Introduction to OPPT Predictive Methods for the Evaluation of New Chemicals and the Sustainable Futures Initiative

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Understanding the U.S. Chemical Regulations Framework

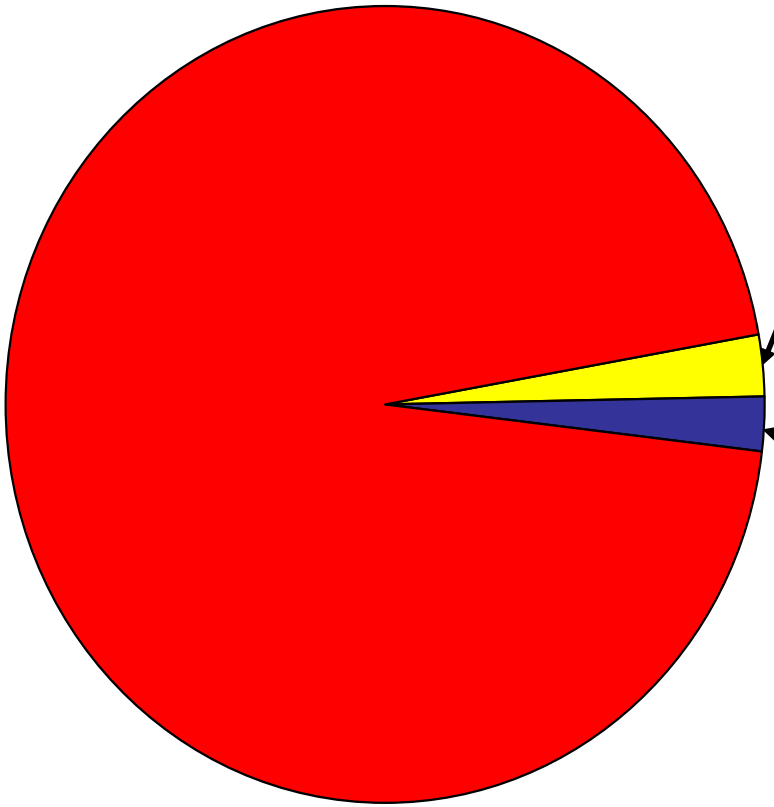
Industrial Chemicals

~80,000 Chemicals

Regulated by the Office of Pollution, Prevention, and Toxics (OPPT)

Under the Toxic Substances Control Act (TSCA)

Submissions do not require generation of "new" data !!



Pesticides

~2000 Chemicals (Active Ingredients)

Regulated by Office of Pesticides (OPP)

FIFRA requires experimental data

Drugs, Cosmetics, Food Additives

~2,000 AI

Federal Food, Drug, and Cosmetic Act requires experimental data

Challenge: Evaluating Chemicals Lacking Data Under TSCA

- Under TSCA, EPA/OPPT has authority to evaluate and regulate “new” industrial chemicals intended to be manufactured and/or sold within the U.S.
- EPA must complete a review of the PreManufacture Notice (PMN) for these chemicals within 90 days
- EPA reviews on average 1,500 PMNs per year
- Submitters are not required to conduct any new testing
- EPA can require testing if risk concerns exist – but burden of proof is on EPA!

U.S. EPA New Chemicals Program

- Regulatory decisions regarding new chemicals often have to be made with very little experimental data on the chemical of interest.

- OPPT (Q)SAR tools were developed to:
  - Help fill data gaps
  - Prioritize assessment needs
    - Focus activities on chemicals of greatest concern
  - Facilitate reviews given resource constraints

Moving Beyond Agency Applications of OPPT Tools

- OPPT Tools available for free from Agency website
- PMN submitters can use methods EPA developed to prescreen PMNs
  - Identify areas of concern BEFORE submission - gain greater certainty about the new chemical review process
- Assist in R&D and Business Planning
  - Identify potential concerns at R&D allowing for development of safer chemicals (testing is costly!)
  - Identify safer chemical substitutes for existing materials
- Tools are a mechanism for the Agency to capture and transfer chemical knowledge to the public

Moving Beyond Agency Applications of OPPT Tools

- What is the Sustainable Futures Initiative?
  - Mechanism for providing hands-on training in the use and application of predictive methods EPA has developed
- Training focuses on various applications of the tools
  - Prescreening of PMN substances
  - Identifying “greener” chemical substitutes
  - Molecular design of safer chemicals

What is Sustainable Futures?

