EPA CompTox Research

Thousands of chemicals

High throughput biology and chemistry

Bioinformatics/machine Learning

Benefits
- Less expensive
- More chemicals
- Fewer animals
- Solution Oriented
- Innovative
- Multi-disciplinary
- Collaborative
- Transparent

Predictive toxicology and exposure science
Focusing on Current and Future Applications of CompTox Tools

- Prioritization of chemicals based on high throughput biological and chemical profiling

- Targeted testing based on outcomes from predictive computational models

- Replacing traditional (in vivo) testing using quantitative Adverse Outcome Pathways
CompTox Research in Chemical Safety for Sustainability (CSS)

8 Research Themes

• Chemical Inherency
• Systems Models
• Biomarkers
• Cumulative Risk
• Life Cycle Considerations
• Extrapolation
• Dashboards
• Evaluation

CompTox
CSS Research Theme: Inherent Chemical Properties

❖ Inherency includes
  • chemical characterization
  • data storage
  • model development and improvement

❖ Chemical structure-based tools
  • DSSTox, PPC (w/in EFS), MOA profiler, PReParE, DockScreen
  • Analysis of models and chemical domains

❖ Outputs and linkages
  • Systems (human health & eco)
  • Screening & Prioritization (exposure, effects, toxicity, etc.)
  • Dashboards (data input streams)

❖ Partners
  • Programs and Regions
  • ORD/NCCT, NERL, NRMRL
Overview of Inherency Tools

Structure-data inventory
- DSSTox

Knowledge base (models)
- PPC within the EFS
- PReParE
- MOA QSAR/profiler
- DockScreen

Chemoinformatics & Analysis
- Identify similarity – i.e., nearest neighbor chemicals (surrogates)
- Identify diversity – coverage of chemicals
- Model relevance – applicability domain
## Project Title

<table>
<thead>
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<th>Project</th>
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<tbody>
<tr>
<td>1</td>
<td>Systems-level approach to adverse outcome pathway (AOP) discovery and application</td>
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<td>Systems modeling of specific tissues and multi-organ pathways</td>
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<td>Metrics and models that define chemical exposures and internal dose</td>
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<td>Systems approaches to assess human and ecological risks</td>
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<td>Screening and prioritization for exposure and adverse outcomes</td>
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<td>An integrated systems approach to assess and predict the toxicity of engineered nanomaterials and their applications</td>
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- Virtual Liver, Virtual Embryo [NCCT, NCEA, NCER, NERL, NHEERL]
- ToxCast, ExpoCast [NCCT, NERL, NHEERL]
- ToxCast [NCCT, NHEERL]
## ToxCast: High-Throughput Screening and Prioritization

<table>
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<tr>
<th>Set</th>
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<td>293</td>
<td>~600</td>
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High Throughput Screening 101 (HTS)

Robots

96-, 384-, 1536 Well Plates

Chemical Exposure

Cell Population

Pathway

Target Biology (e.g., Estrogen Receptor)
**ToxCast Chemical Property Dimension**

- **LOG P** = octanol/water partition coefficient
- **TPSA** = log (Total Polar Surface Area)
- **Complexity** = log (complexity based on paths, branching, atoms)

**EPA**

**Office of Research and Development**
National Center for Computational Toxicology
ToxCast HTS Assay Overview
(>1100 Assay Endpoints/Readouts)

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<td>NHEERL MESC</td>
<td>Rabbit</td>
<td>regulation of gene expression</td>
<td>Spectrophotometry</td>
<td>Testis</td>
<td>Cholinesterase</td>
<td>inducible reporter</td>
</tr>
<tr>
<td>NHEERL NeuroTox</td>
<td>Cattle</td>
<td>receptor activity</td>
<td>Reporter activity</td>
<td>Uterus</td>
<td>Phosphatase</td>
<td></td>
</tr>
<tr>
<td>NHEERL Zebrafish</td>
<td>guinea pig</td>
<td>receptor binding</td>
<td>Luminescence</td>
<td>Brain</td>
<td>Protease</td>
<td></td>
</tr>
<tr>
<td>Novascreen</td>
<td></td>
<td></td>
<td>Radioactivity</td>
<td>Bladder</td>
<td>Metabolism</td>
<td></td>
</tr>
<tr>
<td>Odyssey Thera</td>
<td></td>
<td></td>
<td>HPLC</td>
<td>Ovary</td>
<td>GPCR</td>
<td></td>
</tr>
</tbody>
</table>
Predictive Model Development from ToxCast and Other Data

