

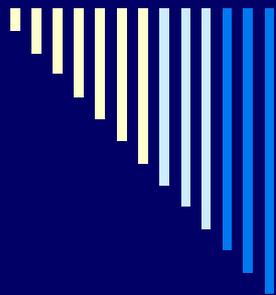
U.S. EPA QSAR and Expert System Tools for Predicting Toxicity

Tala Henry

**Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, DC**

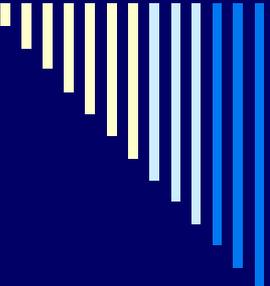


Cal/EPA Symposium
Sacramento, California
October 2, 2007



Office of Pollution Prevention and Toxics

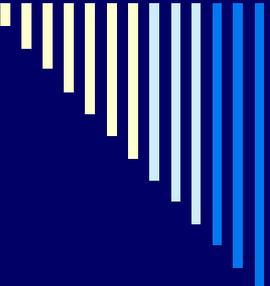
- Review Pre-Manufacture Notices (PMN) for new industrial chemicals
- Testing, assessment, and risk reduction of existing industrial chemicals
- Management of “national chemicals” (e.g. PCBs, Hg)
- International chemical issues (e.g. POPs)
- Pollution prevention advocacy
- Partnership programs, e.g. HPVC Challenge, Green Suppliers Network, DfE and Green Chemistry



Overview of Screening Level Models

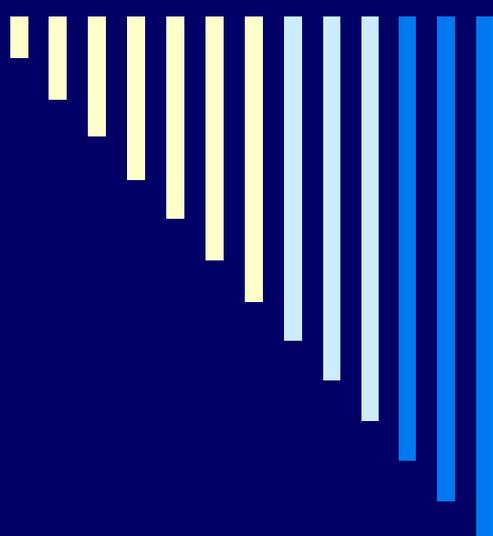
- Analogs & Categories
- AIM
- ECOSAR
- Oncologic[®]
- PBT Profiler

- EPI Suite[™]
- ChemSTEER
- E-FAST

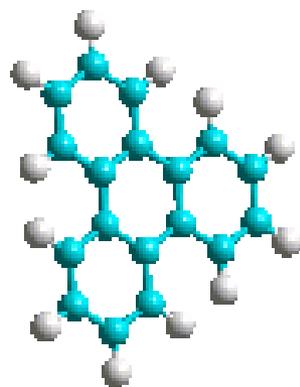


Analogs & Categories

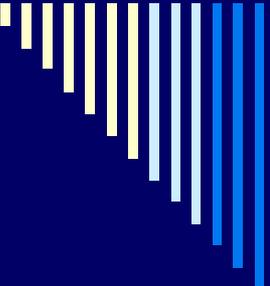
- Analogs - chemicals whose physicochemical and toxicological properties are likely to be similar as a result of structural similarity.
- Category - A group of analogs
- Similarities based on:
 - a common functional group (e.g., aldehyde, epoxide, ester, etc.)
 - common precursors and/or breakdown products
 - similar biological mechanisms of action
- Analogs & Categories Facilitate:
 - Evaluation of the reliability of model estimates
 - Filling data gaps
 - Evaluations based on a greater weight of evidence
 - Strategic testing
 - Identification of safer alternative or substitutes



Analog Identification Methodology (AIM)