- Training available for all – industry, academia, international stakeholders, NGOs, consultants, etc.
- For “formal” participants of the Sustainable Futures Initiative:
  - Opportunity for regulatory relief under the EPA New Chemicals Program
  - Public recognition for SF graduates

Sustainable Futures Initiative

- In addition to gaining greater certainty about the new chemical review process, there is also potential for submitters to gain “regulatory relief” from EPA in the form of an expedited review of their chemicals.
- FR Notice announcing Sustainable Futures Initiative explains what submitters must do to earn expedited review of low hazard / low risk PMNs
  - FR Vol. 67, No. 238, pp. 76281-76292; Dec. 11, 2002

    [http://www.epa.gov/fedrgstr/EPA-TOX/2002/December/Day-11/t31243.htm]

Process for SF Graduation

- **Step 1:** Access to and training in SF methods
- **Step 2:** Participants submit a minimum of 5 prescreened low hazard/low risk PMN submissions to demonstrate knowledge of tools
- **Step 3:** Tell EPA you are ready to “graduate” under the program – petition agency, file request, EPA review previous cases
- **Step 4:** After graduating, become eligible for Regulatory Relief by submitting combined PMN & TME which reduces time to market from 90 days to 45 days.

Successful Training and Outreach Efforts

- Sustainable Futures (SF) Training Workshops
  - EPA/OPPT has provided over 50 Sustainable Futures workshops within the U.S. since 1996
  - Over 650 individuals trained representing more than 280 chemical companies and regulatory/academic stakeholders

EU Training Activities

- There has been a recent increase in international interest in OPPT/SF models and methods
  - Likely drivers include evolution of REACH, the EU Cosmetics Directives, new focus on “Supply Chain” communication and lifecycle analysis, etc.
- EPA’s computational tools are being shared internationally via inclusion in the OECD QSAR Applications Toolbox
- OPPT has also provided workshops within Europe
  - Ascot, England - October 2004, Sophia, Bulgaria - October 2005, Rome, Italy - June 2006, Ispra, Italy - July 2006, Brussels, Belgium - October 2006, Paris, France - October 2007

Sustainable Futures Training Opportunities and Partnerships

- Training workshops often provided with assistance from our Sustainable Futures partners
  - Software developers, grantees, trade organizations, academic organizations, industry sponsors
- 2 sessions currently organized
  - March 20 – 21, 2008 at SOCMA HQ in DC
  - April 28 – May 1, 2008 in Chicago, IL
- Visit the EPA or SOCMA booths to obtain information on the SF program, models, upcoming workshops, and information on 3rd party technical assistance

More Information on SF

- Link to Sustainable Futures website:

  http://www.epa.gov/oppt/sf/

- Information and links to all of the Sustainable Futures tools can be found on the website above
- EPA contacts for Sustainable Futures:

