Chemical Screening Visualization Tool:
Resource for Rapid Chemical Assessment

Mario Chen
Environmental & Toxicological Modeling
DuPont Haskell Global Centers for Health & Environmental Sciences
Abstract

The implementation of new chemical regulations, such as REACH (Registration, Evaluation, Authorization of CHemicals) in the European Union and the role of Product Stewardship has prompted the development of new tools and methodologies to allow researchers and businesses to rapidly assess the environmental profile of new or existing products. Current data formats, such as spreadsheets and text tables, make interpretations of environmental relevance and concern difficult for non-experts to put into context.

The Chemical Screening Visualization Tool (CSVT) utilizes a novel graphical visualization approach to easily view and assess the environmental, toxicological and societal concerns for chemical compounds. The unique graphical layout clusters the various endpoints enabling the user to rapidly visualize potential areas of concern. Additional charts display the environmental partitioning based on different emission scenarios (Air, Water or Soil) in order to determine the compartment of concern. The Chemical Screening Tool can be customized to display most types of data found in the Metanomics Information System (METIS), which is a proprietary data resource for environmental fate and hazard assessment.
Presentation Overview

• Current needs
• Visualization of chemical hazard information
• Application of environmental exposure
• Multi-chemical search feature
• Read-across examples
• Data access
• Industrial applications
Current Needs?

Integrating New Advances in Exposure science and Toxicity Testing: Next steps (ICCA-LRI Workshop – Stresa, Italy)

• **Innovative Approaches to Generating, Integrating, and Interpreting Hazard Data.** Examine new experimental cell systems and computational analytical and integrative methods for predictive toxicology and utilization to support chemical assessment.

• **Communicating Scientific Information.** Develop a framework for a research agenda to determine how the scientific information exchange between decision makers, scientists, and the public can better meet the needs of society.

• **Exposure Science.** Consider relevant research activities for addressing gaps in exposure science required to meet both immediate needs for rapid prioritization as well as longer term objectives for chemical evaluation and risk management.
Integrating New Advances in Exposure science and Toxicity Testing: Next steps

• **Innovative Approaches to Generating, Integrating, and Interpreting Hazard Data.** Examine new experimental cell systems and computational analytical and integrative methods for predictive toxicology and utilization to support chemical assessment.

**Meeting the objectives:**

• Data integration (METIS)
  • Environmental fate
  • Toxicity
  • Hazard
  • Regulatory information
• Predictive tools and (Q)SAR methodology to fill in data gaps and/or provide weight of evidence approaches
• Statistical and analytical tools to validate tools and models
• Visualization techniques to aid in the interpretation of data
The Metanomics Information System (METIS) is a proprietary database that has been developed to manage and quickly access information from nearly 1300 public databases and resources from a single point of entry. METIS is the underlying information resource for a variety of business and/or research applications and can be used to quickly evaluate large chemical inventories.

**Greek Mythology:**

Metis ("wisdom" or "wise counsel") was a Titaness who was the first great spouse of Zeus and the mother of Athena. She presided over all wisdom and knowledge. Metis was seduced by Zeus and became pregnant with Athena. It had been prophesied that Metis would bear children more powerful than Zeus himself. To avoid this Zeus ate her. It is said that she is the source for Zeus' wisdom and that she still advises Zeus from his belly.
METIS Data Integration

Data repository
- Centralized
- Relational database
- Chemical and regulatory information (~1300 databases & lists)

Application modules
- Property estimation
- Clustering/Binning
- Metabolism/reactivity
- Structural alerts
- Data mining
- Data visualization
- (Q)SAR modeling/reporting
Training data and test data sets are compared with predictive model outputs along with chemical clustering/binning.

Various methods can be applied to identify a model’s applicability domain or performance of the model across different chemical classes.

Integrating New Advances in Exposure science and Toxicity Testing: Next steps

- **Communicating Scientific Information.** Develop a framework for a research agenda to determine how the *scientific information exchange between decision makers, scientists, and the public can better meet the needs of society.*

  - Data integration
    - Scientific
    - Regulatory
    - Societal
    - Business

  - Data visualization for collective context

*Scientific exchange throughout the commercialization process by the elucidation of potential roadblocks?*
Identifying Roadblocks to Commercialization

- Regulatory requirements
- Non-governmental constraints
- Societal perception
- Direct competition
- Cost to business
Avoiding Roadblocks

- Identify potential regulatory and/or societal hurdles
- Develop a regulatory strategy
- Refine product selection
- Competitive analysis
- Minimize costs with a targeted/integrated testing approach
Societal Hurdles?

“Public perception is the primary societal hurdle. It can be seen as the difference between an absolute truth based on facts and a virtual truth shaped by popular opinion, media coverage and/or reputation.”