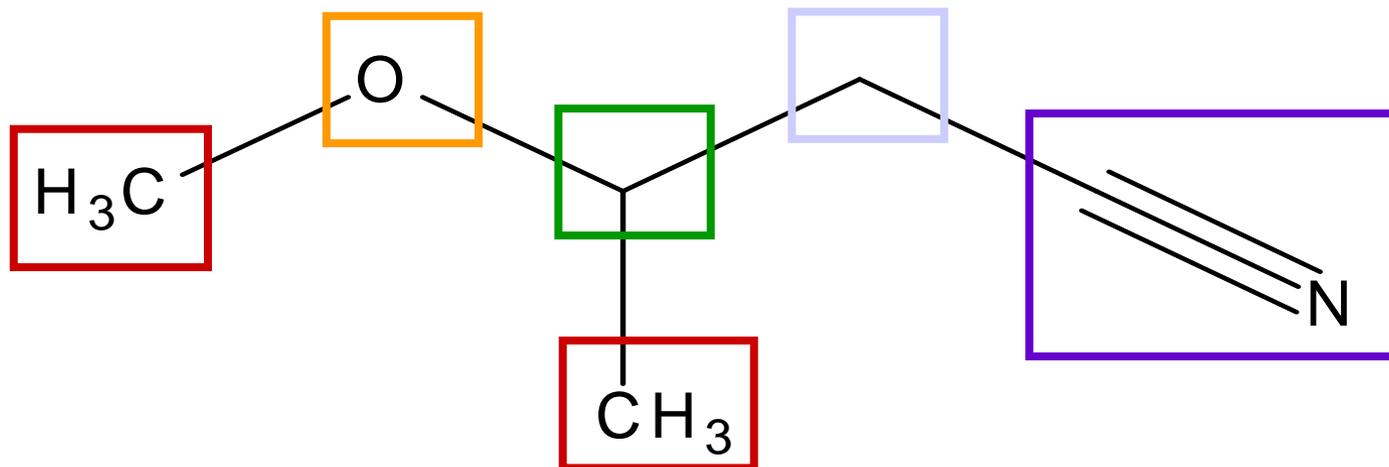
**Analog
Identification
Methodology**



AIM Methodology

- A pre-indexed database of 645 molecular fragments
- A second database with links to [publicly available toxicity data](#)
 - 31,031 potential analogs with publicly available toxicity data
 - On-Line Databases: TSCATS, HSDB, IRIS
 - U.S. Government Documents
 - NTP, ATSDR, HPV Challenge Program
 - Other Sources: RTECS, IUCLID, AEGLS

AIM identifies analogs using a chemical fragment-based approach with 645 individual *fragments* indexed in the database.



-CH₃ [aliphatic carbon]

-O- [oxygen, aliphatic attach]

-CH₂- [aliphatic carbon]

-CH [aliphatic carbon]

-C#N [cyano, aliphatic attachment]



Analog Identification Methodology

The Analog Identification Methodology (AIM) was designed to help identify publicly available, experimental toxicity data on closely related chemical structures

Main

CAS

SMILES

Name

Draw

Results

The AIM database contains 31,031 chemicals.

[Home](#)

[Methodology](#)

[Data Sources](#)

[Security and Anonymity](#)

[Terms of Use](#)

[Comments](#)

The following chemical will be run in AIM:

CAS Number:

141322

Update CAS

Chemical Name:

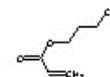
2-Propenoic acid, butyl ester

Update Name

Smiles Notation:

O=C(OCCCC)C=C

Chemical Structure:

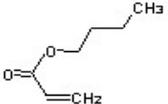


Find Analogs

Clear All

Found 12 Analog(s) for 2-Propenoic acid, butyl ester:

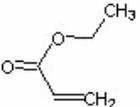
Exact Chemical Match:

