



ExpoCast™: Exposure Science for Prioritization and Toxicity Testing

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research & development

Science Question

A new generation of tools has emerged to rapidly measure signals from cells, tissues, and organisms following exposure to chemicals. High visibility efforts to apply these tools for efficient **chemical prioritization** and **toxicity testing** raise important research questions in exposure science. As an explosion of data from HTS *in vitro* toxicity assays becomes available, this new toxicity information must be translated to assess potential for risks to human health from environmental exposures. Exposure information is required to link information on potential toxicity of environmental contaminants to real-world health outcomes.

Chemical Prioritization

Globally, tools are required to characterize and classify thousands of environmental chemicals in a rapid and efficient manner to assess potential for risk to human health. A critical need is development of robust analytical approaches that use a wide range of human exposure data, product use information, and modeled human behavior to systematically prioritize potential for exposure based on chemical properties, product lifecycle, individual and population characteristics.

Toxicity Testing

The authors of the National Academies Vision for Toxicity Testing (NRC, 2007) emphasize that population-based data and human exposure information are required to *translate new toxicity information* to assess potential for real-world human health risk.

- Assessing complex human-health risks requires that hazard, susceptibility, and exposure are all reliably characterized.
- Currently, balance of efforts to improve measuring hazard and exposure less than ideal: *One measure of the hazard-exposure equation continues to be refined while the other remains subject to crude characterization.*
- Accurate assessment of many environmental exposures remains an outstanding and largely unmet challenge in toxicology and risk assessment.

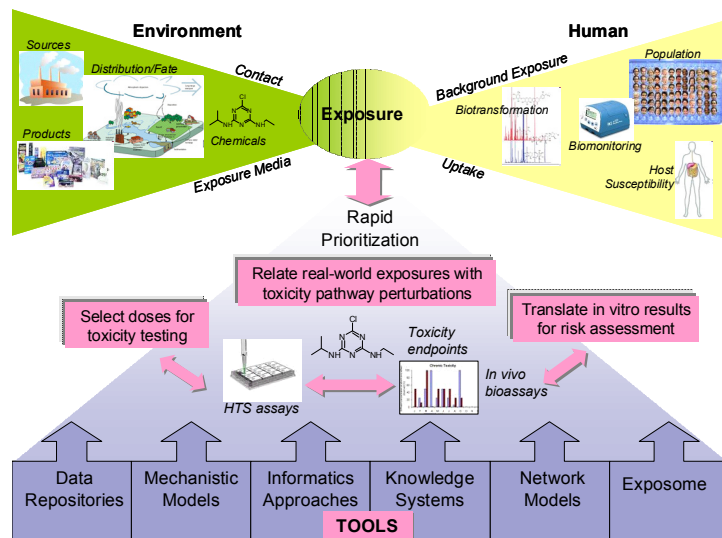
Research Goals

Goal: 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 public health.

ExpoCast™ will provide an overarching framework for the science required to characterize biologically-relevant exposure in support of the Agency computational toxicology program. Broadly and long-term, the ExpoCast™ program will foster novel exposure science research to

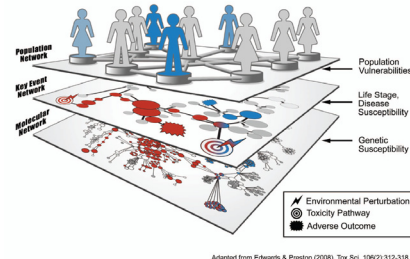
- Inform chemical prioritization,
- Increase understanding of system response to chemical perturbations resulting from environmentally relevant exposures and how these translate to relevant biological changes at the individual and population levels,
- Link information on potential toxicity of environmental contaminants to real-world health outcomes.

