Chemical Screening Visualization Tool:

Resource for Rapid Chemical Assessment

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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:

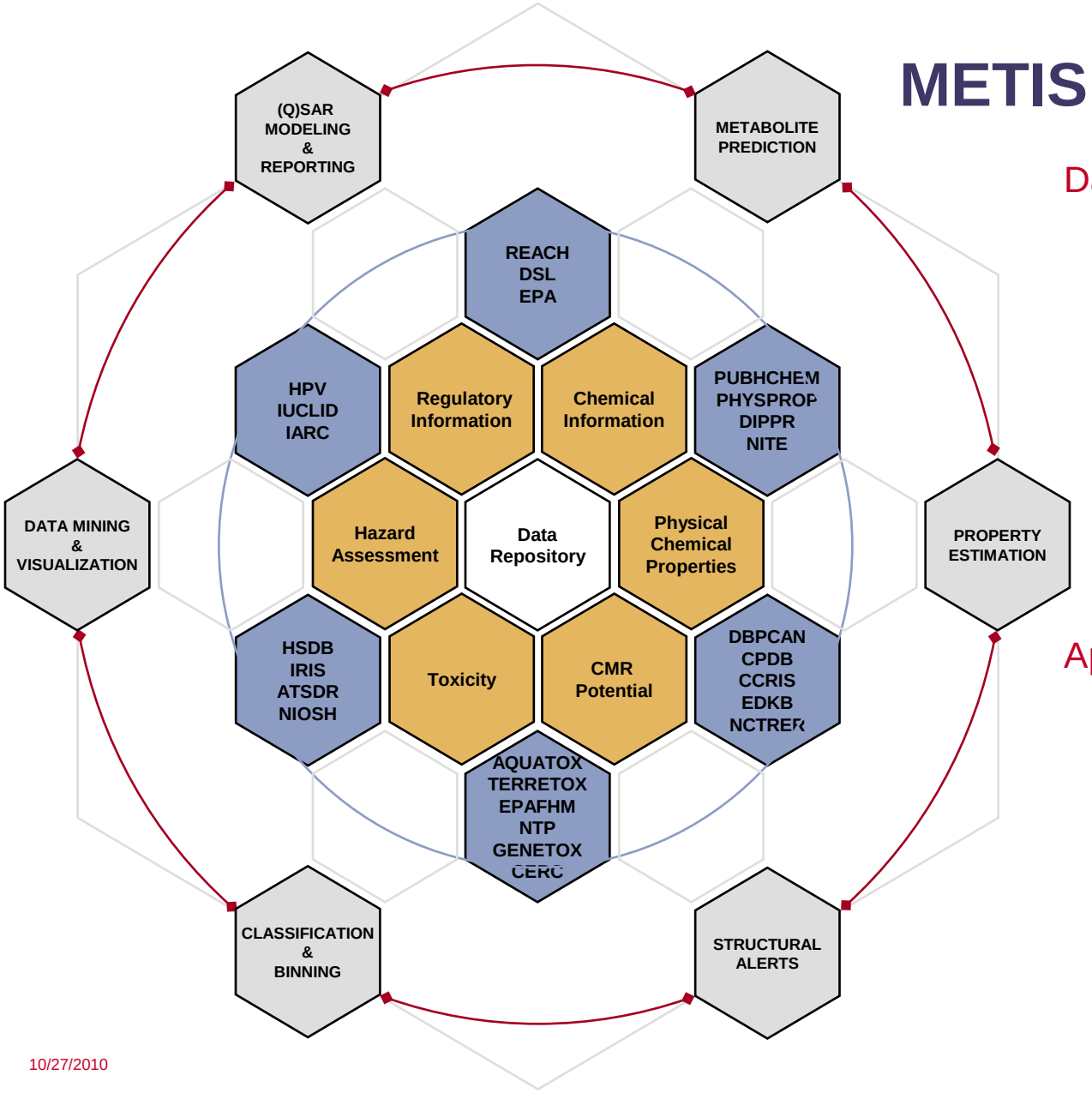
- Data integration (METIS)
  - Environmental fate
  - Toxicity
  - Hazard
  - Regulatory information
- Predictive tools and (Q)SAR methodology to fill in data gaps and/or provide weight of evidence approaches
- Statistical and analytical tools to validate tools and models
- Visualization techniques to aid in the interpretation of data

Metanomics Information System (METIS)

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

Predictive Model Applicability Overview

Compound X

Compound Clustering

Database

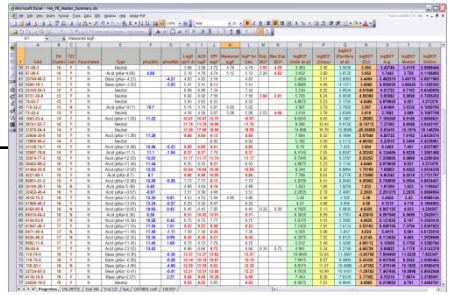
Model#1

Model#2

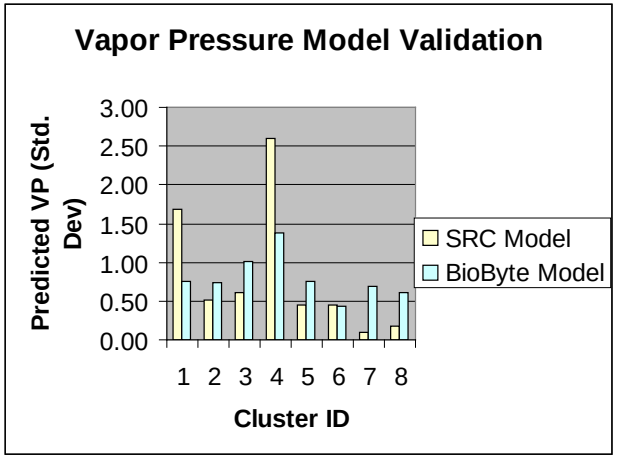
Model#3

Model#4

Empirical Data



Training data and test data sets are compared with predictive model outputs along with chemical clustering/binning.



Domain Analysis

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

Model Applicability

Non-testing approaches under REACH – help or hindrance? Perspectives from a practitioner within industry. G. Patlewicz*, M.W. Chen and C.A. Bellin, *SAR and QSAR in Environmental Research. In press.*

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

    } Commercial stakeholders

  - 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 = Hazard x Exposure

Societal concept of risk:
Risk = Hazard x Outrage

Chemical Screening Visualization Tool (CSVT)

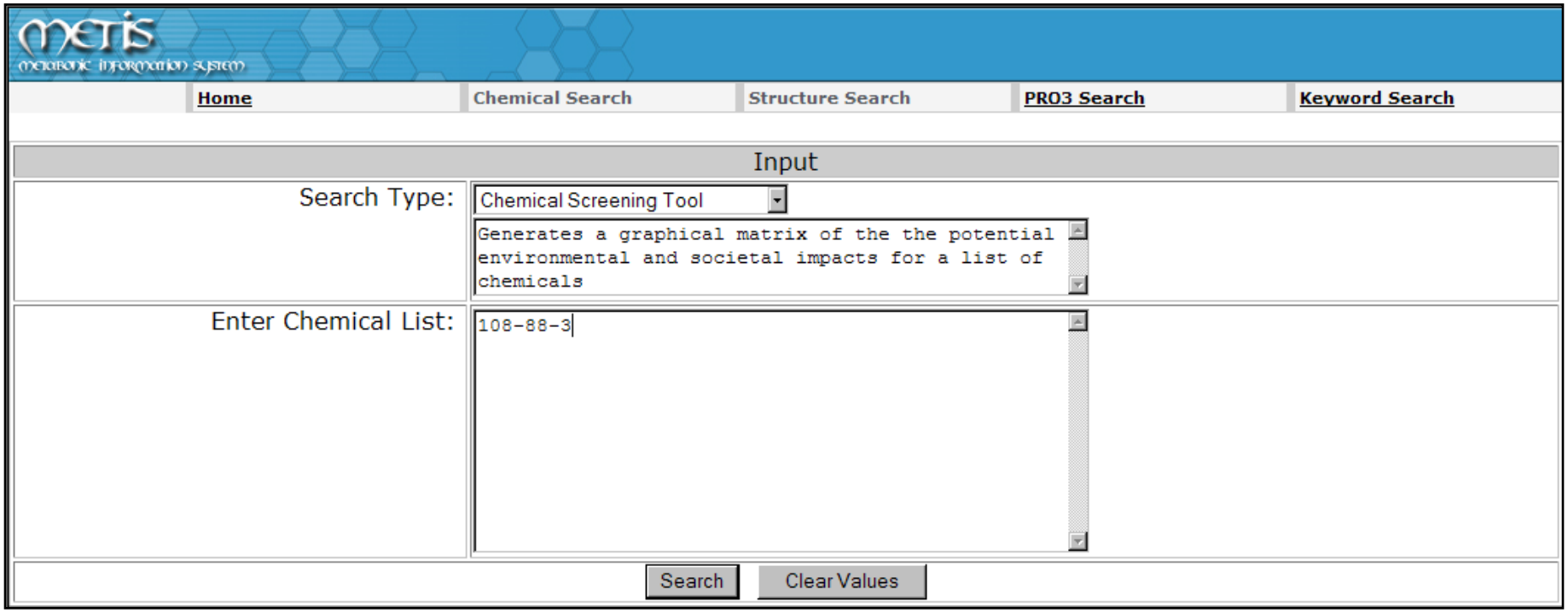
- This tool provides a screening level chemical profile for environmental, hazard and societal endpoints using publicly available information.
- The tool represents a "public's eye" view to identify areas of potential concern.
- Values and classifications from external sources have not been reviewed 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

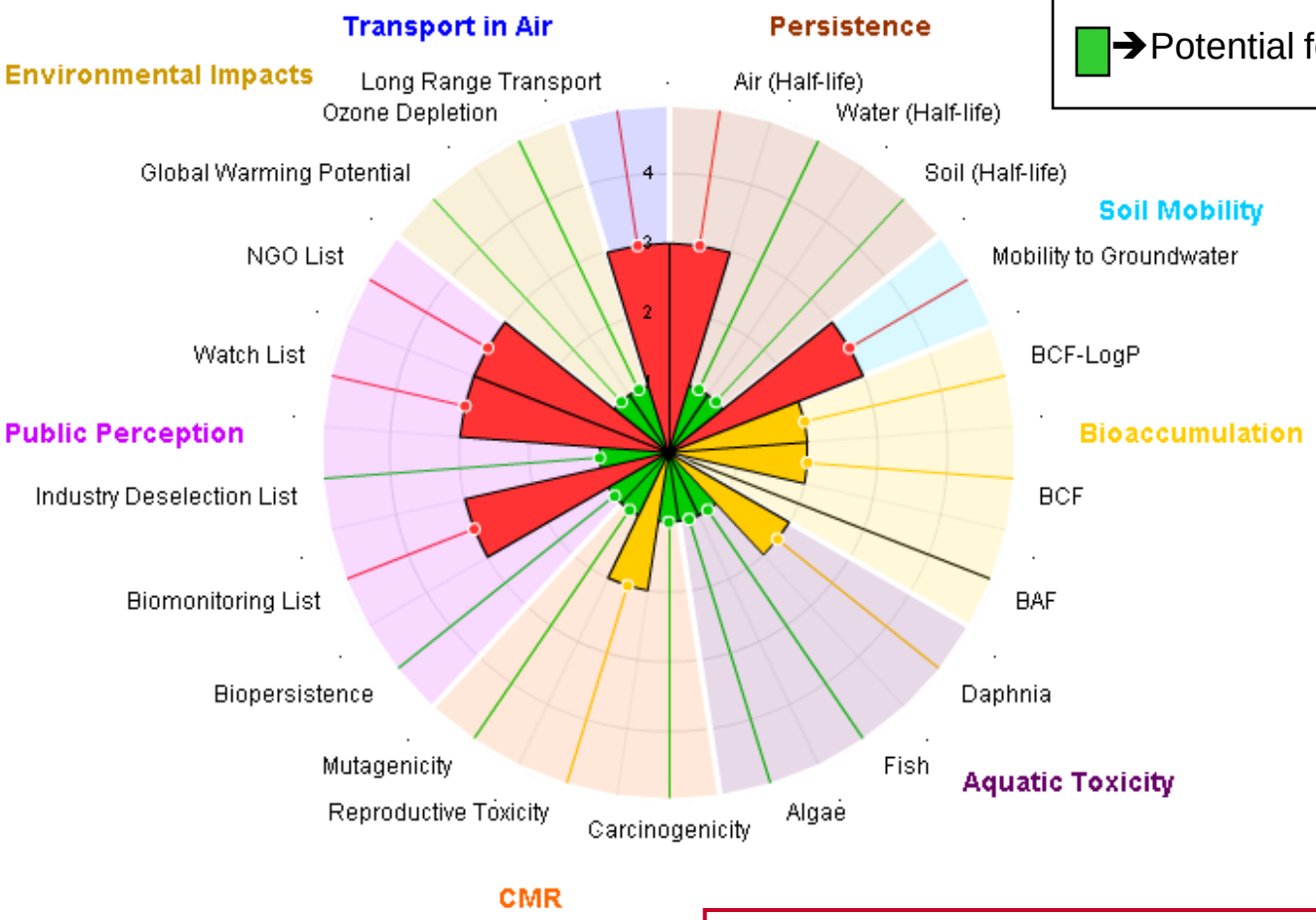


Chemicals can be entered using any type of synonym (CAS, EINECS, IUPAC or trade name, etc)