Public perception affects us at a consumer level and changes the concept of risk.

Toxicologists concept of risk:
\[ Risk = \text{Hazard} \times \text{Exposure} \]

Societal concept of risk:
\[ Risk = \text{Hazard} \times \text{Outrage} \]
Chemical Screening Visualization Tool (CSVT)

• This tool provides a screening level chemical profile for environmental, hazard and societal endpoints using publicly available information.

• The tool represents a "public's eye" view to identify areas of potential concern.

• Values and classifications from external sources have not been reviewed for data quality.

• Computational models may be used to provide estimates or predicted values, however, no claims can be made for the applicability of each model to various chemical classes.

• *Chemicals profiled in the following presentation are representative based on data availability and diversity*
Feature Summary

• Web-based chemical search system
• Linked to the METanomics Information System (METIS) containing nearly 1300 databases and regulatory lists
  • e.g. PubChem, ACToR, DSSTox, HSDB, ToxCast, ToxRefDB…
• Hierarchical data search – measured vs. predicted
• Interactive chart represents relevant environmental, hazard and societal endpoints
  • Endpoints are logically organized
  • Endpoint values are color coded to indicate a potential level of concern
  • Bar graphs show environmental partitioning based on emission source (directly to Air, Water or Soil)
• At-a-glance determination of potential area(s) of concern
• Identify data gaps and needs for additional testing
• Chemical class and structural similarity comparisons
• Customizable
Web-based Chemical Selection

Chemicals can be entered using any type of synonym (CAS, EINECS, IUPAC or trade name, etc)
Inherent Hazards

Key
- Potential for High level of concern (3-4)
- Potential for Moderate level of concern (2)
- Potential for Low level of concern (1)

Hazard ➔ Length ➔ Color ➔ Concern
Chemical Attributes

- **Environmental Persistence** – indicates the predicted half-life in each environmental compartment.
- **Soil Mobility** – the potential for a chemical to migrate from soil into groundwater.
- **Bioaccumulation** – uses measured or estimated values to indicate the potential for a chemical to sorb to lipids.
- **Aquatic Toxicity** – the measured or estimated toxicity to aquatic organisms.
- **CMR** – indicates whether the compound is classified as known or suspected animal and/or human carcinogen, mutagen or reproductive toxin.
- **Public Perception** – indicates the chemical is present on a variety of regulatory, industrial and/or non-governmental list that may influence how the public views a particular chemical.
- **Environmental Impact** – indicates the potential for the chemical to affect global warming and ozone depletion as compared to reference compounds.
- **Long Range Transport (Air)** – the potential for the chemical to travel long distances from its point of entry into the environment.
- **Environmental Partitioning (Fugacity)** – steady-state partitioning of a chemical in the environment (Air, Water, Soil, Sediment) based on different emission scenarios.
Inherent Hazards - Persistence

Persistent in Air (>2 days) with potential for long-range transport. Not considered to be persistent in water and/or soil nor contribute to Global Warming and/or Ozone Depletion.
Based on the Soil Adsorption Coefficient (LogKoc), this compound has a high potential to migrate to groundwater.
In an aquatic environment, this compound has a moderate potential for bioaccumulation based on an experimental Octanol-Water Partition Coefficient (LogKow) = 2.73 and a measured LogBCF = 1.96. Based on MITI data, a measured EC50 = 4.1 mg/l indicates a moderate concern for toxicity to daphnia. Additional measure values would indicate low concern for toxicity to Fish and Algae.
This compound has been classified under the European Commission (EC) Annex VI as a Category 3 Reproductive Toxin. This compound is not considered to carcinogen and/or a mutagen.
This compound is part of a biomonitoring study but has not been detected. It has not been targeted for deselection or replacement by any industry groups. It is an EU HPV, US HPV and part of the Voluntary Children's Chemical Evaluation Program (VCCEP) and is considered to be an EU REACH Priority compound.
Integrating New Advances in Exposure science and Toxicity Testing: Next steps

- **Exposure Science.** Consider relevant research activities for addressing gaps in exposure science required to meet both immediate needs for *rapid prioritization as well as longer term objectives for chemical evaluation and risk management.*

**Meeting the objectives:**
- Identifying relevant environmental partitions
- Product life stage and risk assessment
- Business applications
- Data visualization for prioritization and strategic development
How does a chemical partition in the environment?