Approach

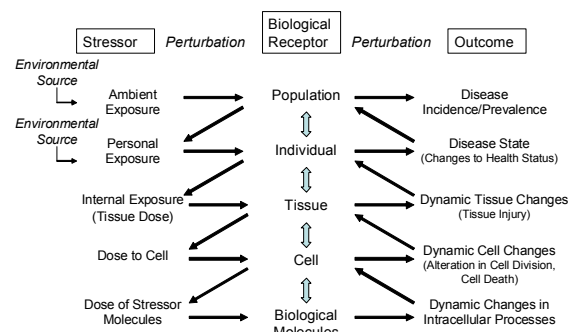


Systems Exposure Science : Exposure at All Levels of Biological Organization

- Consider coupled networks spanning multiple levels of biological organization
- Mechanistic understanding derived by characterizing networks and impacts of perturbations
- Networks at different levels used to merge molecular-level changes with measured events at the individual or population level



- Molecular networks based on data from 'omic measurement
- Key event networks, each node represents a toxicity pathway, abstracted from molecular network based on biological interpretation and targeted experimentation
- Adverse outcome driven by impact of individual's genetics, epigenetics and exposure profile
- Connectivity at the population level driven by common genetics, lifestyle, environment



Cohen Hubal et al, 2008

Priority Exposure Research for Computational Toxicology

Integrate human vulnerability and life-stage aspects into:

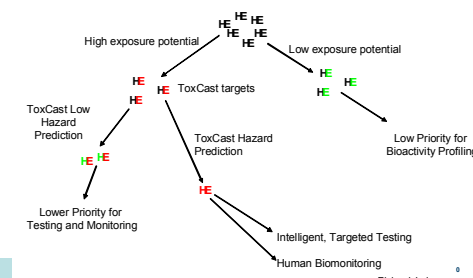
- Accessible and linkable exposure databases
- Exposure screening tools for accelerated chemical prioritization
- Advanced computational approaches for interpreting *in vitro* toxicity data in the context of individual and population health
- Biologically-relevant exposure metrics (biomarkers reliably associated with exposure)

ExpoCoP: US EPA Exposure Science Community of Practice

NCCT, NERL, NCEA, NHEERL, ORD, NCEER, OPP, OPPT, OSW, OW, OCHPEE, CDC, NIEHS, NSF, NICHD, USACE, HC, RIVM, KTL, JRC, Stockholm U, Technion, U of Ottawa, U of FL, UMDNJ, EOHHS, U of Wash, VT, UC Berkeley, EDF, Silent Spring, LifeLine Group, Summit Toxicology, Infoscience, ACC LRI, L'Oreal, DuPont, Bayer Crop Science, CropLife America, P & G, Exxon Mobil, Dow, ACC

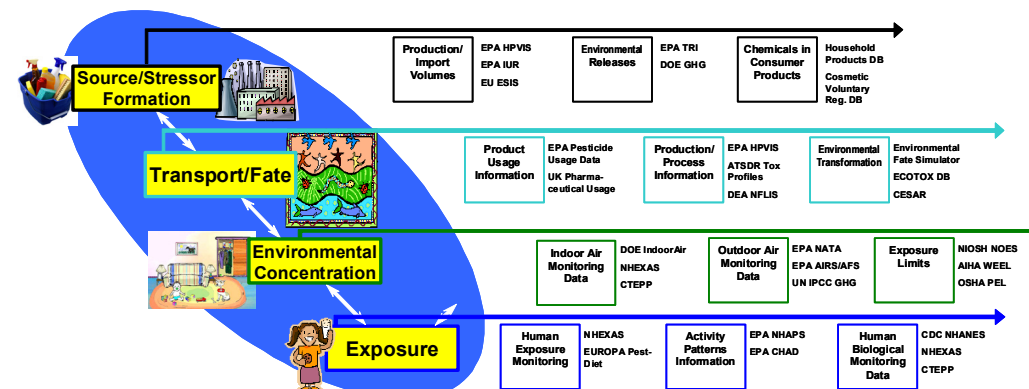
- Mass-Balance Approaches**
 - Integrative Approaches, CCL, EOHHS
 - SVOCs in Residential Env, Virginia Tech
 - USEtox and IMPACT, U of Michigan
 - RAIDAR, U of Toronto
- Regulatory Prioritization**
 - ChAMP, US EPA/OPPT
 - Exposure categorization of the DSL, U of Ottawa
 - CEPST (ComET plus), The LifeLine Group
 - Exposure for Chemicals Management, EDF
- REACH and EU Exposure**
 - Exposure Science Program, EC - JRC
 - ECETOC Tool for REACH, ExxonMobile
 - GEXFRAME, Infoscience
- Linking Exposure-Hazard-Susceptibility**
 - Exposure-Dose-Toxicity Relationship, The Hamner
 - Biological Equivalents, Summit Toxicology
 - Exposure data: structure annotation, NCCT
 - Genomics Applications, UNC Chapel Hill