Inherent Hazards

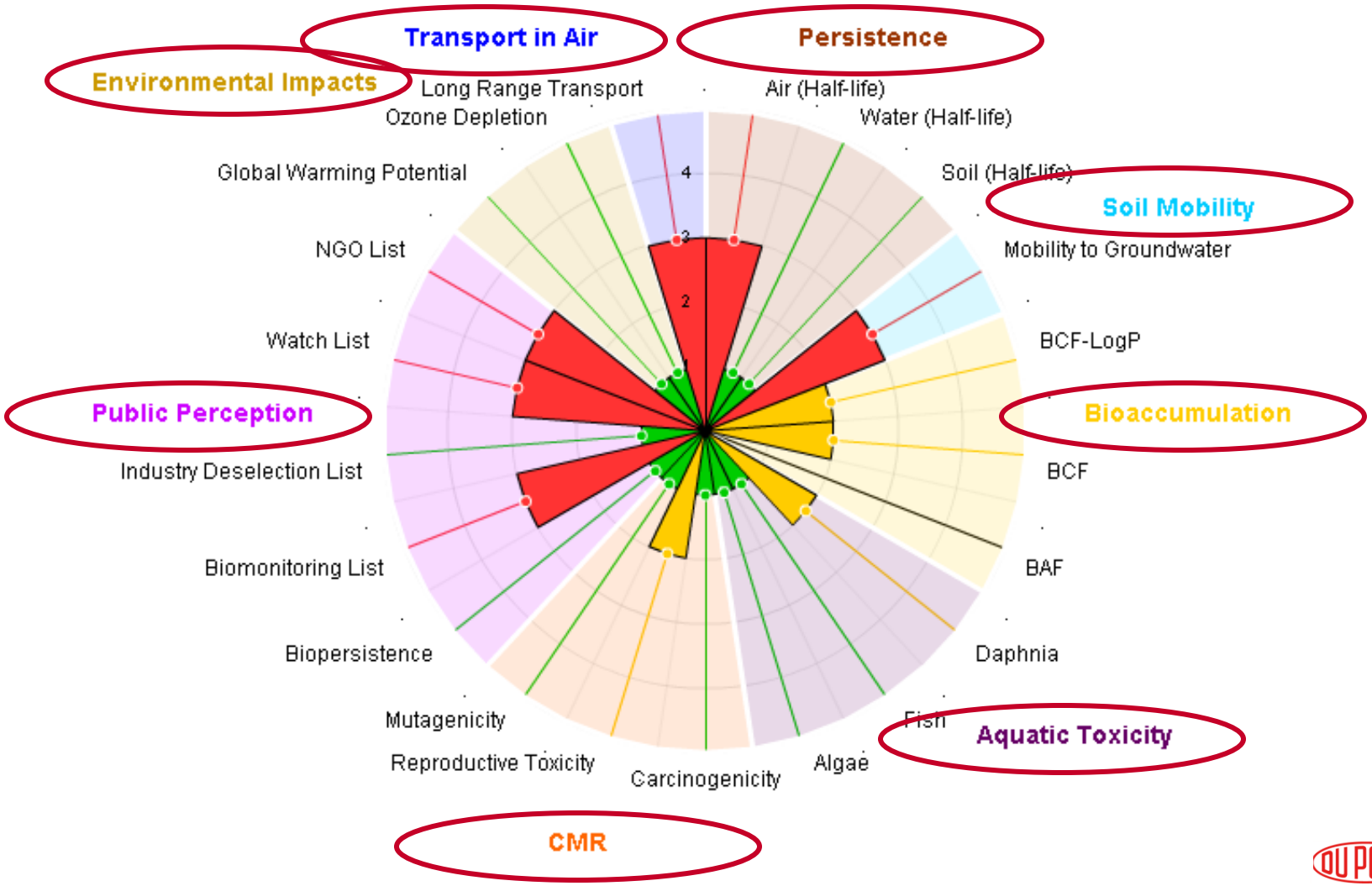
Key

- ➔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

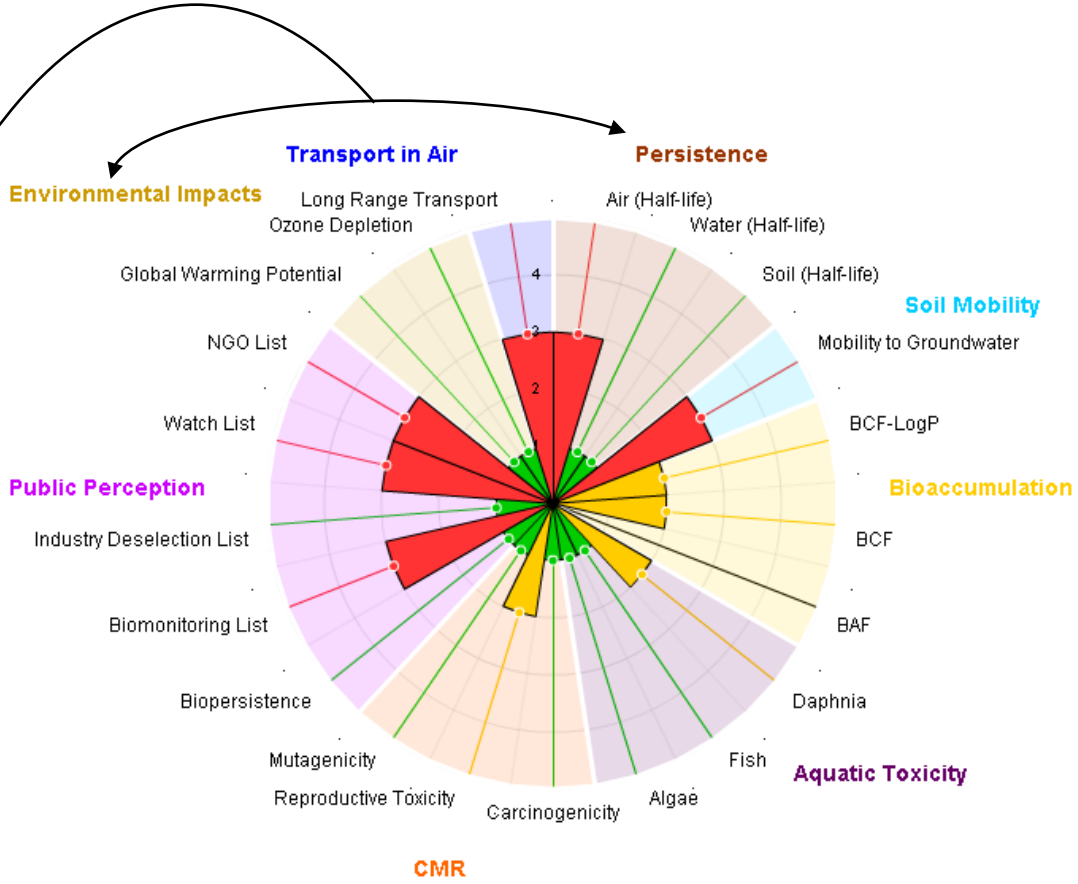
CSVT Chart


Transport in Air
Persistence
Environmental Impacts
Long Range Transport
Air (Half-life)
Ozone Depletion
Water (Half-life)
Global Warming Potential
Soil (Half-life)
Soil Mobility
NGO List
Mobility to Groundwater
Watch List
BCF-LogP
Public Perception
Bioaccumulation
Industry Deselection List
BCF
Biomonitoring List
BAF
Biopersistence
Daphnia
Mutagenicity
Fish
Aquatic Toxicity
Reproductive Toxicity
Algae
Carcinogenicity
CMR
4
3
2
1

Chemical Attributes

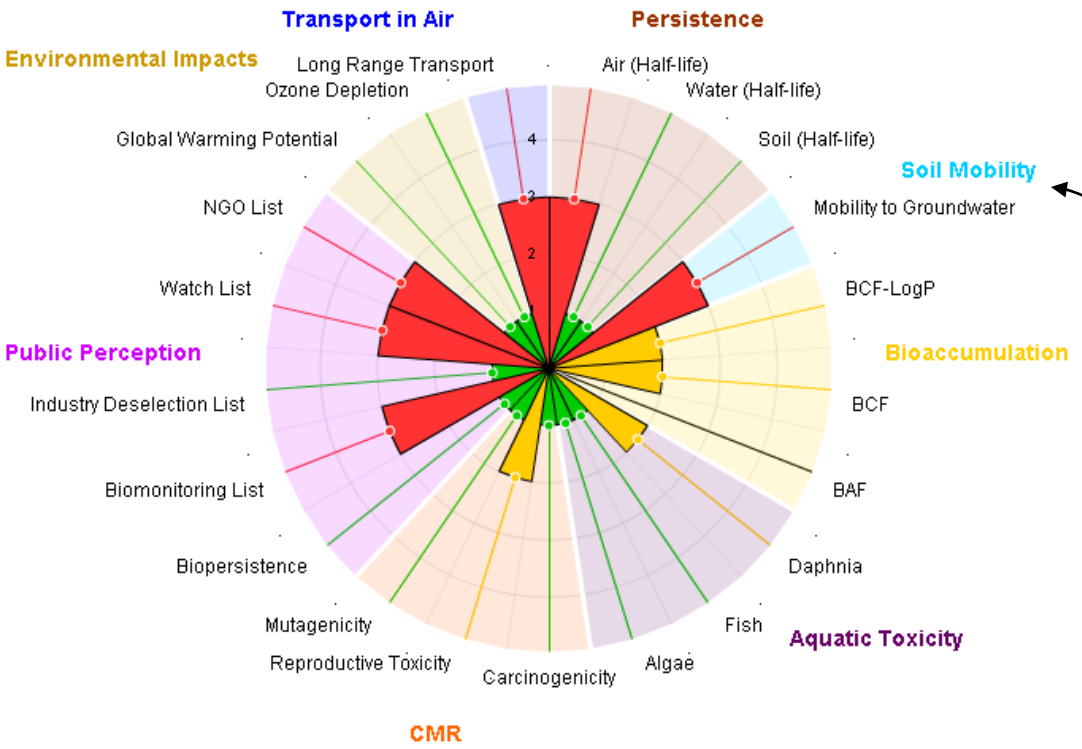
- **Environmental Persistence** – indicates the predicted half-life in each environmental compartment.
- **Soil Mobility** – the potential for a chemical to migrate from soil into groundwater
- **Bioaccumulation** – uses measured or estimated values to indicate the potential for a chemical to sorb to 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



