Exposure Science for Chemical Prioritization and Toxicity Testing

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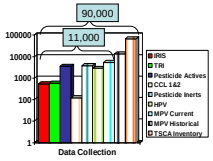
GOAL STATEMENT

Advance the characterization of exposure required to ***translate*** advances and findings in computational toxicology to information that can be directly used to support exposure and risk assessment for decision making and improved environmental health.

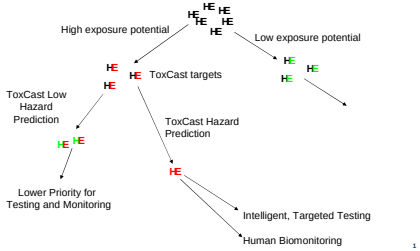
MANDATE TO ADDRESS THOUSANDS OF CHEMICALS

Clear need to develop methods to evaluate a large number of environmental chemicals for their potential toxicity



- CEPA Prioritization Program (DSL)
- REACH
- HPV
- Endocrine Disruptor Screening Program (EDSP)
- Chemical Assessment and Management Program (ChAMP)

USING HAZARD AND EXPOSURE INFORMATION TO PRIORITIZE TESTING AND MONITRING



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References:

Cohen Hubal EA, Richard AM, Imran S, Gallagher J, Kavlock R, Blancato J, Edwards S. (2008) Exposure science and the US EPA National Center for Computational Toxicology. JESEE doi: 10.1038/jes.2008.70.

Edwards, SW, Preston, RJ. (2008) Systems Biology and Mode of Action Based Risk Assessment. Tox Sci 106(2), 312–318.

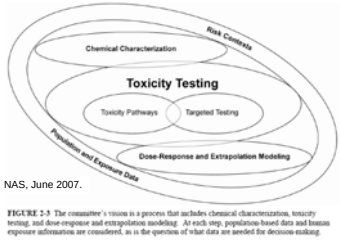
NRC (2007) Toxicity Testing in the 21st Century: A Vision and a Strategy. The National Academies Press. Washington, DC.

TRANSFORMING TOXICOLOGY

The key aspect of the NRC vision and the proposed paradigm shift in Toxicity Testing is that new tools are available to examine toxicity pathways in a depth and breadth that has not been possible before.

Efforts underway to apply high-throughput-screening (HTS) approaches for chemical prioritization and toxicity testing have been accelerated in response to NRC reports.

An explosion of HTS data for *in vitro* toxicity assays will become available over the next few years.



NAS, June 2007.

FIGURE 2-3 The committee's vision is a process that includes chemical characterization, toxicity testing, and dose-response and extrapolation modeling. At each step, population-based data and human exposure information are considered, as is the question of what data are needed for decision-making.

EXPOSURE SCIENCE IN NRC VISION

Population-based data and human exposure information required at each step of vision; critical role in both guiding development and use of the toxicity information. Components include:

- Use of information on host susceptibility and background exposures to interpret and extrapolate *in vitro* test results.
- Use of human exposure data to select doses for toxicity testing so we develop hazard information on **environmentally-relevant effects**.
- Use of biomonitoring data to relate real-world human exposures with concentrations that perturb toxicity pathways to identify potentially important (**biologically-relevant**) exposures.

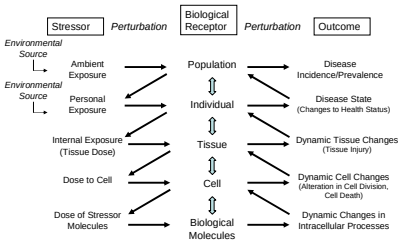
A PATH FORWARD: ANCHORING STRESSORS TO REAL-WORLD HUMAN EXPOSURES

The NRC Vision of a shift to characterizing toxicity pathways requires a commensurate shift to characterizing exposure across all levels of biological organization.

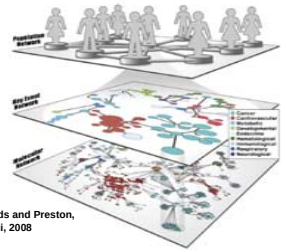
Interpretation of toxicogenomic hazard data requires contextual relevance. Pathways identified using HTS approaches are being anchored to apical endpoints using conventional toxicity data.

Similarly, understanding relevant perturbations leading to these toxicogenomic endpoints require anchoring stressors to real-world human exposure (e.g., biomonitoring data and other conventional exposure metrics).

New approaches to risk assessment require exposure science to predict exposures down to the molecular level. Requires systems-based consideration of interactions between exposure and effect.



JESEE, 2008



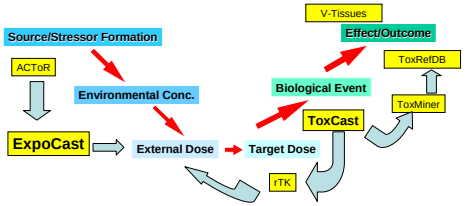
Edwards and Preston, Tox Sci, 2008

EXPOCAST: EXPOSURE SCIENCE FOR TOXICITY TESTING

How can we characterize exposure efficiently and support development of toxicity information to facilitate prioritization of thousands of compounds?

Paradigm shift in exposure science required

- From resource and time intensive measurement and modeling
- To rapid, inexpensive approaches for characterizing and predicting **biologically-relevant** exposure.
- Leverage advanced and emerging technologies and approaches



EPA COMMUNITY OF PRACTICE: EXPOSURE SCIENCE FOR TOXICTY TESTING, SCREENING AND PRIORITIZING

The primary purpose of the EPA Exposure Science Community of Practice (ExpoCoP) is to provide a forum for promoting the advancement and utilization of exposure science to address Agency needs for chemical screening, prioritization and toxicity testing.

Membership of over 70 individuals from over 30 public and private sector organizations

http://epa.gov/ncct/practice_community/exposure_science.html