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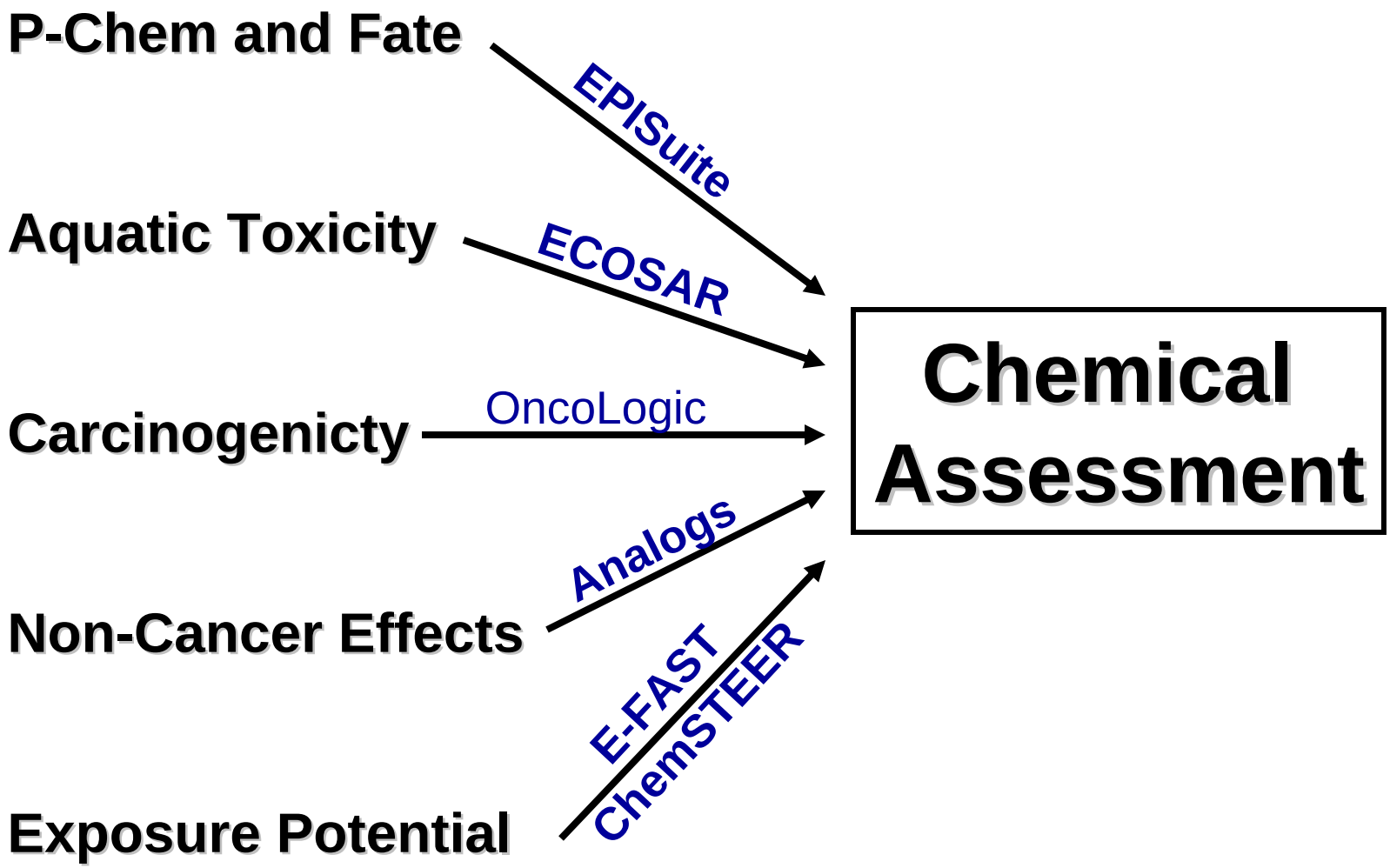
Today's Presentations on SF Models and Methods

- Designed to provide a *brief* introduction to endpoints of interest and EPA methods to fulfill those endpoints
- Full Sustainable Futures Workshops provide in-depth information on:
  - Hazard classification schemes
    - (i.e. what constitutes low, moderate, high concerns
  - Quantitative risk assessment methods
  - Validation of the models discussed
  - Additional training materials
  - Hand-on experience with models where participants use the tools to complete example screening level risk assessments

EPA OPPT Models

(Sustainable Futures - P2 Framework Models)



Descriptions for Predictive Models

- Structure Activity Relationship (SAR)
  - The relationship between the chemical structure of a molecule and its activity
- Quantitative Structure Activity Relationship (QSAR)
  - Provides numeric value for the relationship
- Typically 3 kinds of Predictive Models:
  - **Mathematical Model** – uses chemical descriptors (i.e. Kow, MW, HOMO/LUMO) and mathematical equations to derive predictions (EPISuite)
  - **Fragment based Methods** – evaluates how the atoms, backbone, and functional groups in a molecule correlate to an endpoint (EPISuite)
  - **Expert Model** – uses decision logic and chemical rules to make predictions (OncoLogic)
    - Decision Trees, Artificial Neural Networks, Molecular Models
  - **Combination Models** integrate multiple techniques from above (ECOSAR)