The Future State: Using Hazard and Exposure Information for Prioritizing Testing and Monitoring



Exposure Data and Databases

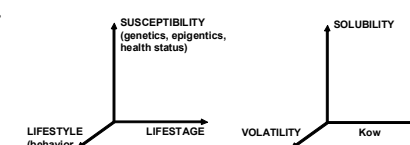
An important early component of ExpoCast™ is to establish a preferred approach for consolidating and linking human exposure and exposure factor data for chemical prioritization and toxicity testing.



Exposure Landscape

Define "EXPOSURE SPACE" analogously to "chemical space" (based on chemical properties and exposure endpoints).

- Chemical properties (MW, vol, sol, pbt)
- Products (formulation, lifecycle)
- Pathway (media, routes)
- Dosimetry (ADME)
- Target characteristics (individual, population)



Results

Early efforts have focused on identifying research needs, establishing collaborations, and building consensus in the scientific community. Results include:

- Established active Community of Practice (over 70 individuals from over 30 public and private sector organizations)
- Three publications defining role of exposure science in computational toxicology
- Workshop "Connecting Innovations in Biological, Exposure and Risk Sciences"
- Workshop "SVOCs in the Residential Environment"
- ISES 2009 Annual Conference, "Transforming Exposure Science for the 21st Century"
- Symposium at ISES 2009, "Integrative Exposure Biology and Computational Toxicology for Risk Assessment"
- Survey and identification of high priority exposure data resources

Future Directions

Focus will be on identifying/evaluating a range of promising tools/approaches.

Specific tasks may include:

- Apply exposure modeling tools such as RAIDAR (unit exposure), USEtox 1.0 (decoupled from dose/response) to ToxCast phase 1 and then possibly phase 2 compounds to evaluate potential for prioritization.
- Evaluate utility of approaches such as Biomonitoring Equivalent (BE), Threshold of Toxicological Concern (TTC) for linking ToxCast results with human exposure information.
- Complete and test portal of entry model suites (note: dermal exposure is driving exposure prioritization in CEPA DSL)

Impact and Outcomes

Short term, this initiative will advance Agency tools for efficiently characterizing and classifying chemicals based on potential for biologically-relevant exposure; as well as inform characterization of environmentally-relevant toxicity. Longer term, advance exposure science required so that fundamental knowledge of toxicity pathways can be used to improve understanding of real-world human-health.

Milestones/Products:

- FY09**
 - ExpoCast™ conceptual framework and research plan
- FY10**
 - Problem formulation workshop with stakeholders and evaluation/ground-truthing of exposure prioritization tools
 - Position paper recommending standards for exposure data representation
 - White paper defining exposure space and plan for assessing exposure data landscape
 - White paper exploring development/application of human exposure knowledge base
 - Begin implementing standards across exposure databases of highest utility for NCCT
- FY11**
 - Manuscript describing extant data analyses to identify critical determinants for exposure classification and chemical prioritization based on potential for exposure
- FY12**
 - Evaluate exposure index for prioritization on subset of ToxCast compounds

References

- Cohen Hubal EA.(2009) Biologically-Relevant Exposure Science for 21st Century Toxicity Testing. Toxicol. Sci., July 14. [Epub ahead of print]. In Press
- 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. *J Expo Sci Environ Epidemiol*. [Online: Nov 5 2008]
- Edwards, SW, Preston, RJ. (2008) Systems biology and mode of action based risk assessment. *Toxicol Sci*. 106(2):312-318.
- McCarthy MI, Abecasis GR, Cardon LR, Goldstein DB, Little J, Ioannidis JP, Hirschhorn JN. (2008) Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nature Reviews Genetics* 9:356-369.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY



COMPUTATIONAL TOXICOLOGY