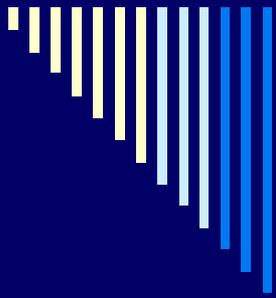
# of Studies: 3	BUTYL ACRYLATE [CAS No. 141-32-2]		
	Toxicity Data Available for this Compound		
	On-Line Databases	U.S. Government Documents	Other Sources
	TSCATS HSDB		RTECS IUCLID

▶ Based on its structure, this chemical may belong to the acrylates/methacrylates. Members of this category may have potential human health concerns. [More information and category definitions](#)

▶ This compound may metabolize in the body to products that may cause concerns for human health. Analogs for metabolites should also be investigated. Metabolism classes found: terminal double bond, ester, and acrylate

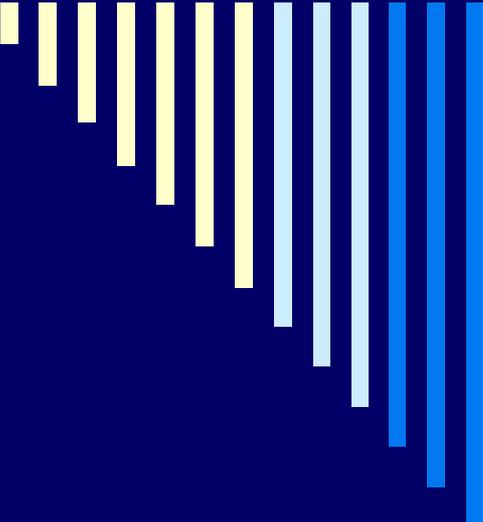
Analogs, Ordered by Number of Studies:

# of Studies: 5	ETHYL ACRYLATE [CAS No. 140-88-5]		
<u>Analog # 1</u> 	Toxicity Data Available for this Compound		
	On-Line Databases	U.S. Government Documents	Other Sources
	TSCATS HSDB	NTP	RTECS IUCLID DSSTox Cancer



Screening Level Tools and Models

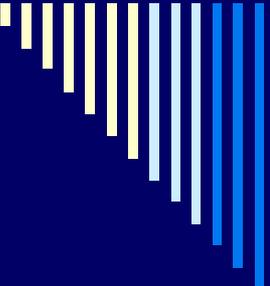
- “Best estimate” of the real value
- Intended to be used in the absence of data
- Enable OPPT to quickly screen and identify chemicals of potential concern
- Provides guidance for developing safer chemicals



ECOSAR

Aquatic toxicity estimates based on
Structure Activity Relationships (SAR)

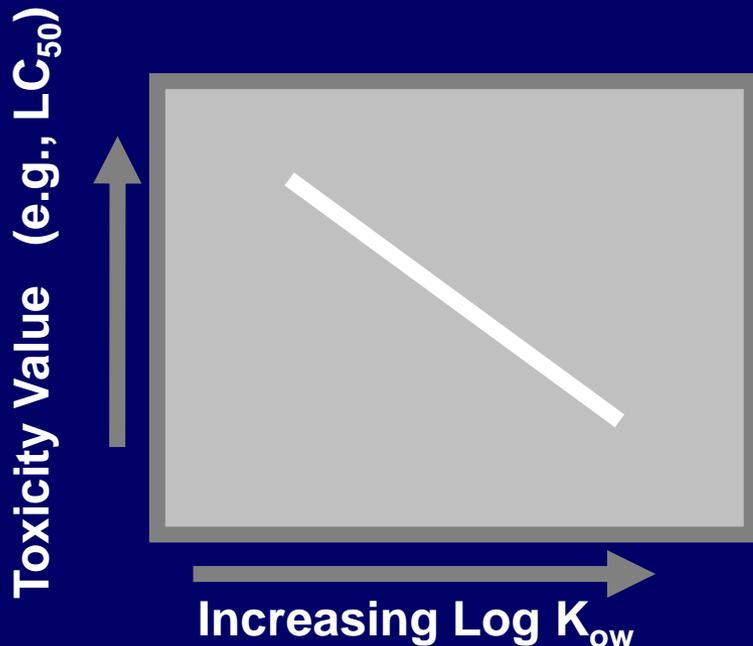




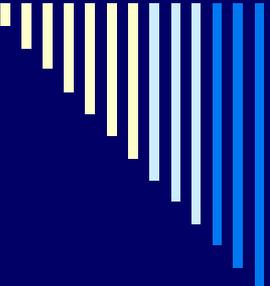
What is ECOSAR?

