of resulting computational models in risk assessment (long term)

Researchers Involved

Tox21 Memorandum of Understanding (EPA participants)
Chair: Robert Kavlock
NHEERL: Chris Corton, Julian Preston, Kevin Crofton, Michael DeVito, Ram Ramabhadran, Stephanie Padilla, Stephen Edwards, Steve Simmons, Vickie Wilson, William Mundy
NCCT: David Dix, Imran Shah, Keith Houck, Richard Judson, Thomas Knudson

NHEERL Integrated Toxicology Working Group
Chair: Julian Preston
Andrew Geller, David Diaz-Sanchez, Gary Ankley, Jack Fowle, Jeffrey Ross, John Nichols, Kevin Crofton, Michael DeVito, Ram Ramabhadran, Sid Hunter, Stephen Edwards, William Mundy

Virtual Tissue and BBDR Participants
NHEERL: Elaina Kenyon, Hisham El-Masri, Michael DeVito, Sid Hunter, Stephanie Padilla
NHEERL/NCEA: Annie Jarabek
NCCT: Imran Shah, Jerry Blancato, Rory Conolly, Thomas Knudson

Use of Mechanistic Data in Risk Assessment

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