DATABASES
- ToxCastDB (in vitro)
- ToxRefDB (in vivo)

ASSAY SELECTION
- Univariate Analysis
  - p-value statistics

ASSAY AGGREGATION
- Condense by gene, gene family, or pathway

ASSAY SET REDUCTION
- Reduce by statistics (e.g. correlation)

MULTIVARIATE MODEL
- LDA
  - Model Optimization
Example: Predictive Model of Reproductive Toxicity

LDA WEIGHTS

36 Assays Across 8 Features
80% Balanced Accuracy

Martin et al Biology of Reproduction 2011
Predictive Toxicity Modeling Based on ToxCast Data

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Predictive models: endpoints
liver tumors: Judson et al. 2010, Env Hlth Persp 118: 485-492
cancer: Kleinstreuer et al. 2012, submitted
zebrafish vs ToxRefDB: Sipes et al. 2011, Birth Defects Res C 93: 256-267

汕

Predictive models: pathways
endocrine disruption: Reif et al. 2010, Env Hlth Persp 118: 1714-1720
angiogenesis: Kleinstreuer et al. 2011, Env Hlth Persp 119: 1596-1603

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Continuing To Expand & Validate Prediction Models
Generally moving towards more mechanistic/AOP-based models
ExpoCast: Exposure Science in the 21st Century

Goal: provide a high-throughput analog to ToxCast hazard identification

EPA Case Studies:
TSCA21:
Prioritization of approximately ~500 Toxic Substances Control Act (TSCA) chemicals
EDSP21:
Prioritization of ~2000 Endocrine Disruptors Screening Program (EDSP) chemicals based on endocrine disrupting potential
OW21:
Support future CCL development

Using high-throughput fate and transport models – predict the contribution from industrial use to overall exposure

Developing new models of consumer use
Exposure-based prioritization challenge identified two models capable of high throughput operation (RAIDAR, USETOX).

Models predict partitioning into environmental media, and describe human interaction with that media.

Treat different models like related high-throughput assays.

Need to validate with biomonitoring data.
CDC reports chemical concentrations every two years for varying demographics (> 6 years in age)

Focusing on U.S. median initially

Capable of adding population variability, but will need consumer use models

“Ground-truthing” Chemicals

NHANES volatile, insoluble

30 50

Production / Release Data

IUR (6759 compounds with production of >25,000 lbs a year)

CPRI (242 pesticides with total lbs applied)
CSS Systems Models: Virtual Tissues

Systems modeling is a major CSS research theme

“Use a systems-based research approach, aligned with the National Research Council’s vision and strategy for toxicity testing in the 21st century, to advance scientific knowledge and predictive tools to effectively use mechanism-based biological endpoints and data in chemical safety assessments concerned with human health and/or ecosystem sustainability.”

Virtual Tissues Predictive models of chemical-induced disruption of normal functions

- Virtual Liver
- Virtual Embryo
- Virtual Endocrine System

Virtual Tissues Goals

- Elucidate adverse outcome pathways (AOPs) – leverage in vitro data
- AOP-driven data collection - toxicokinetics and dynamics
- Quantitative computational predictive models of AOPs
Virtual Liver Goals

- Address research issues in screening, targeted testing and dose-response estimation of hepatic effects
- Produce decision support tools to more effectively
  - Prioritize hepatotoxicants
  - Estimate tissue dosimetry
  - Quantitatively estimate chemical-induced [chronic] liver injury
- Produce experimental models/data to reduce uncertainty
  - Absorption, distribution, metabolism and excretion (ADME)
  - Molecular, cellular and tissue level effects
v-Liver

- Identify key hepatic AOPs of environmental relevance

- Knowledgebase of hepatic AOPs

- Predictive model of dosimetry
  - Microdosimetry in Virtual Lobule (Wambaugh 2010)
  - Experimental data: ToxCast, Hamner, EPA/NERL

- Predictive model of cell phenotypes
  - Signaling cross-talk network model (Jack et al, 2011)
  - Experimental data: ToxCast, In-life technologies, EPA/NHEERL, JRC

- Predictive model of tissue-effects
  - Integrated agent-based model
  - Experimental data: ToxCast, EPA/NHEERL, JRC
Virtual Embryo: systems models linking HTS data with adverse outcome pathways