- A library of QSARs for predicting aquatic toxicity and an expert system for selecting the appropriate QSAR
 - Acute and chronic toxicity endpoints
 - Fish, aquatic invertebrates, algae, and others
- Extensive documentation and User's Manual

How ECOSAR Predicts Toxicity



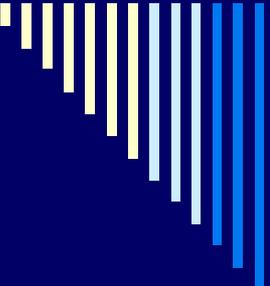
- Chemicals are grouped into classes. For **most** classes, regression equations relate *predicted* log K_{ow} to toxicity
 - Example SAR, acrylates
 - $\log \text{LC}_{50} \text{ (mM/L)} = -1.46 - 0.18 \log K_{ow}$
- SARs are based on measured toxicity data
 - Toxicity is predicted at pH 7, TOC < 2 mg/L, moderate water hardness (150 mg/L CaCO₃), 100% active ingredient



Chemical Domains in ECOSAR

- Neutral Organics
- Classes with Excess Toxicity
- Surfactants
- Polymers*
- Dyes*
- Inorganics*
- Organometallics*

* SARs for polymers, organometallics, or inorganics are not yet available, and only a limited number of dye SARs are available in the current version of ECOSAR

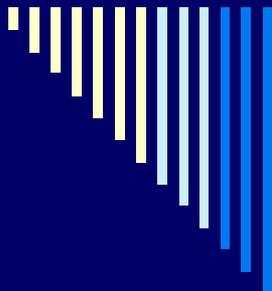


ECOSAR Chemical Classes with Excess Toxicity

40 Chemical Classes

ECOSAR will identify appropriate SAR class

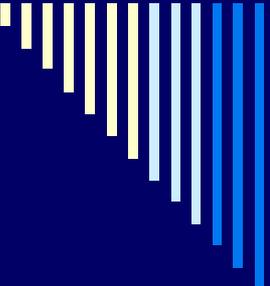
- Acid chlorides
- Acrylates
- Acrylates, methacrylates
- Alcohols, propargyl
- Aldehydes
- Amines, aliphatic
- Anilines
- Anilines, amino, meta or 1,3-substituted
- Anilines, amino, ortho or 1,2-substituted
- Anilines, amino, para, or 1,4-Substituted anilines, dinitroanilines
- Diazoniums, aromatic
- Epoxides, monoepoxides
- Epoxides, diepoxides
- Esters
- Esters, monoesters, aliphatic
- Esters, diesters, aliphatic
- Esters, phosphate
- Esters, phthalate
- Hydrazines
- Ketones, diketones, aliphatic



ECOSAR

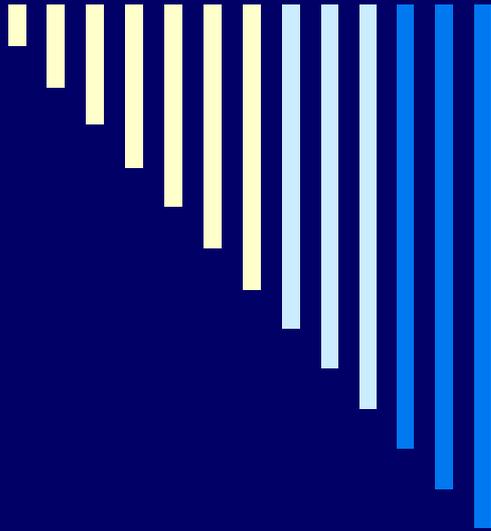
Aquatic Toxicity Profile

6 Endpoints
Fish LC ₅₀
Daphnid LC ₅₀
Green Algae LC ₅₀
Fish Chronic Value (ChV)
Daphnid Chronic Value (ChV)
Green Algae (ChV)