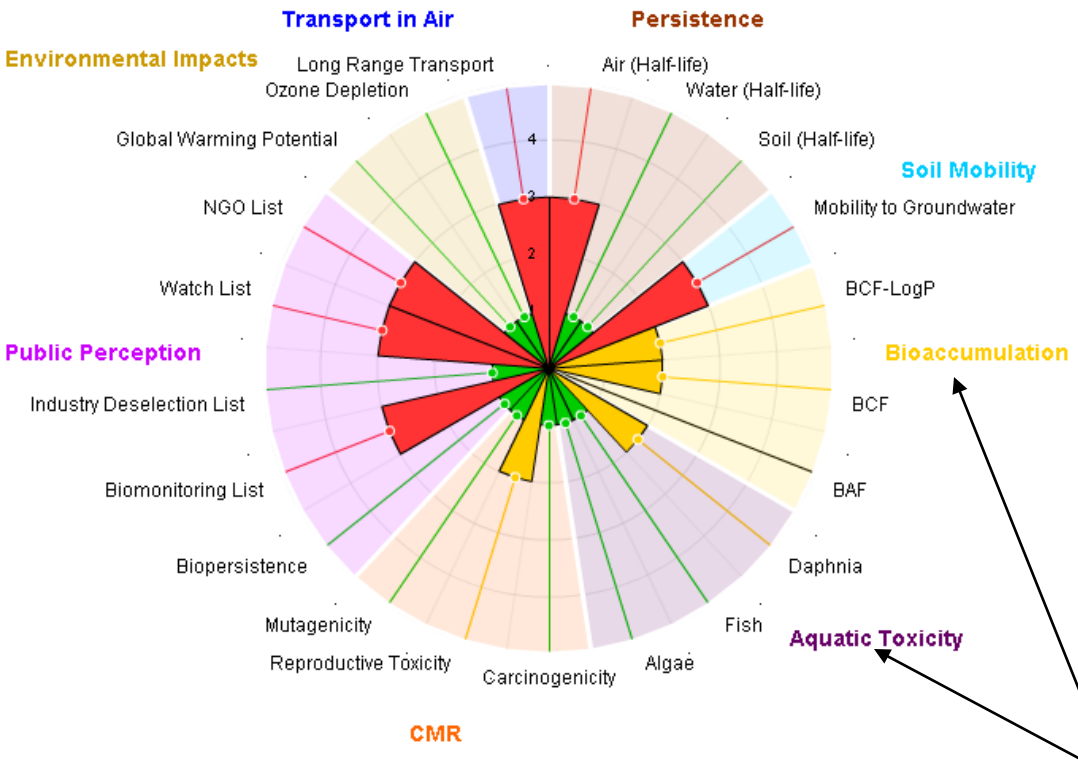
Persistent in Air (>2 days) with potential for long-range transport. Not considered to be persistent in water and/or soil nor contribute to Global Warming and/or Ozone Depletion.

Inherent Hazards – Mobility



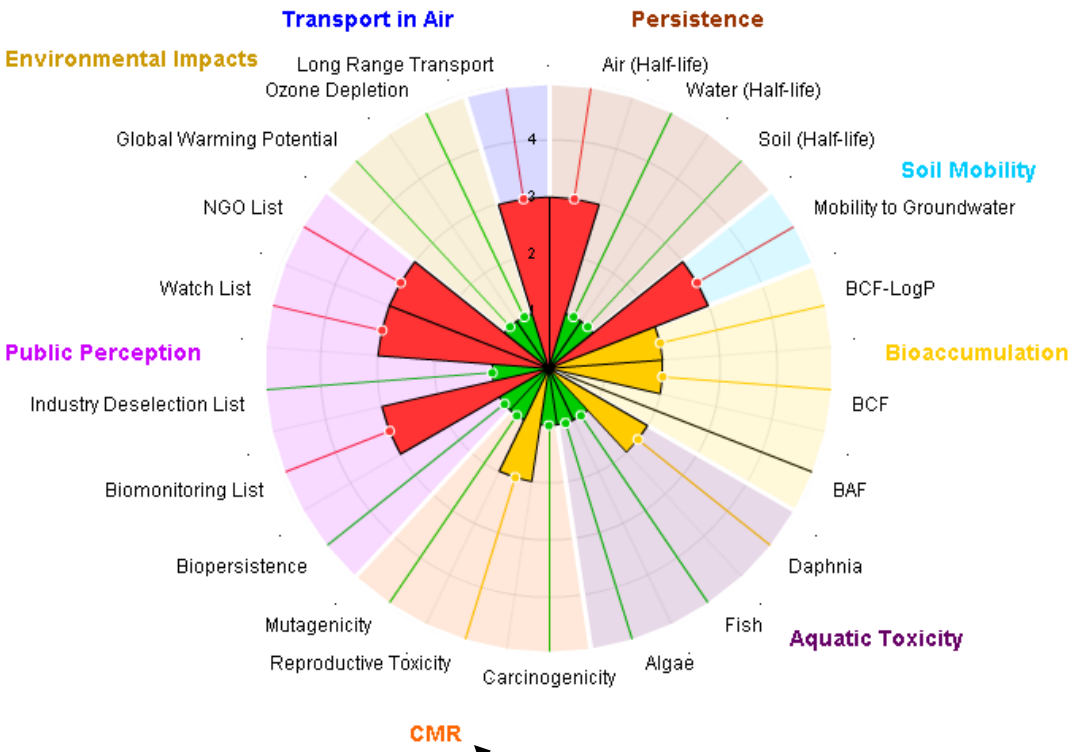
Based on the Soil Adsorption Coefficient (LogKoc), this compound has a high potential to migrate to groundwater.

Inherent Hazards – Aquatic Environment



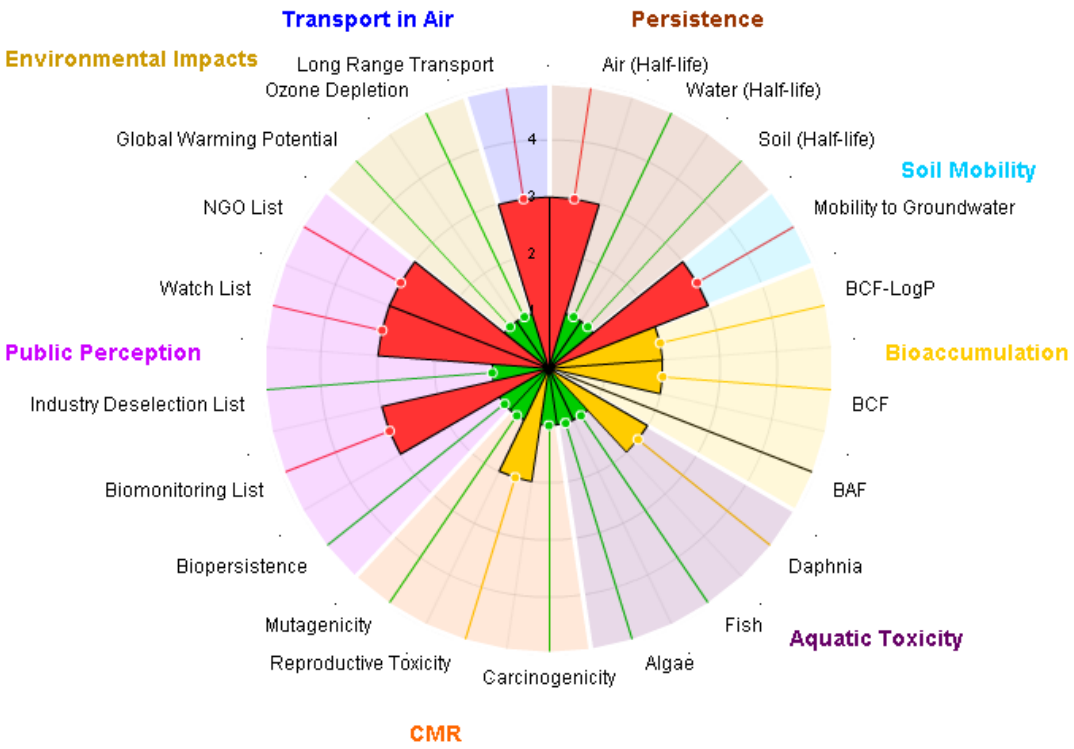
In an aquatic environment, this compound has a moderate potential for bioaccumulation based on an experimental Octanol-Water Partition Coefficient (LogKow) = 2.73 and a measured LogBCF = 1.96. Based on MITI data, a measured EC50 = 4.1 mg/l indicates a moderate concern for toxicity to daphnia. Additional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

Inherent Hazards – Health Hazard



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.

Inherent Hazards – Public Perception



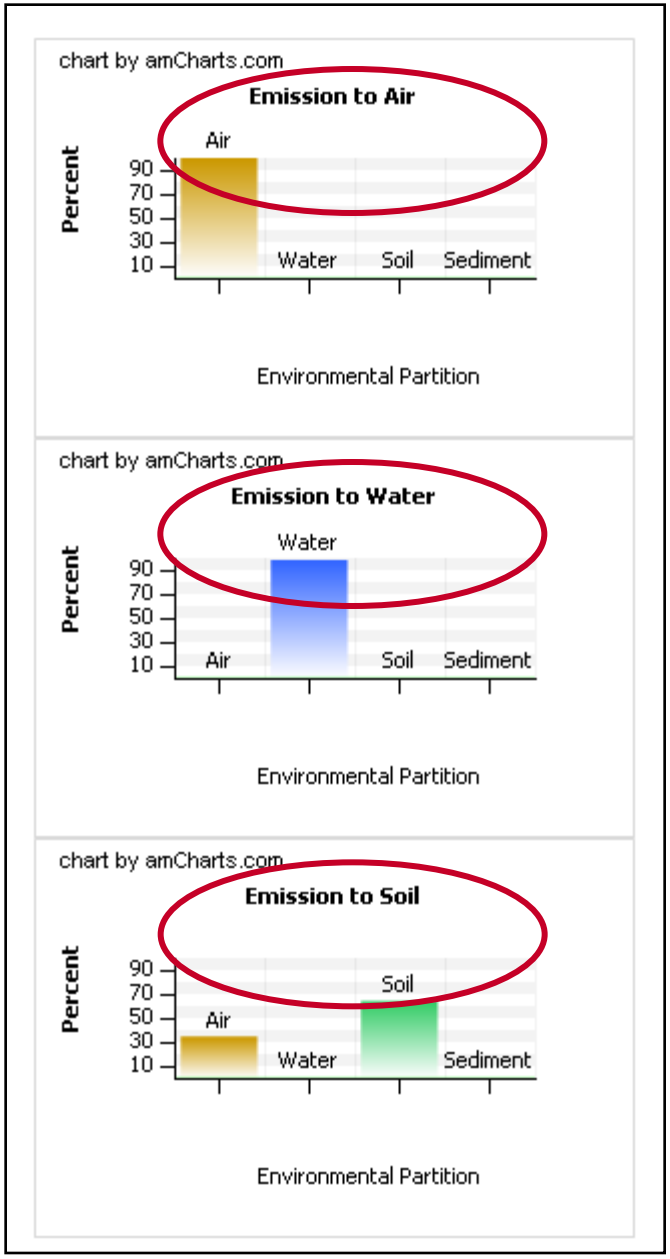
This compound is part of a biomonitoring study but has not been detected. It has not been targeted for deselection or replacement by any industry groups. It is an EU HPV, US HPV and part of the Voluntary Children's Chemical Evaluation Program (VCCEP) and is considered to be an EU REACH Priority compound.