EPA Models for the Prediction of Physical-Chemical Properties and Environmental Fate (EPISuite)

U.S. Environmental Protection Agency

EPISuite - Modules

- EPISuite™ – Estimation Programs Interface
  - P2 Framework tool developed over the past 20 years to screen new chemicals lacking experimental data
  - EPISuite is a computer platform (shell) that houses 15 individual predictive modules
  - A user can run EPISuite and retrieve predictions for *ALL* 15 modules
  - Or, modules can be run individually as stand alone programs – in some cases allow users opportunity to change defaults

Experimental Data

- Always look for reliable measured data before employing predictive methods
  - Models often use experimental data to improve the estimations of the other endpoints
  - Having both measured and estimated data can help in a weight of evidence approach
- Various sources for experimental data can be found in the public domain

EPISUITE™ - Built in Databases

- EPI Interface is linked to Syracuse Research Corporation's PHYSPROP Database
  - Contains >25,000 chemicals with experimental data:
    - MP 10,800
    - BP 6,629
    - WS 6,340
    - K_{ow} 13,500
    - VP 2,837
    - pK_A 1,652
    - HLC 1,713
- Experimental values are automatically retrieved (if available) when user runs EPISuite on a chemical of interest
- Those values can then be used as input to the model to refine estimations

EPISUITE™ - Introduction

- Provides 3 types of results
  - Physical/chemical (P/Chem) properties
  - Environmental fate properties
  - Advanced environmental fate models

- Free!!
  - http://www.epa.gov/oppt/exposure/pubs/episuite.htm

Why Collect P-Chem and Fate Information for a Chemical?

- Once released, will the chemical go to air, water, soil, sediment?
- How long will it persist in the environment?
- What is the predominant removal pathway for the chemical in the environment?
- How might humans and the environment be exposed to the chemical?

MP and BP, Interpreting Results

(Is it a solid, liquid, or a gas?)

- General Environmental Partitioning
  - Gases are volatilized in the atmosphere
  - Solids are present in the atmosphere as particulates (dusts)
  - Liquids tend to dissolve more rapidly and have high water solubility
- Worker and general population exposure
  - Gases through inhalation
  - Liquids through dermal contact
  - Solids through dermal contact and inhalation of dust
  - Liquids and solids through ingestion

Vapor Pressure
(Will it be volatile?)

- Environmental Partitioning
  - High VP means more likely to be present in the atmosphere as vapor
  - Can be used to gauge the rate of volatilization from soil, plants, and other *dry* surfaces (see HLC for wet surfaces)

- Indicate potential for human exposure from inhalation of vapors

Octanol/Water Partition Coefficient

(Does is prefer aqueous or organic phase and will it be absorbed?)

- Concentration in octanol / concentration in water
- Indicates partitioning characteristics in environmental and biological systems
- K_{ow} affects absorption through biological membranes
- Important parameter used to by EPISuite to estimate numerous other properties
  - Water solubility
  - Bioconcentration
  - Soil adsorption
  - Aquatic toxicity

Water Solubility (WS)

- High water solubility means the chemical is more likely to be:
  - Removed from soil into ground water by rain run-off
  - Removed from the atmosphere into ground water by rain washout
- Potential environmental exposure may occur through release to aquatic compartment
  - Aquatic species exposed in water column
  - Humans though fish consumption and drinking water ingestion

Henry’s Law Constant (HLC)
(Will it volatilize from water to air?)

- The ratio of a chemical's concentration in the gas phase to that in the aqueous phase (at equilibrium)
- Indicates stripping potential from sewage treatment plants in aeration tanks
- Indicates potential volatilization from environmental waters (rivers and lakes)

Dissociation Constants – pKa/pKb

- Provides the concentration of the dissociated (ionized) and undissociated (neutral) forms of an acid, base, or organic salt in water.