ECOSAR

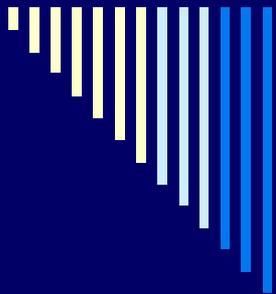
- “Stand-alone”, available for download at:
www.epa.gov/oppt/newchems/21ecosar.htm
- Integral part of EPI Suite™, available for download at:
www.epa.gov/opptintr/exposure/docs/EPISuitedl.htm



Oncologic[®]

Cancer Expert System

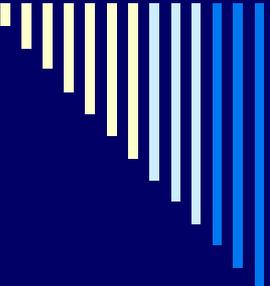
Prediction of concern levels for cancer potential
based on “knowledge rules”



OncoLogic® - Expert System

How it Works

- Mimic the thinking and reasoning of human experts using knowledge based rules for chemical classes to predict cancer concern
 - Assigns a baseline concern level ranging from low to high
 - Evaluates how substituents on the chemical may affect carcinogenicity

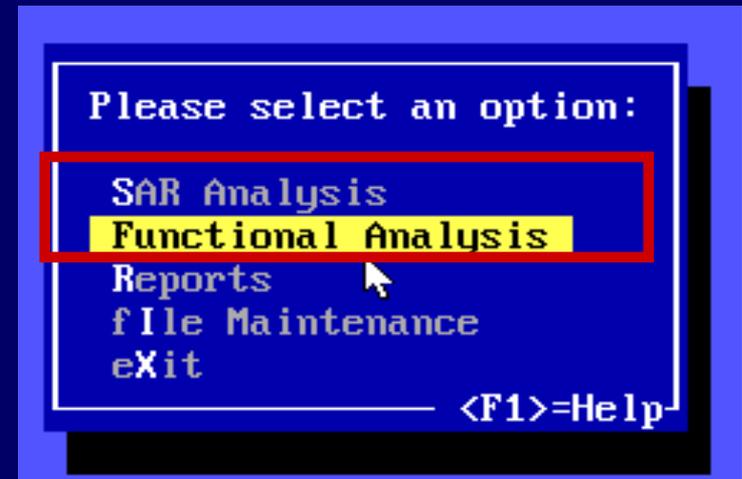


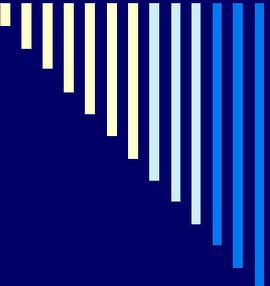
Major Data Sources Used to Develop Cancer Knowledge Rules

- ❑ Chemical Induction of Cancer monograph series
- ❑ IARC monograph series
- ❑ NCI/NTP technical reports
- ❑ Survey of compounds which have been tested for carcinogenic activity, PHS Publ. 149
- ❑ Non-classified EPA submission data from various EPA program offices

Running OncoLogic®

- Two methods to predict carcinogenicity
 - SAR Analysis
 - Knowledge rules
 - Functional Analysis
 - Uses results of specific mechanistic/non-cancer studies





The Functional Arm of OncoLogic®

- OncoLogic® can use results from some shorter-term tests to support a cancer concern.
- Results indicate whether chemical may be an initiator, promoter, or progressor

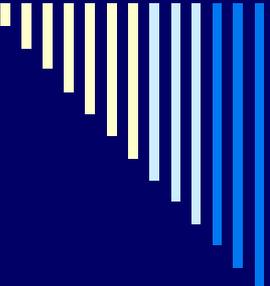
Test Category Screen

Please select one or more categories of data which are known to be correlated with carcinogenicity. After all applicable tests/endpoints have been entered, select 'Evaluate'.