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

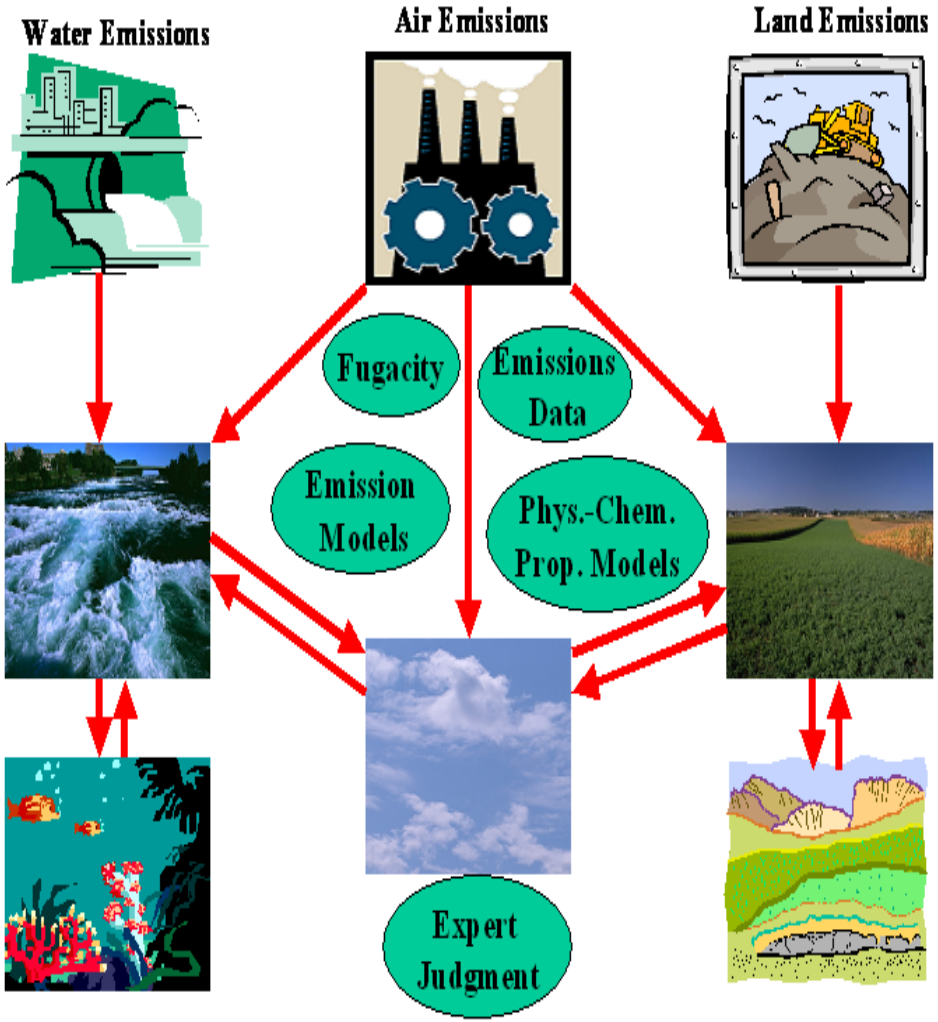
- **Exposure Science.** Consider relevant research activities for addressing gaps in exposure science required to meet both immediate needs for *rapid prioritization as well as longer term objectives for chemical evaluation and risk management*.

Meeting the objectives:

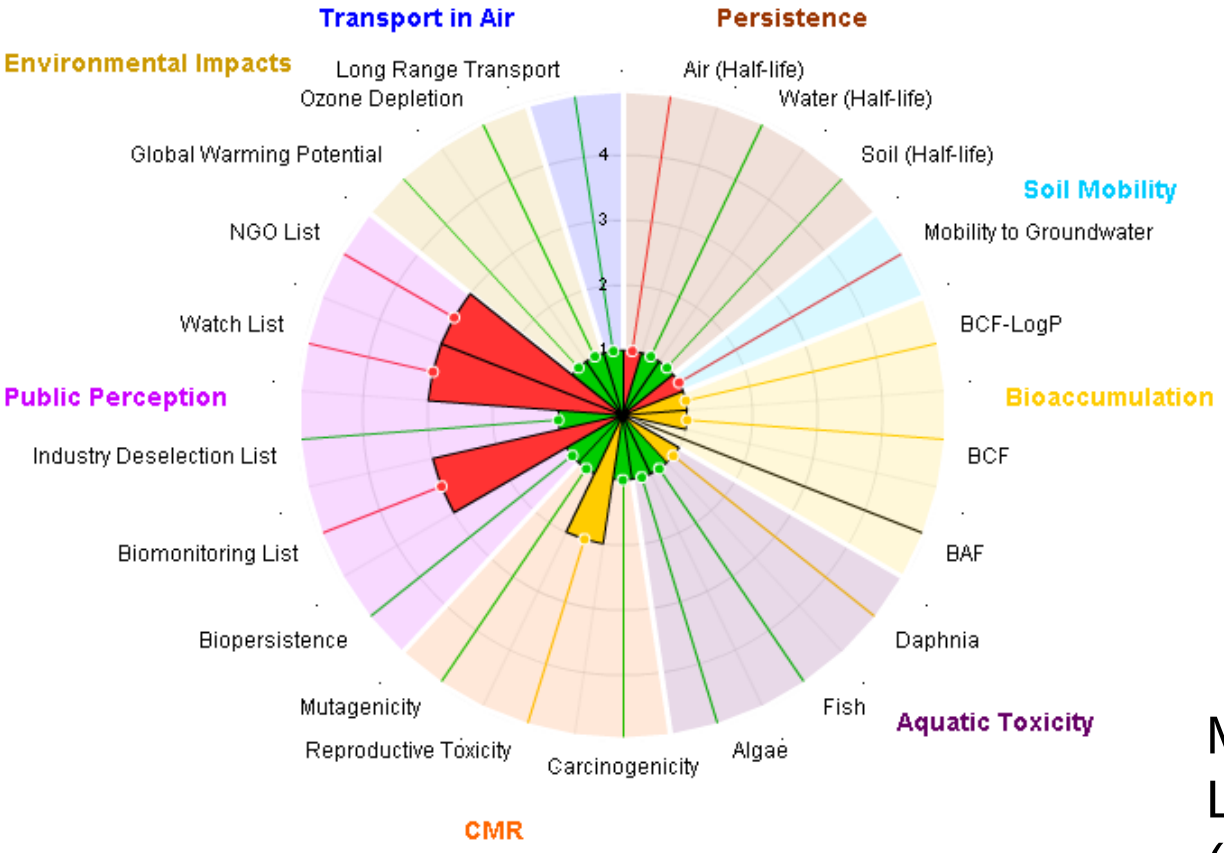
- Identifying relevant environmental partitions
- Product life stage and risk assessment
- Business applications
- Data visualization for prioritization and strategic development

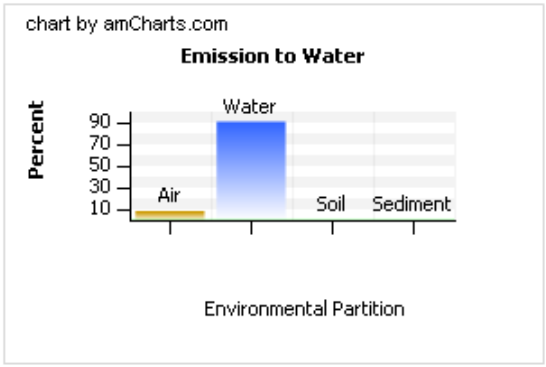


How does a chemical partition in the environment?



CSVT – Emission Scenario Example



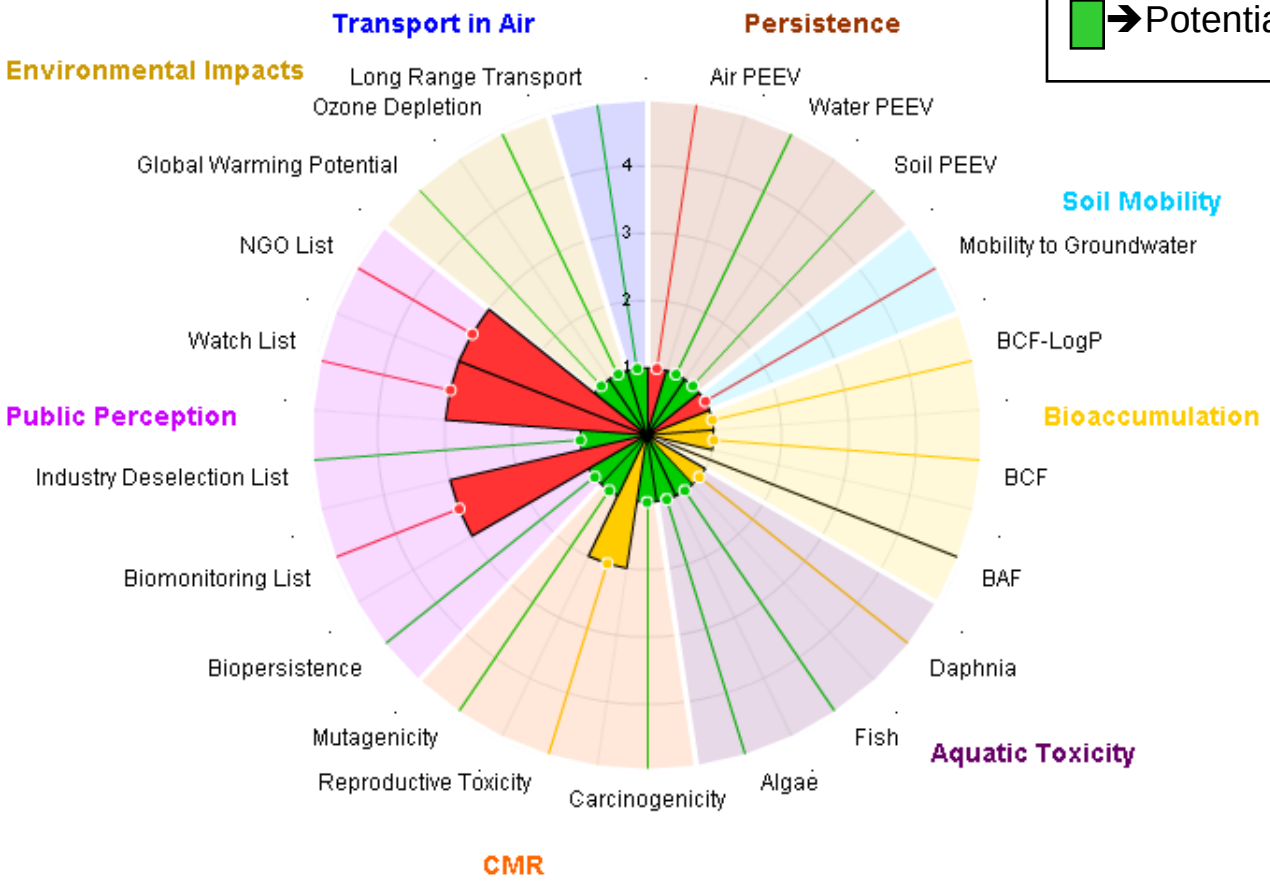


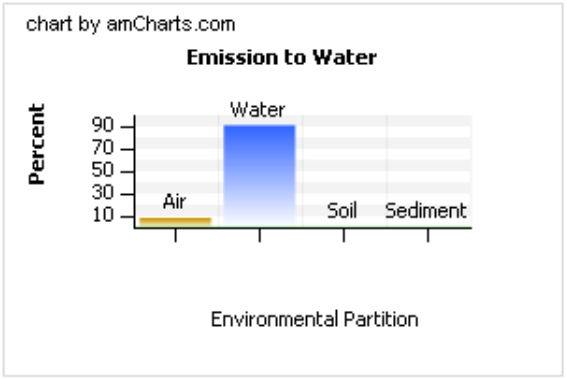
Mackay
Level III Fugacity Models
(EpiSuite v4)

Potential Environmental Exposure Value (PEEV)

Hazard Key

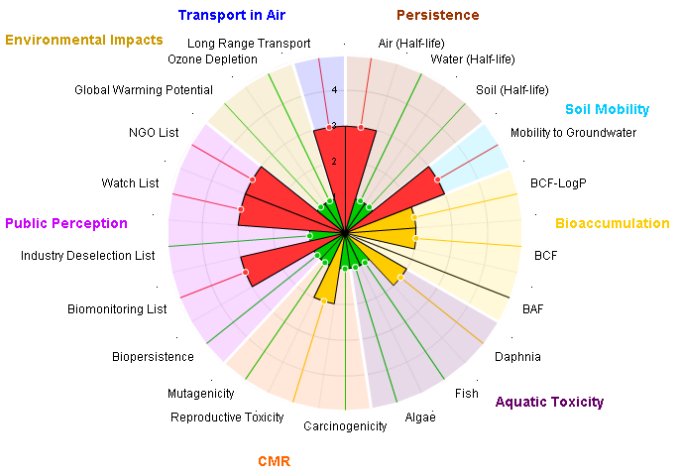
- ➔Potential for High level of concern
- ➔Potential for Moderate level of concern
- ➔Potential for Low level of concern