Water Emissions

Air Emissions

Land Emissions

Fugacity Data

Emission Models

Phys.-Chem. Prop. Models

Expert Judgment
CSVT – Emission Scenario Example

Environmental Impacts
- Long Range Transport
- Ozone Depletion
- Global Warming Potential
- NGO List
- Watch List

Public Perception
- Industry Deselection List
- Biomonitoring List
- Biopersistence
- Mutagenicity
- Reproductive Toxicity
- Carcinogenicity

Transport in Air
- Air (Half-life)
- Water (Half-life)

Persistence
- Soil (Half-life)
- Mobility to Groundwater
- BCF-LogP
- BCF
- BAF
- Daphnia
- Fish
- Algae

Aquatic Toxicity
- CMR

Bioaccumulation
- Mobility to Aquatic Food Chain

Mackay
Level III Fugacity Models (EpiSuite v4)
Potential Environmental Exposure Value (PEEV)

Hazard Key
- Red: Potential for High level of concern
- Yellow: Potential for Moderate level of concern
- Green: Potential for Low level of concern

Environmental Impacts
- Transport in Air
  - Long Range Transport
  - Ozone Depletion
- Global Warming Potential
- NGO List
- Watch List
- Industry Deselection List
- Biomonitoring List
- Biopersistence
- Mutagenicity
- Reproductive Toxicity
- Carcinogenicity
- Algae
- Fish
- Aquatic Toxicity

Persistence
- Air PEEV
- Water PEEV
- Soil PEEV

Soil Mobility
- Mobility to Groundwater

Bioaccumulation
- BCF-LogP
- BCF
- BAF

Hazard vs. Color
- Hazard ➔ Color

Exposure vs. Length
Inherent Hazard Assessment:

In an aquatic environment, this compound has a moderate potential for bioaccumulation based on an experimental Octanol-Water Partition Coefficient (LogKow) = 2.73 and a measured LogBCF = 1.96. Based on MITI data, a measured EC50 = 4.1 mg/l indicates a moderate concern for toxicity to daphnia. Additional measure values would indicate low concern for toxicity to Fish and Algae.

Environmental Exposure Assessment:

If emitted to an aquatic environment, this compound is likely to remain in water with some loss to the atmosphere through volatilization. In the aquatic environment, this compound is likely to degrade and not considered to be persistent. Potential aquatic exposure is low thereby reducing the level of risk.
Inherent Hazard vs PEEV

All potential emission scenarios
### Multiple Chemical Search

**Chemicals can be entered using any type of synonym (CAS, EINECS, IUPAC or trade name, etc)**
## Multiple Chemical Search - Matrix

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>CAS Number</th>
<th>Chart Link</th>
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</thead>
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<td><a href="http://www.amCharts.com">Chart</a></td>
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<tr>
<td>Phenol, 4,4″-(2,2-trichloroethylidene)bis-</td>
<td>2071-36-0</td>
<td><a href="http://www.amCharts.com">Chart</a></td>
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<tr>
<td>METHOXYCHLOR</td>
<td>72-43-5</td>
<td><a href="http://www.amCharts.com">Chart</a></td>
</tr>
<tr>
<td>FORMALDEHYDE</td>
<td>50-00-0</td>
<td><a href="http://www.amCharts.com">Chart</a></td>
</tr>
<tr>
<td>TOLUENE</td>
<td>108-88-3</td>
<td><a href="http://www.amCharts.com">Chart</a></td>
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<tr>
<td>PHENOL</td>
<td>108-95-2</td>
<td><a href="http://www.amCharts.com">Chart</a></td>
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Structure Searching – Structure Input

[Image of a chemical structure editor with options for chemical elements and structures.]
Structure Searching – Database Selection

- TSCA Inventory
- All Organic Compounds
- Canadian Inventory (DSL)
- EU Inventory (EINECS)
- TSCA Inventory
- EPA Aquatic Toxicity Database (AQUIRE)
- EPA Carcinogenic Potency Database (CPDB)
- EPA Water Disinfection Products Database (DBPCAN)
- EPA DSSTox Compounds
- EPA Fathead Minnow Database (FHM)
- FDA Maximum Daily Dose Database (FDD)
- High Production Volume Challenge Program (HPVCSI)
- EPA Integrated Risk Information System (IRIS)
- FDA Estrogen Receptor Binding Database (NCTRER)
- NTP Chemical Bioassay Database (NTPBSI)
- NTP High-throughput Screening Project (NTPHTS)
- RTECS
- MITI Biodegradation Database
### Structure Searching - Results

#### Search by:
- Structural similarity
- Structural features
- Functional similarity
- Classification
- Compound clustering

<table>
<thead>
<tr>
<th>CAS</th>
<th>Tanimoto Coefficient</th>
<th>Structure</th>
<th>Canadian DSL Classification</th>
<th>Persistence</th>
<th>Bioaccumulation</th>
<th>Inherent Toxicty</th>
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<td>106-44-5</td>
<td>1.00</td>
<td><img src="image1" alt="Structure 1" /></td>
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<td>Not B - QSAR</td>
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Analog Comparison

- Identify common attributes
- Data gap filling
- Product selection/substitution
Business Application - Product Life-Cycle

Current focus of chemical screening is for product registration.