Oncogene/Tumor Suppressor Gene Data
Transgenic Rodent Data
Genotoxicity and DNA Reactivity Data
Epigenetic Test Data
Subchronic Toxicity Data

Evaluate

<F1>=Help <Esc>=Exit



OncoLogic Concern Levels

OncoLogic Concern	Definition
Low	Unlikely to be carcinogenic
Marginal	Likely to have equivocal carcinogenic activity
Low – Moderate	Likely to be weakly carcinogenic
Moderate	Likely to be a moderately active carcinogen
Moderate – High	Highly likely to be a moderately active carcinogen
High	Highly likely to be a potent carcinogen

QSAR Application Toolbox

The Toolbox development is a collaborative effort to make specialized QSAR software and data from individual organisations accessible to all OECD stakeholders.

Danish Ministry of the Environment

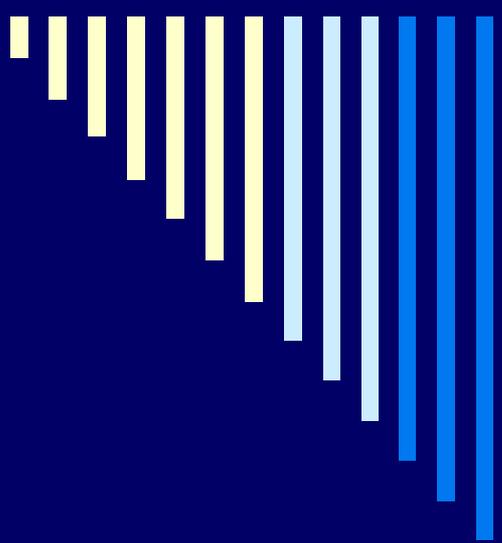
Environment Canada

European Chemicals Bureau

Japanese MITI

US EPA

...



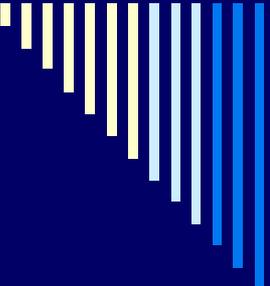
The PBT Profiler

PBT Profiler

A Component of OPPT's
P2 Framework

*Assessing Chemicals in the
Absence of Data*

<http://www.epa.gov/pbt/tools/toolbox.htm>

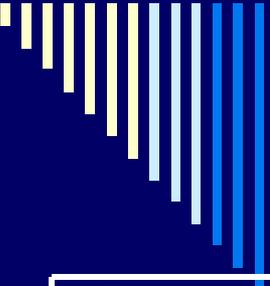


The PBT Profiler

- Estimates physical/chemical and fate properties
 - Persistence
 - Bioaccumulation: as fish BCF
 - Toxicity: fish chronic value (ChV) from ECOSAR

- Estimates distribution in water, soil, sediment, and air using Level III Fugacity model

- Compares P, B, and T estimates to EPA criteria and formats results in color-coded output
 - *New Chemicals PBT Policy – Federal Register: November 4, 1999 (Volume 64, Number 213), pages 60194-60204*
 - *TRI Reporting Criteria – Federal Register: October 29, 1999 (Volume 64, Number 209), pages 58666-58753*



P, B & T Criteria

Persistence	Not Persistent	Persistent	
Water, soil, sediment	< 60 d	≥ 60 d	> 180 d
Air	≤ 2 d	> 2 d	

Bioaccumulation	Not Bioaccumulative	Bioaccumulative	
Fish BCF	< 1,000	≥ 1,000	≥ 5,000