Hazard ➔ Color
Exposure ➔ Length

Environmental Exposure – Aquatic Environment



Inherent Hazard Assessment:

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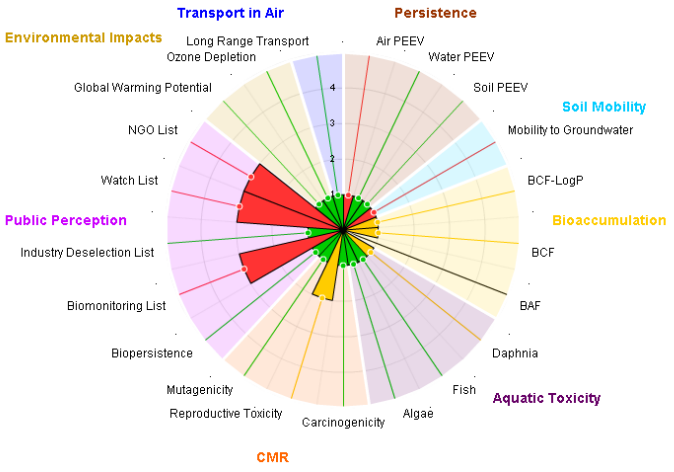
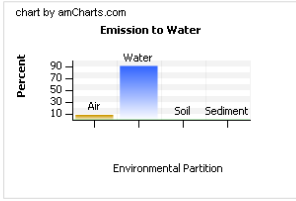
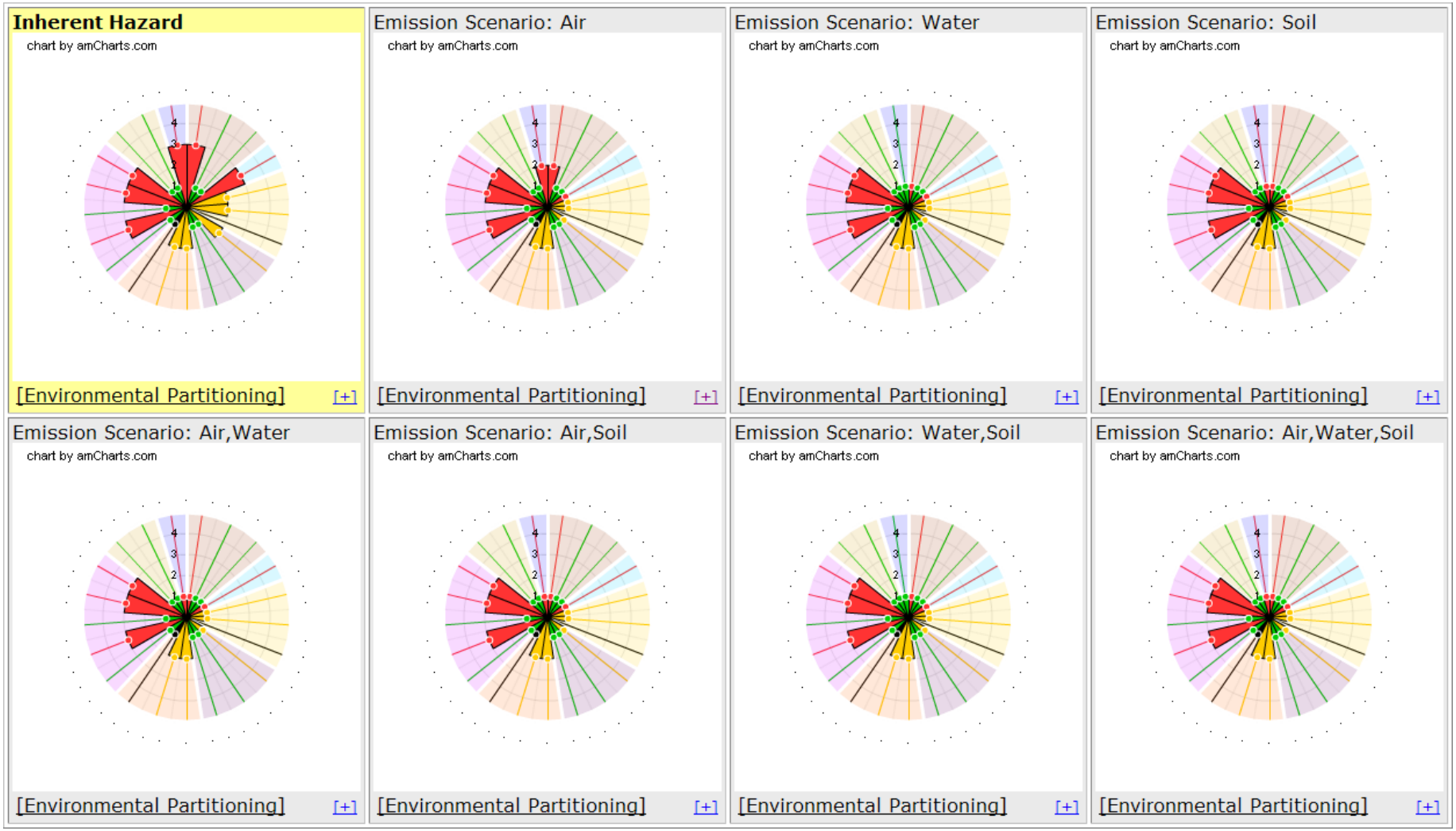




Environmental Exposure Assessment:

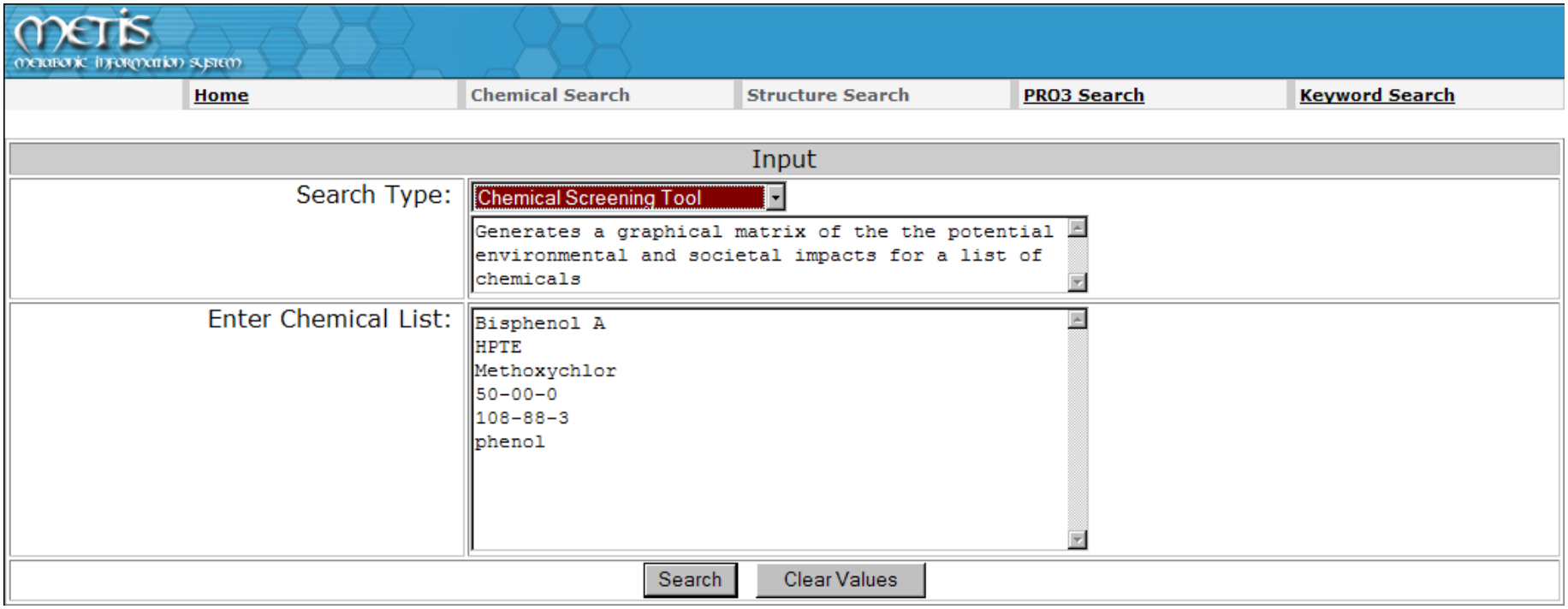
If emitted to an aquatic environment, this compound is like to remain in water with some loss to the atmosphere through volatilization. In the aquatic environment, this compound is likely to degrade and not considered to be persistent. Potential aquatic exposure is low thereby reducing the level of risk.