Chemical screening can be applied throughout the product life-cycle.
Chemical Screening in the Product Life-Cycle

**Concept Generation**
- Identify performance requirements
- Define environmental and hazard criteria
- Virtual screening
- Compound prioritization
- Regulatory considerations

**Discovery**
- Identify lead compounds
- Hazard characterization
- Risk assessment

**Optimization**
- Improve performance
- Reduce environmental footprint

**Development**
- Guideline intelligent testing strategies

**Registration**
- Fulfill regulatory requirements

**Commercialization**
- Consumer protection
- Exposure reduction

**Product Stewardship**
- Knowledge discovery and retention
- Three R’s
  - Replacement
  - Reduction
  - Refinement

**Remediation**
- Evaluate potential environmental degradants
- Optimize remediation strategy
Business Applications Examples

- **Discovery programs** – identify candidates with potential for long-term sustainability
- **Product stewardship** – evaluation and prioritization of a business’s complete chemical portfolio
- **Product selection** – comparison of raw materials to create products with a lowest possible environmental footprint
- **Intelligent testing strategy** – guide environmental testing to reduce costs for the business
- **Remediation Strategies** – identify environmental profile of potential degradation products

View by:
- Chemical classes
- Structural similarity
- Scaffolds
- Formulation
Product Selection

Selecting products with the least amount of concern?

Note: Black color code indicates “No Data”. This would indicate potential data gaps and trigger possible testing needs.
# Remediation Strategy

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<td><img src="chart-by-emCharts.com" alt="Emission Scenario: Air Chart" /></td>
<td><img src="chart-by-emCharts.com" alt="Emission Scenario: Water Chart" /></td>
<td><img src="chart-by-emCharts.com" alt="Emission Scenario: Soil Chart" /></td>
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<tr>
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10/27/2010
Global Inventories

- Australia
- China
- Canada
- Austria - European Union
- Belgium - European Union
- Bulgaria - European Union
- Cyprus - European Union
- Czech Republic - European Union
- Germany - European Union
- Denmark - European Union
- Estonia - European Union
- Spain - European Union
- Finland - European Union
- France - European Union
- United Kingdom (Great Britain) - European Union
- United Kingdom - European Union
- Hungary - European Union
- Ireland - European Union
- Italy - European Union
- Lithuania - European Union
- Luxembourg - European Union
- Latvia - European Union
- Malta - European Union
- Netherlands - European Union
- Poland - European Union
- Portugal - European Union
- Romania - European Union
- Sweden - European Union
- Slovenia - European Union
- Slovakia - European Union
- Japan
- Korea
- New Zealand
- Philippines
- Switzerland
- United States
Data Access

### Chemical List

<table>
<thead>
<tr>
<th>CAS RN</th>
<th>Chemical Name</th>
<th>LC50 (μg/L)</th>
<th>LC50 Note</th>
<th>LC50 Ratio</th>
<th>Mode of Action (MOA)</th>
<th>MOA Confidence</th>
<th>Mixed MOA</th>
<th>Tox Index</th>
<th>Remarks</th>
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<tbody>
<tr>
<td>61006-84-2</td>
<td>(Hexyloxy)-m-aniside</td>
<td>23.9</td>
<td>Nonmonotonic pattern of death; geom mean of 2 experiments</td>
<td>1.10 μg/L</td>
<td>UNSURE</td>
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<td></td>
<td>0.4</td>
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<tr>
<td>5710-93-2</td>
<td>Dibutyl phthalate</td>
<td>96.4</td>
<td></td>
<td>1.92 μg/L</td>
<td></td>
<td></td>
<td></td>
<td>3.8</td>
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<tr>
<td>88-75-6</td>
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<td>1.92 μg/L</td>
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<td></td>
<td>3.8</td>
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### EPA ECOTOX Aquatic Toxicity Database

- **Species**: Fathead minnow (Pimephales promelas)
- **Test Duration**: 7 days
- **LC50 (μg/L)**: 66.6 μg/L
- **Remarks**: Test conducted by the University of Maryland, College Park, Maryland.

### EPA Fathead Minnow Acute Toxicity Database (EPAFHM)

- **Name**: DSSTox EPAFHM
- **Substance Count**: 617
- **Description**: EPA Fathead Minnow Acute Toxicity Data (DSSTox)
CSVT versus ToxPi

Not a replacement, but convergence of methodologies…

• Hazard Data Integration
• Incorporate Exposure Science.
• Communication of Scientific Information.

Divergence:

• Industrial Focus
• Environmental Impacts
• Societal Perception Issues
• Regulatory Drivers
• Global Inventories