  $HA \longleftrightarrow H^+ + A^-$

- An increase or decrease in percent ionization can change:
  - Water solubility
    - Ions are more soluble
  - Vapor pressure and Henry's Law constant
    - Ions are less volatile
  - Log K_{ow}
    - Ions prefer the aqueous phase

Soil Adsorption Coefficient (Koc)

(Will the chemical “stick” to organic matter?)

- Indicates potential for the chemical to leach through soil and be introduced into ground water
- Indicates partitioning of the chemical between water and suspended solids and sediment in the water column
- Strong adsorption to organic matter will impact other fate properties

Atmospheric Oxidation Processes

(Will the chemical be removed from air or be available for transport?)

- Hydroxyl radicals (OH• radicals)
  - Primary Daytime reaction
    - The dominant atmospheric oxidant
    - Produced by UV radiation in sunlight
- Ozone (O_3) - Secondary
    - Selective oxidant
- Nitrate radicals (NO_3)
  - Important at night (when no OH present)
    - Limited primarily to urban areas with NOx pollution

- Indicates how long the chemical may reside in the atmosphere

Hydrolysis

(Does the compound react with water?)

- How fast does the reaction occur?
- Indicates potential persistence of a chemical substance in the environmental
- Indicates when hydrolysis products (not just the parent compound) also need to be considered in the assessment

Biodegradation

(Will microorganisms breakdown the chemical?)

- Provides the degradation of a chemical substance by the action of microorganisms
- Indicates persistence potential in soil, water, and sediment
- Indicates amount of a chemical that may be removed in sewage treatment plants

Bioconcentration Factor (BCF)

(Will the chemical “build-up” in organisms?)

- Bioconcentration is the increase in the concentration of a chemical over that in an organism’s surroundings (e.g., water for fish)

- Indicates the potential for a chemical to concentrate in lipids (fatty tissue) of aquatic organisms and the potential to accumulate in higher trophic levels
  - Humans often exposed to chemicals through fish ingestion

Volatilization From Water Model

- Provides and indication of how fast a chemical will volatilize from moving (river) and still (lake) bodies of water
- Based on Henry's Law Constant
- Indicates partitioning in the environment

Removal in Wastewater Treatment

- Provide information on the amount of a compound removed in a model sewage treatment plant via:
  - Sludge adsorption
  - Air stripping
  - Biodegradation

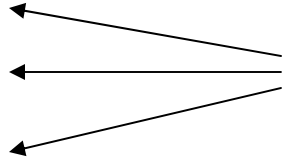
- Indicates how much of the chemical will eventually be discharged to surface water
  - The remaining amount may impact aquatic life or humans through downstream exposure

Multi-Media (Fugacity) Model

- Indicates potential partitioning of a chemical to air, water, soil, and sediment based on a particular release scenario

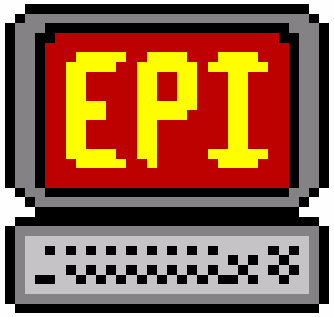
Example Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	2.92	15.6	1000
Water	22.4	360	1000
Soil	60.1	360	1000
Sediment	14.6	1.44e+003	0