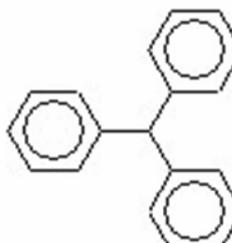
Toxicity	Low Concern	Moderate Concern	High Concern
Fish ChV (EPA New Chemical Program Criteria)	> 10 mg/L Or No Effects at Saturation	0.1-10 mg/L	< 0.1 mg/L

P2 and the PBT Profiler

PBT Profiler Estimate = PBT

Screening estimates indicate this chemical may be a PBT - a P2 Assessment may allow further evaluation

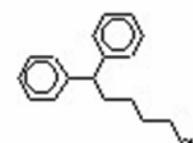
<u>Media</u>	<u>Half-Life</u> (days)	<u>Percent in</u> <u>Each Medium</u>	<u>BCF</u>	<u>Fish ChV</u> (mg/l)
Water	38	■ 8%	2,700	0.027
Soil	75	■ 53%		
Sediment	340	■ 39%		
Air	1	1%		



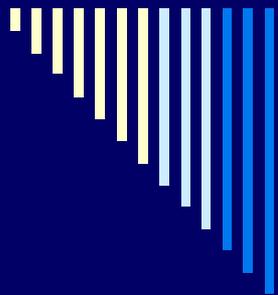
[P2 Considerations and more information](#)

PBT Profiler Estimate = PBT

<u>Media</u>	<u>Half-Life</u> (days)	<u>Percent in</u> <u>Each Medium</u>	<u>BCF</u>	<u>Fish ChV</u> (mg/l)
Water	15	■ 18%	170	0.12
Soil	30	■ 73%		
Sediment	140	■ 9%		
Air	0.75	1%		

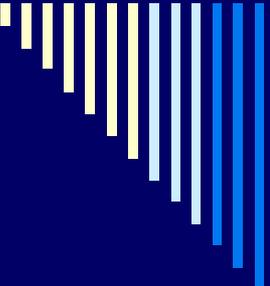


[P2 Considerations and more information](#)



Sustainable Futures

- Encourages companies to screen chemicals at R&D for potential hazards and risks using OPPT's predictive models and methods
- Promotes the design of safer chemicals and the use of safer chemical alternatives



Sustainable Futures Chemical Assessment

P-Chem and Fate

EPISuite

Aquatic Toxicity

ECOSAR

Carcinogenicity

OncoLogic

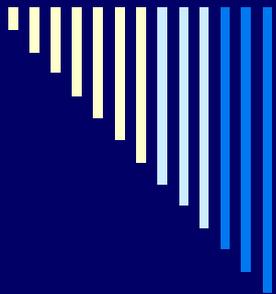
Non-Cancer Effects

Analogs/AIM

E-FAST
ChemSTEER

**SF Chemical
Assessment**

Exposure Potential



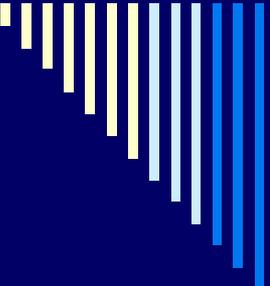
Sustainable Futures

□ Sustainable Futures Initiative:

www.epa.gov/opptintr/newchemicals/pubs/sustainablefutures.htm

□ To request workshop information or ask additional questions, contact:

- **Kelly Mayo-Bean**
- **Ph: 202-564-7662**
- mayo.kelly@epa.gov



Presidential Green Chemistry Challenge - Encourages green chemistry through recognition and grants



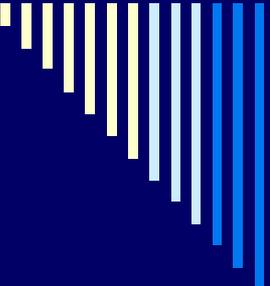
Awards

Research



<http://www.epa.gov/greenchemistry>

**Richard Engler at: engler.richard@epa.gov
or 202-564-8740**



For More Information

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