Inherent Hazard vs PEEV



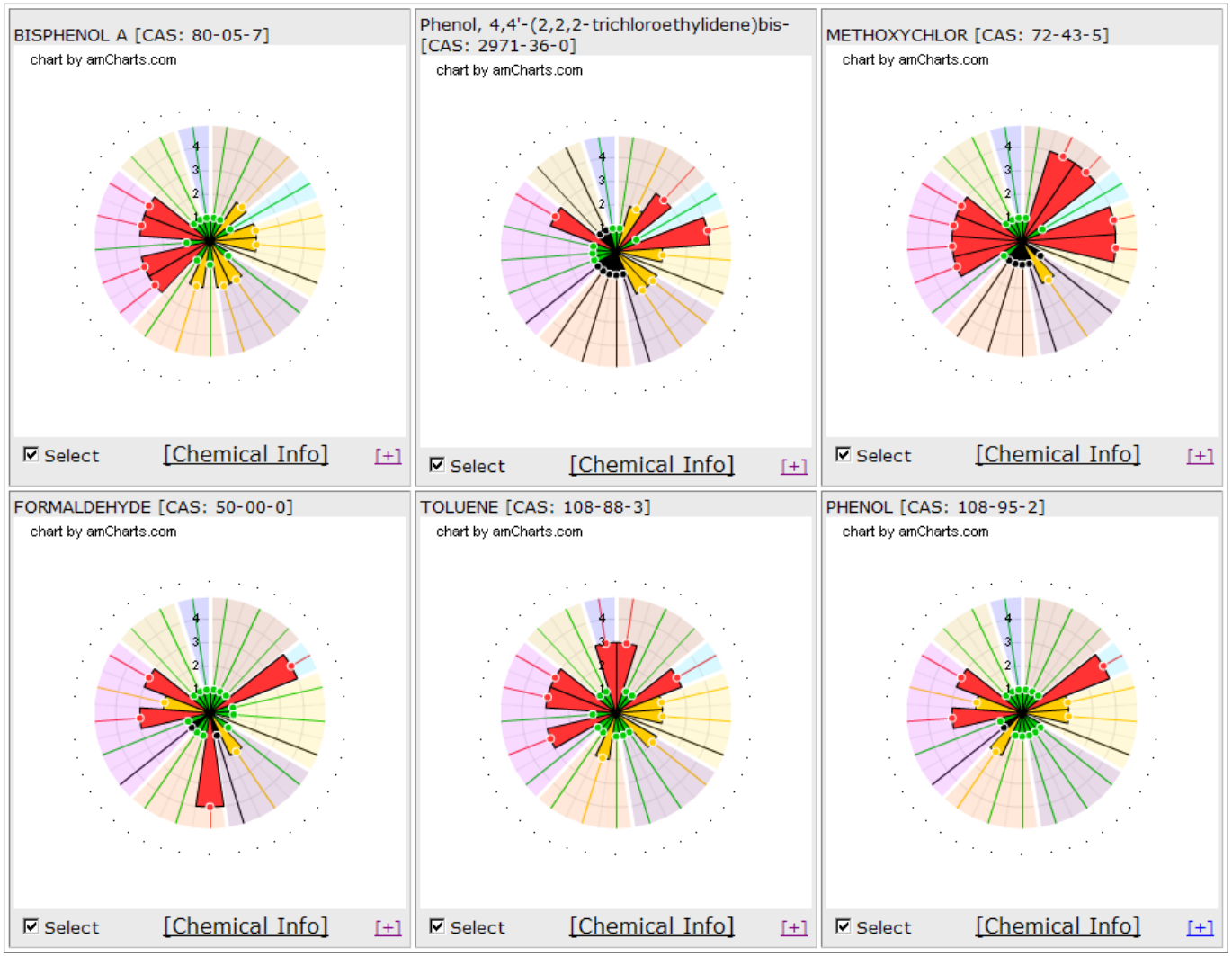
All potential emission scenarios

Multiple Chemical Search

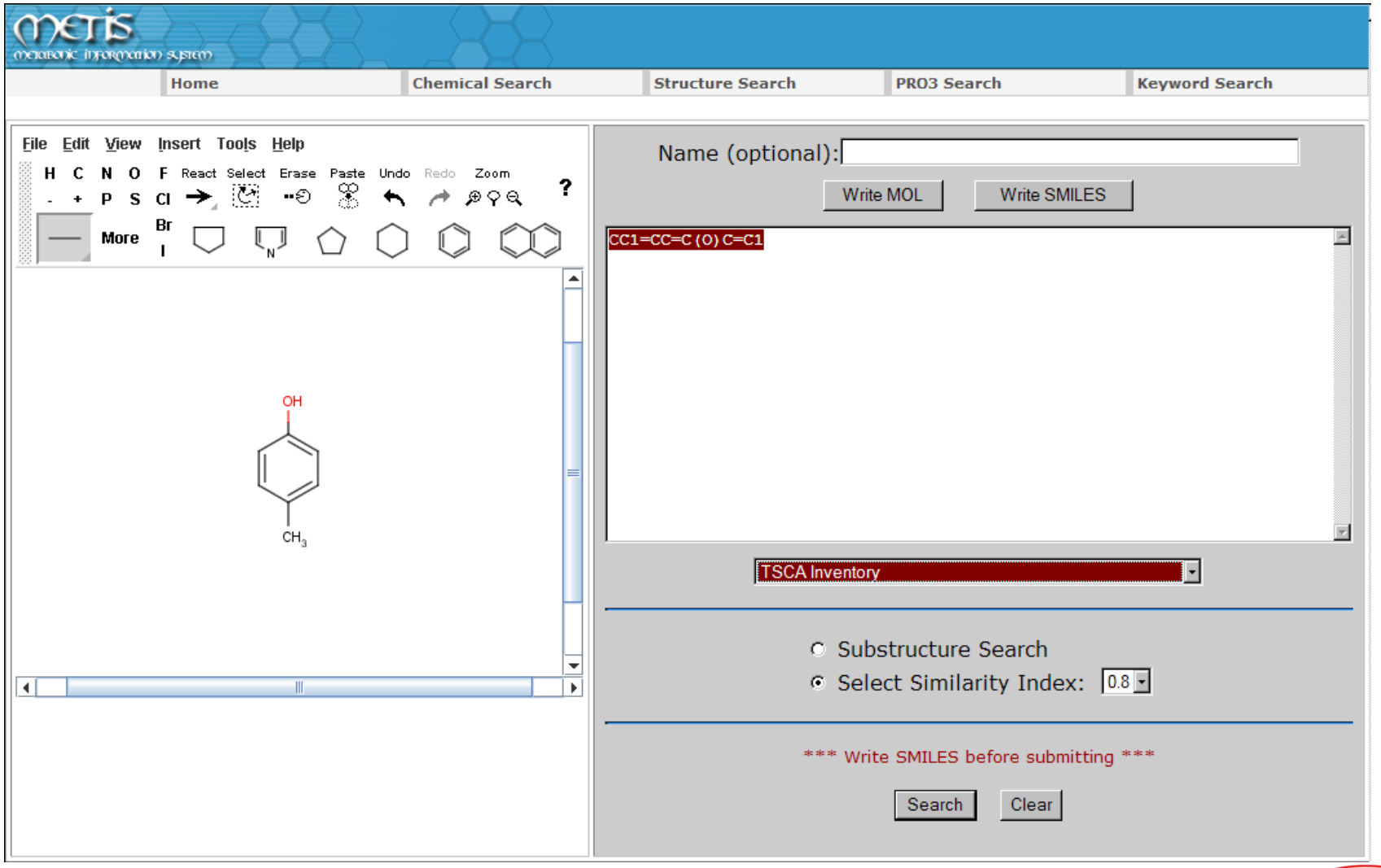


Chemicals can be entered using any type of synonym (CAS, EINECS, IUPAC or trade name, etc)

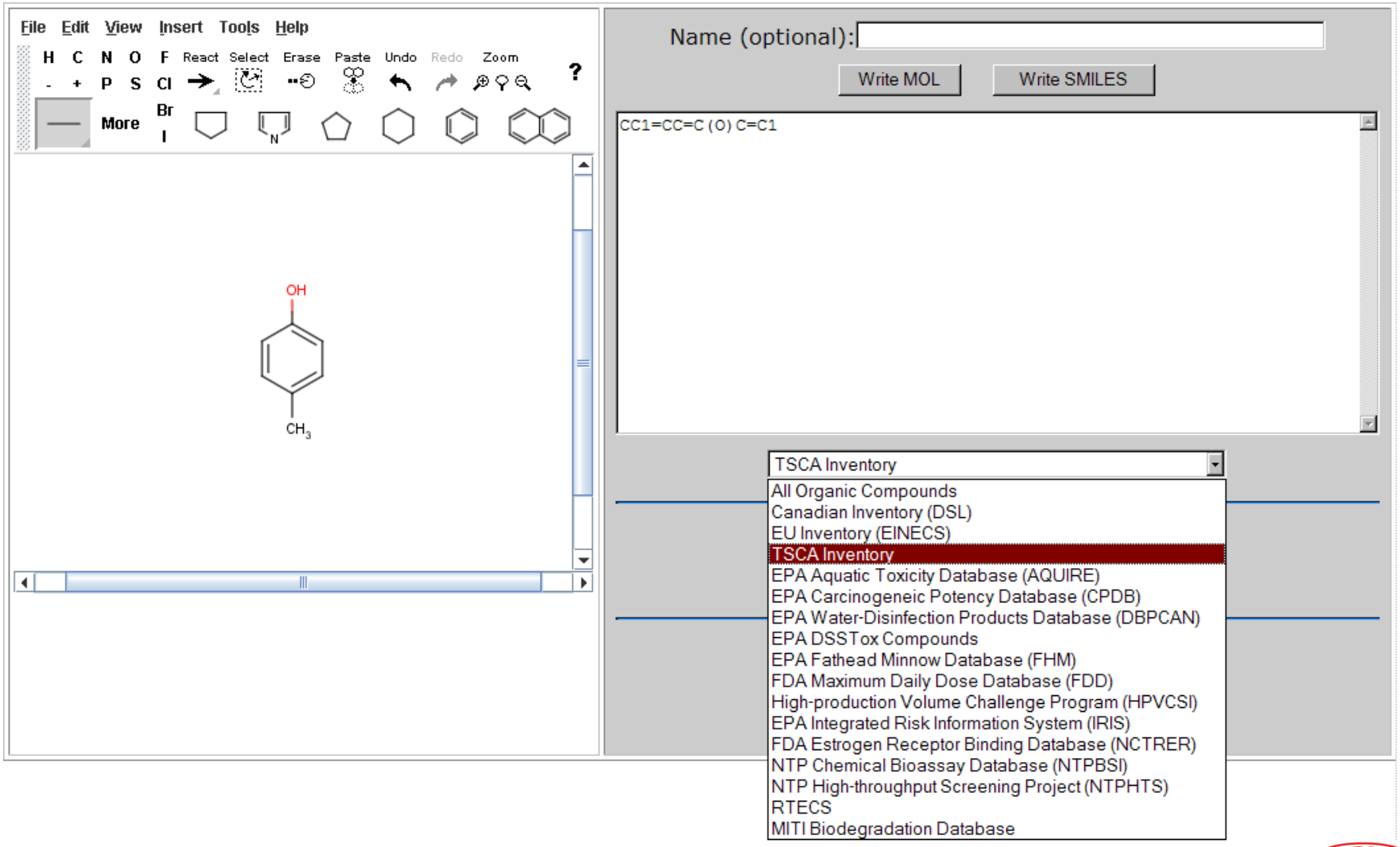
Multiple Chemical Search - Matrix



Structure Searching – Structure Input

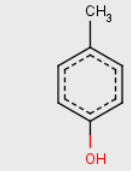
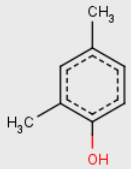
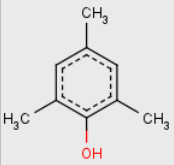
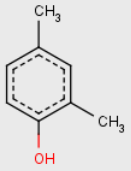
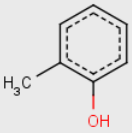


Structure Searching – Database Selection



Structure Searching - Results

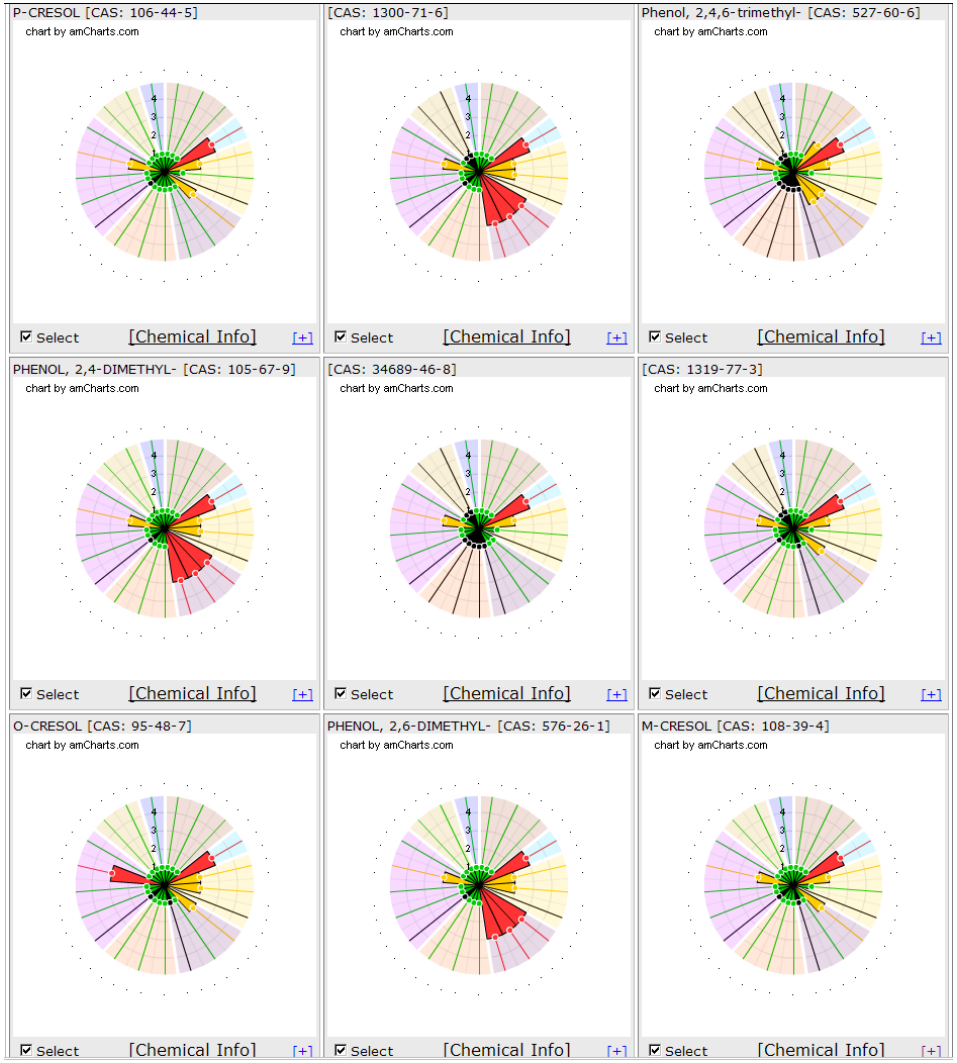
Please select an option | Get View | Clear Selections | View DSL Clusters