- HTS/HCS data and predictive signatures
- Biological architectures and system dynamics
- Surrogates for missing or incomplete information
- Integration of adverse outcome pathways

A computer simulation of normal development (Virtual Embryo) can predict adverse prenatal outcome

http://www.epa.gov/ncct/v-Embryo/
V-Embryo Adverse Outcome Pathway (AOP)

**Proposed AOP: Embryonic Vascular Disruption**

- **VDCs**
  - Hypoxia (↓O2, ↑ROS)
  - HIF1a, AhR
- **Angiogenic switch**
  - VEGF, FGF
- **Notch-Dll4 signals**
- **Chemokine pathway**
  - CCL2, CXCL10, IL-1, TNF-alpha
- **ECM interactions**
  - uPAR, PAI-1, MMPs, Intg
- **Vessel remodelling**
  - TGF-beta, TIE2, PDGFB

**Angioblasts**
- ↓vasculogenesis
- ↓blood islands

**Placenta**
- Nutrient exchange
- Altered physiology
- Impaired blood flow

**Newborn**
- Low birth weight
- Functional deficit
- Malformation
- Lethality

**Population**
- Developmental health consequences

**Endothelial cells**
- ↓erythropoietic cycle
- ↓angiogenic sprouts

**Macrophage cells**
- ↓cell motility
- ↓growth factor release

**Mural cells**
- ↓cell recruitment
- ↓vessel stabilization

**Embryo-Fetus**
- Altered hemodynamics
- Impaired growth
- Dysmorphogenesis
- Altered differentiation

**KEY**
- Established mechanistic linkage with quantitative or semi-quantitative data
- Predictive model linkages based on quantitative concentration-response data
- Plausible linkage with limited data
- Hypothetical linkage
- Assay linked to ToxCast
- Empirical linkage based on quantitative exposure-response data

**SOURCE:** Knudsen and Kleinstreuer (2011) Birth Defects Res. C, 93
Dashboards for Decision Support

- Supporting current in-use computational tools and databases
  - ECOTOX, ACToR, ToxRefDB, ToxCastDB, MetaPath, DER Composers

- Developing new systems to support program office decision-support needs
  - Prioritization tools for OSCP, OPPT, OPP, OW, NCEA
Dashboards Key Points

- Encompasses:
  - Computational tools
  - Databases
  - Web sites
- Goal is to make ORD research results readily available to decision-makers
  - EPA Programs and Regions
  - External stakeholders
- Dashboard projects are not stand-alone
  - Integrate outputs from across CSS and ORD research projects
DASHBOARD

CHEMICAL PAGE

Chemical List Updated Dynamically as User Selects/DeSelects

Chemical | E | A | I | U
---|---|---|---|---
Atrazine | ↑ | - | - | -
Bisphenol A | ↑ | ↓ | - | -
Triadimefon | - | - | - | -
Imazalil | ↑ | - | - | -
Fipronil | - | ↓ | - | -
Propiconazole | - | - | - | -
PFOA | ↑ | - | - | -
PFOS | - | - | - | -
DEHP | ↓ | - | - | -
Chemical...500
EDPS21 – Provide tools to prioritize chemicals for EDSP Tier 1 testing

OW21 – Support prioritization around the CCL process

TSCA21 – Support prioritization built around OPPT’s TSCA Workplan Chemicals: Methods Document

OPP21 – support modeling needs of the pesticides program

OPP / EFED Uber tool – Supporting ecological risk assessment

Infrastructure Development

- Databases and tools to support development of other custom dashboards both inside and external to EPA
Dashboard Summary

- The Dashboards project’s goal is to make ORD science easier to access and use by Programs and Regions.

- 2 Main Tracks:
  - Continued support of current, in-use tools
  - Development of custom tools, databases and decision-support systems
CompTox Communications Strategies

- Media relations
- Fact sheets
- Events
- Social media
- Web
- Communities of Practice
- Asking partners to amplify
- Partner and media database
EPA CompTox Research

Thousands of chemicals

High throughput biology and chemistry

Bioinformatics/machine Learning

Predictive toxicology and exposure science

Benefits

- Less expensive
- More chemicals
- Fewer animals
- Solution Oriented
- Innovative
- Multi-disciplinary
- Collaborative
- Transparent