	CAS	Tanimoto Coefficient	Structure	Canadian DSL Classification		
				Persistence	Bioaccumulation	Inherent Toxicity
☑	106-44-5	1.00		Not P - Exp	Not B - QSAR	Not iT - Exp
☑	1300-71-6	0.90		Not P - Exp	Not B - QSAR	Not iT - QSAR
☑	527-60-6	0.90		Not P - QSAR	Not B - Exp	Not iT - Exp
☑	105-67-9	0.90		Not P - Exp	Not B - QSAR	Not iT - Exp
☑	34689-46-8	0.90		Not P - Exp	Not B - QSAR	Not iT - QSAR

Search by:

- Structural similarity
- Structural features
- Functional similarity
- Classification
- Compound clustering

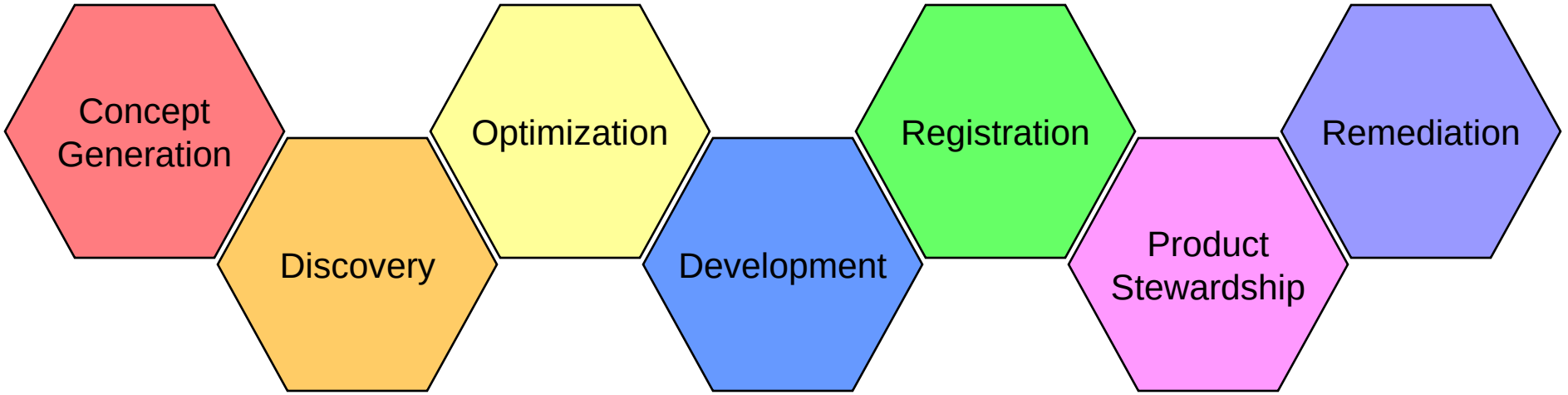
Analog Comparison



- 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

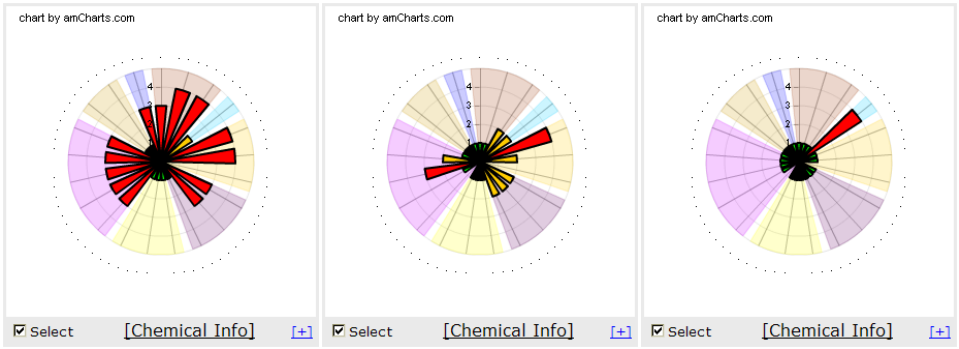
Product Stewardship

- Knowledge discovery and retention
- Three R's
  - Replacement
  - Reduction
  - Refinement

Remediation

- Evaluate potential environmental degradants
- Optimize remediation strategy

Business Applications Examples



[Matrix View]

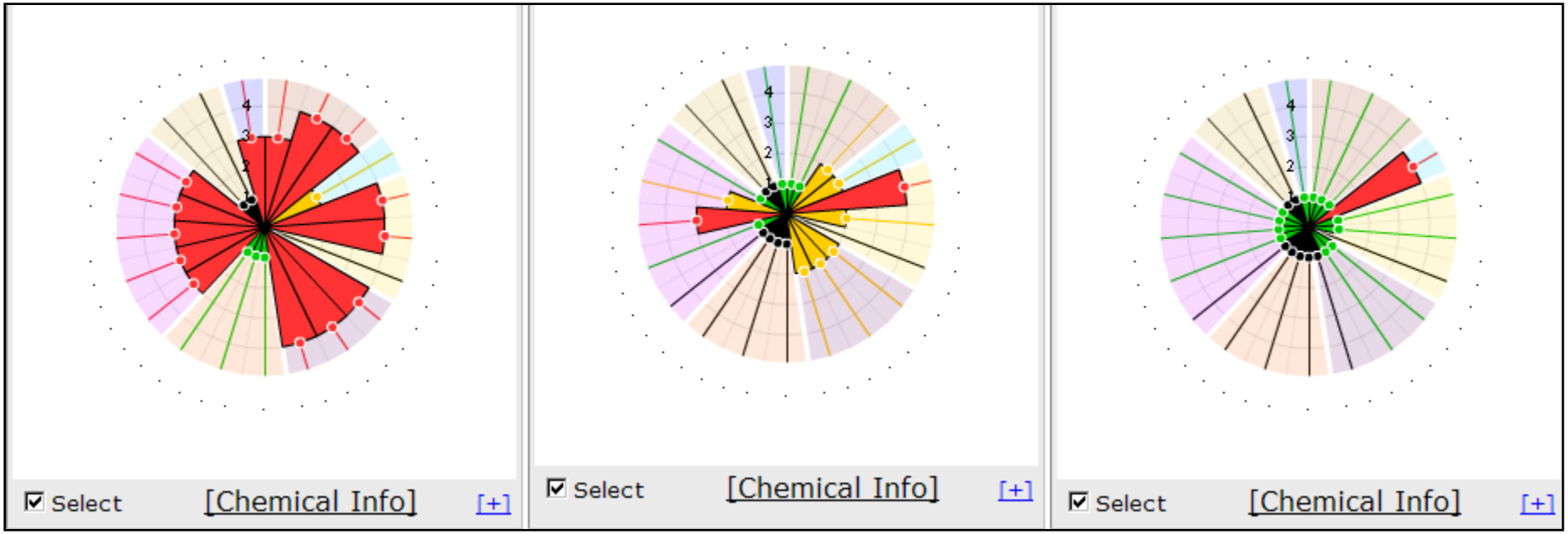
View by:

- Chemical classes
- Structural similarity
- Scaffolds
- Formulation

- 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

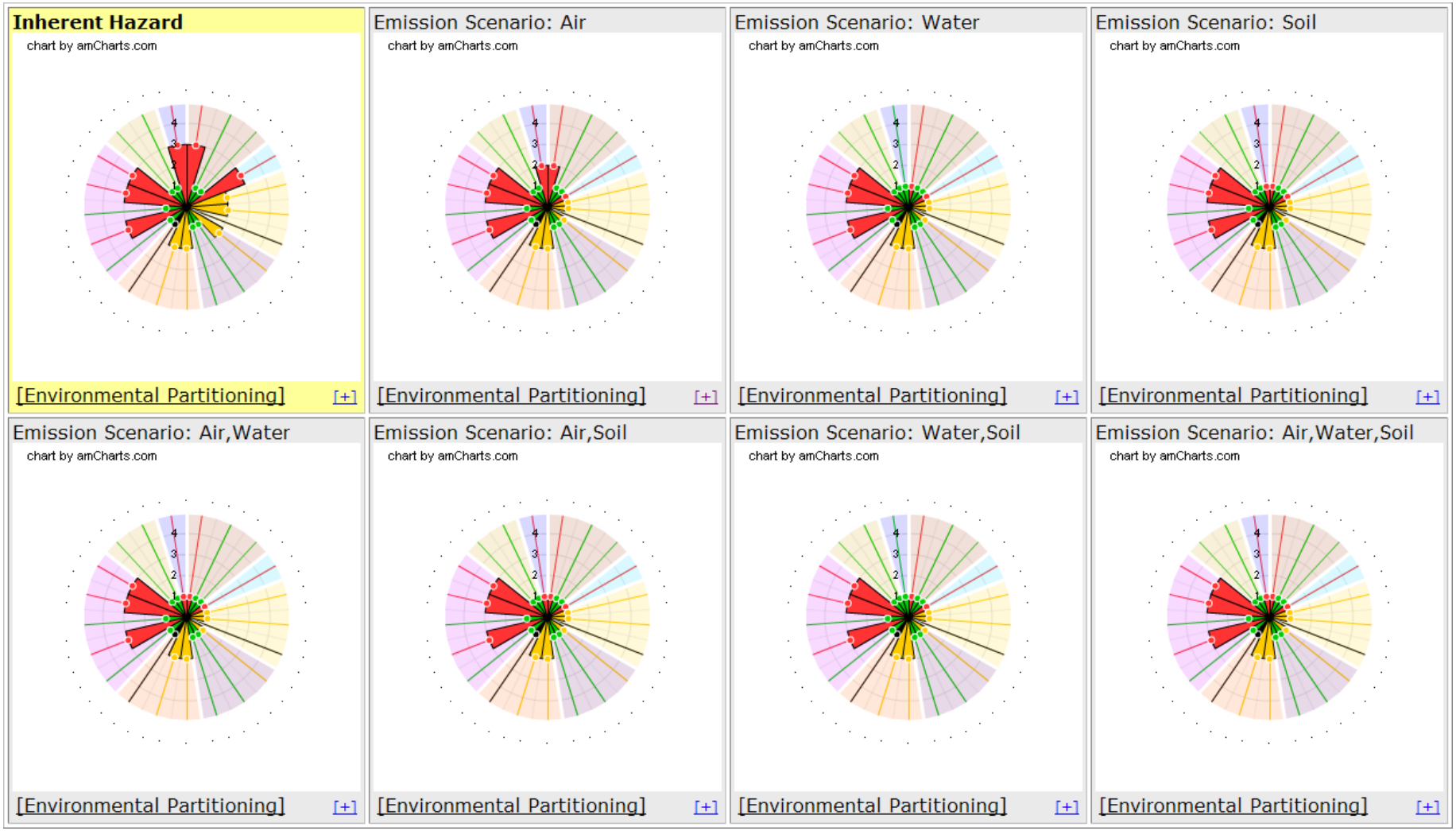
Product Selection

Selecting products with the least amount of concern?

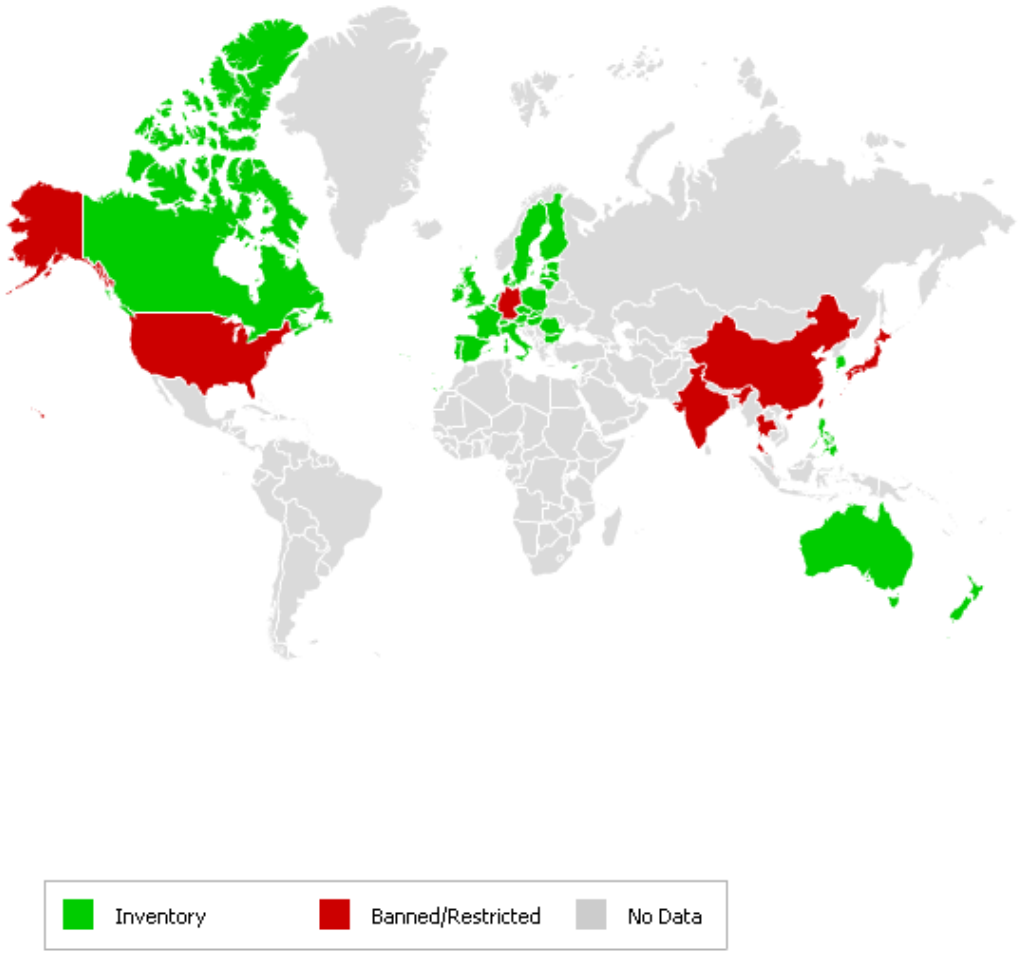


Note: Black color code indicates "No Data". This would indicate potential data gaps and trigger possible testing needs.

Remediation Strategy

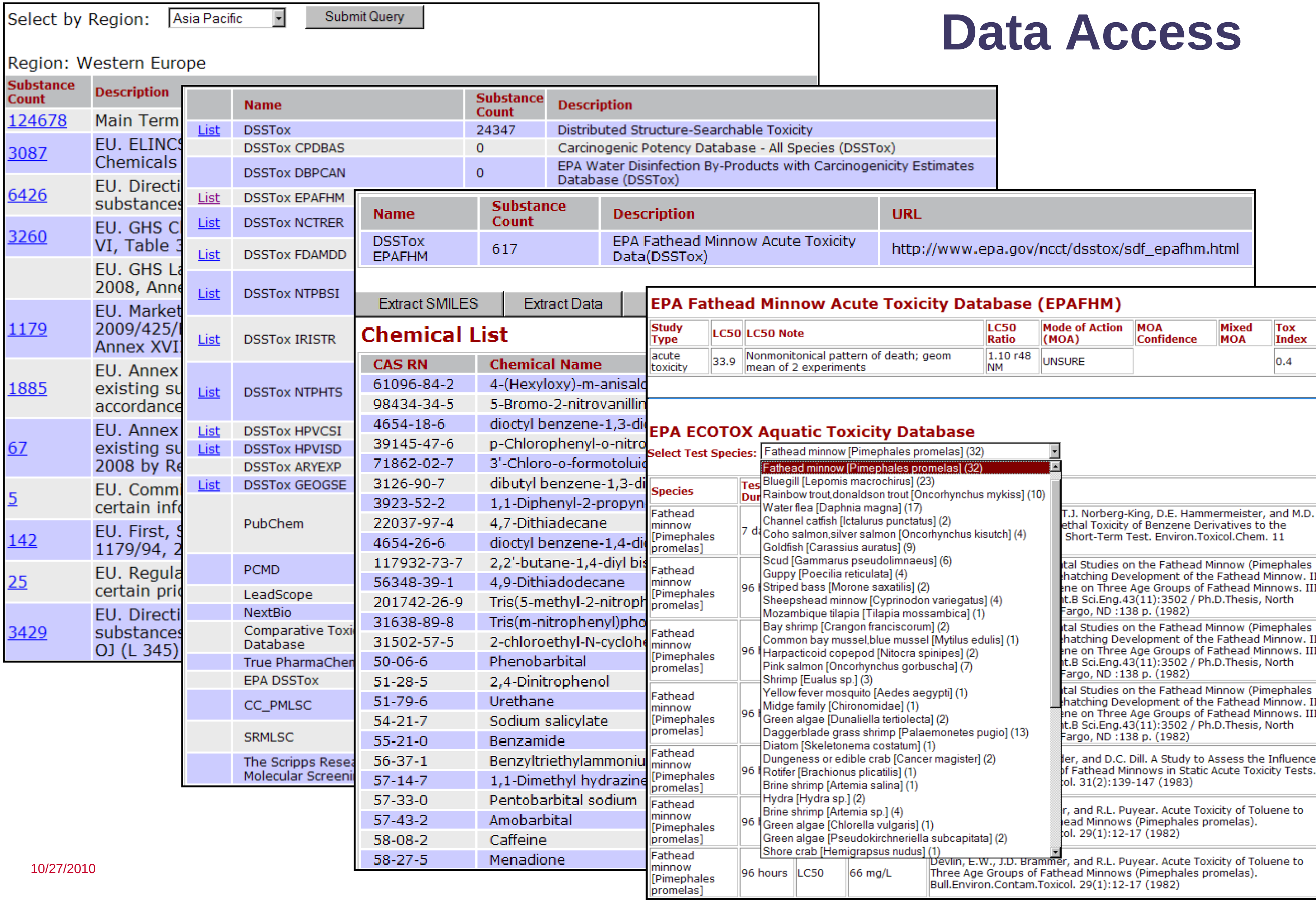


Global Inventories



- 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



Select by Region: Asia Pacific Submit Query
Region: Western Europe
Substance Count | Description
124678 Main Term
3087 EU. ELINCS Chemicals
6426 EU. Directi substances
3260 EU. GHS Cl VI, Table 3
EU. GHS La 2008, Anne
1179 EU. Market 2009/425/ Annex XVI
1885 EU. Annex existing su accordance
67 EU. Annex existing su 2008 by Re
5 EU. Commi certain info
142 EU. First, 1179/94, 2
25 EU. Regula certain pric
3429 EU. Directi substances OJ (L 345)
Name | Substance Count | Description
List DSSTox 24347 Distributed Structure-Searchable Toxicity
DSSTox CPDBAS 0 Carcinogenic Potency Database - All Species (DSSTox)
DSSTox DBPCAN 0 EPA Water Disinfection By-Products with Carcinogenicity Estimates Database (DSSTox)
List DSSTox EPAFHM
List DSSTox NCTRER
List DSSTox FDAMDD
List DSSTox NTPBSI
List DSSTox IRISTR
List DSSTox NTPHTS
List DSSTox HPVCSI
List DSSTox HPVISD
DSSTox ARYEXP
List DSSTox GEOGSE
PubChem
PCMD
LeadScope
NextBio
Comparative Toxi Database
True PharmaChem
EPA DSSTox
CC_PMLSC
SRMLSC
The Scripps Resea Molecular Screeni
Name | Substance Count | Description | URL
DSSTox EPAFHM 617 EPA Fathead Minnow Acute Toxicity Data(DSSTox) http://www.epa.gov/ncct/dsstox/sdf_epafhm.html
Extract SMILES
Extract Data
Chemical List
CAS RN | Chemical Name
61096-84-2 4-(Hexyloxy)-m-anisald
98434-34-5 5-Bromo-2-nitrovanillin
4654-18-6 dioctyl benzene-1,3-di
39145-47-6 p-Chlorophenyl-o-nitro
71862-02-7 3'-Chloro-o-formotolui
3126-90-7 dibutyl benzene-1,3-di
3923-52-2 1,1-Diphenyl-2-propyn
22037-97-4 4,7-Dithiadecane
4654-26-6 dioctyl benzene-1,4-di
117932-73-7 2,2'-butane-1,4-diyl bis
56348-39-1 4,9-Dithiadodecane
201742-26-9 Tris(5-methyl-2-nitroph
31638-89-8 Tris(m-nitrophenyl)pho
31502-57-5 2-chloroethyl-N-cyclohe
50-06-6 Phenobarbital
51-28-5 2,4-Dinitrophenol
51-79-6 Urethane
54-21-7 Sodium salicylate
55-21-0 Benzamide
56-37-1 Benzyltriethylammoniu
57-14-7 1,1-Dimethyl hydrazine
57-33-0 Pentobarbital sodium
57-43-2 Amobarbital
58-08-2 Caffeine
58-27-5 Menadione
EPA Fathead Minnow Acute Toxicity Database (EPAFHM)
Study Type | LC50 | LC50 Note | LC50 Ratio | Mode of Action (MOA) | MOA Confidence | Mixed MOA | Tox Index
acute toxicity | 33.9 | Nonmonitonical pattern of death; geom mean of 2 experiments | 1.10 r48 NM | UNSURE | | | 0.4
EPA ECOTOX Aquatic Toxicity Database
Select Test Species: Fathead minnow [Pimephales promelas] (32)
Fathead minnow [Pimephales promelas] (32)
Bluegill [Lepomis macrochirus] (23)
Rainbow trout,donaldson trout [Oncorhynchus mykiss] (10)
Water flea [Daphnia magna] (17)
Channel catfish [Ictalurus punctatus] (2)
Coho salmon,silver salmon [Oncorhynchus kisutch] (4)
Goldfish [Carassius auratus] (9)
Scud [Gammarus pseudolimnaeus] (6)
Guppy [Poecilia reticulata] (4)
Striped bass [Morone saxatilis] (2)
Sheepshead minnow [Cyprinodon variegatus] (4)
Mozambique tilapia [Tilapia mossambica] (1)
Bay shrimp [Crangon franciscorum] (2)
Common bay mussel,blue mussel [Mytilus edulis] (1)
Harpacticoid copepod [Nitocra spinipes] (2)
Pink salmon [Oncorhynchus gorbuscha] (7)
Shrimp [Eualus sp.] (3)
Yellow fever mosquito [Aedes aegypti] (1)
Midge family [Chironomidae] (1)
Green algae [Dunaliella tertiolecta] (2)
Daggerblade grass shrimp [Palaemonetes pugio] (13)
Diatom [Skeletonema costatum] (1)
Dungeness or edible crab [Cancer magister] (2)
Rotifer [Brachionus plicatilis] (1)
Brine shrimp [Artemia salina] (1)
Hydra [Hydra sp.] (2)
Brine shrimp [Artemia sp.] (4)
Green algae [Chlorella vulgaris] (1)
Green algae [Pseudokirchneriella subcapitata] (2)
Shore crab [Hemigrapsus nudus] (1)
Species
Fathead minnow [Pimephales promelas]
T.J. Norberg-King, D.E. Hammermeister, and M.D. ethal Toxicity of Benzene Derivatives to the Short-Term Test. Environ.Toxicol.Chem. 11
tal Studies on the Fathead Minnow (Pimephales hatching Development of the Fathead Minnow. II. ne on Three Age Groups of Fathead Minnows. III. t.B Sci.Eng.43(11):3502 / Ph.D.Thesis, North Fargo, ND :138 p. (1982)
der, and D.C. Dill. A Study to Assess the Influence of Fathead Minnows in Static Acute Toxicity Tests. ol. 31(2):139-147 (1983)
r, and R.L. Puyear. Acute Toxicity of Toluene to ead Minnows (Pimephales promelas). ol. 29(1):12-17 (1982)
Fathead minnow [Pimephales promelas] 96 hours LC50 66 mg/L Devlin, E.W., J.D. Brammer, and R.L. Puyear. Acute Toxicity of Toluene to Three Age Groups of Fathead Minnows (Pimephales promelas). Bull.Environ.Contam.Toxicol. 29(1):12-17 (1982)

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