Equal Release to Air, Water, Soil

Running EPISUITE™

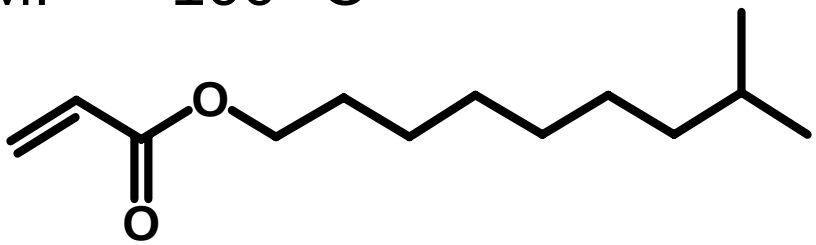


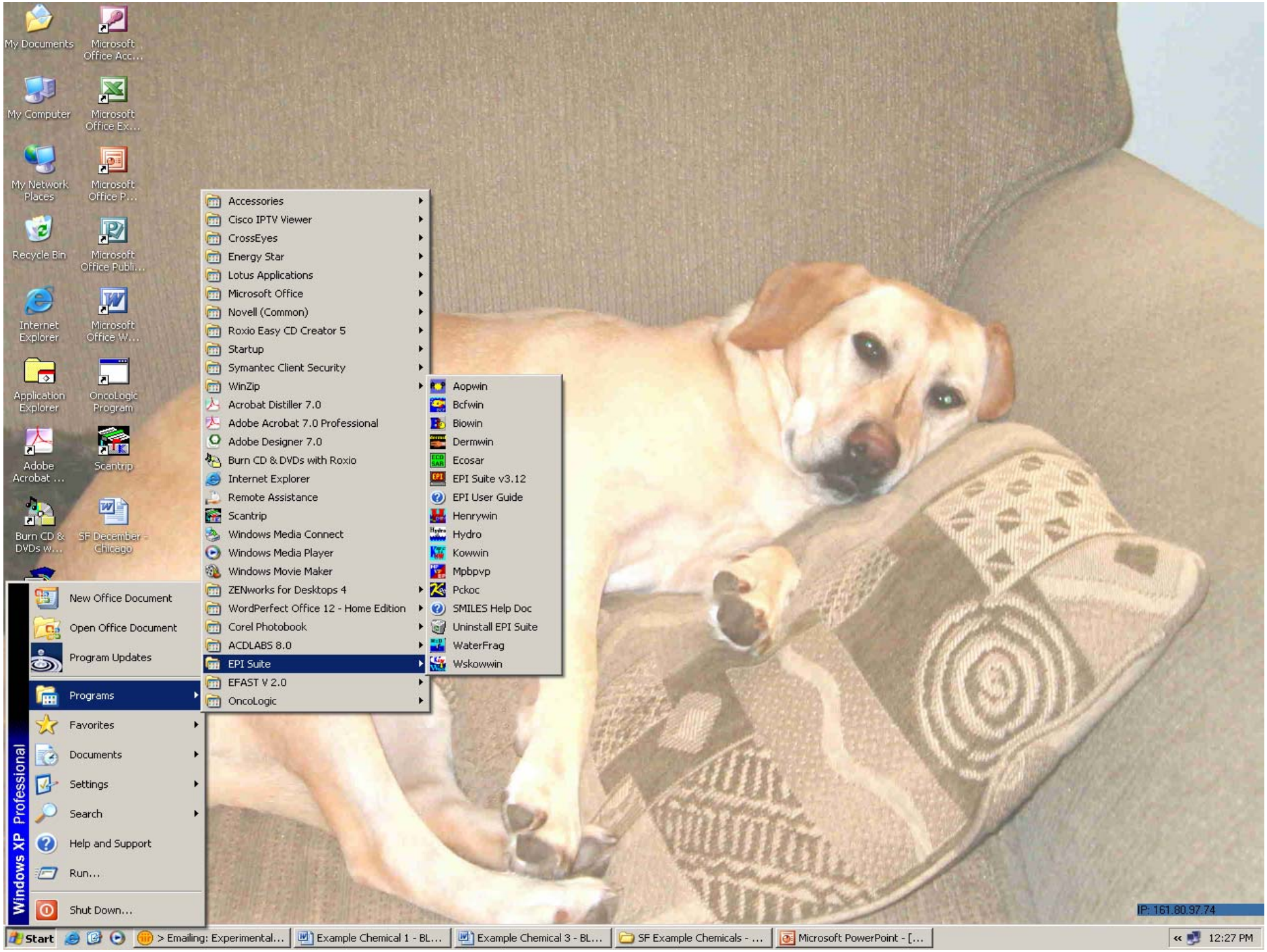
Epiwin v3.10

CAS # 1330-61-6

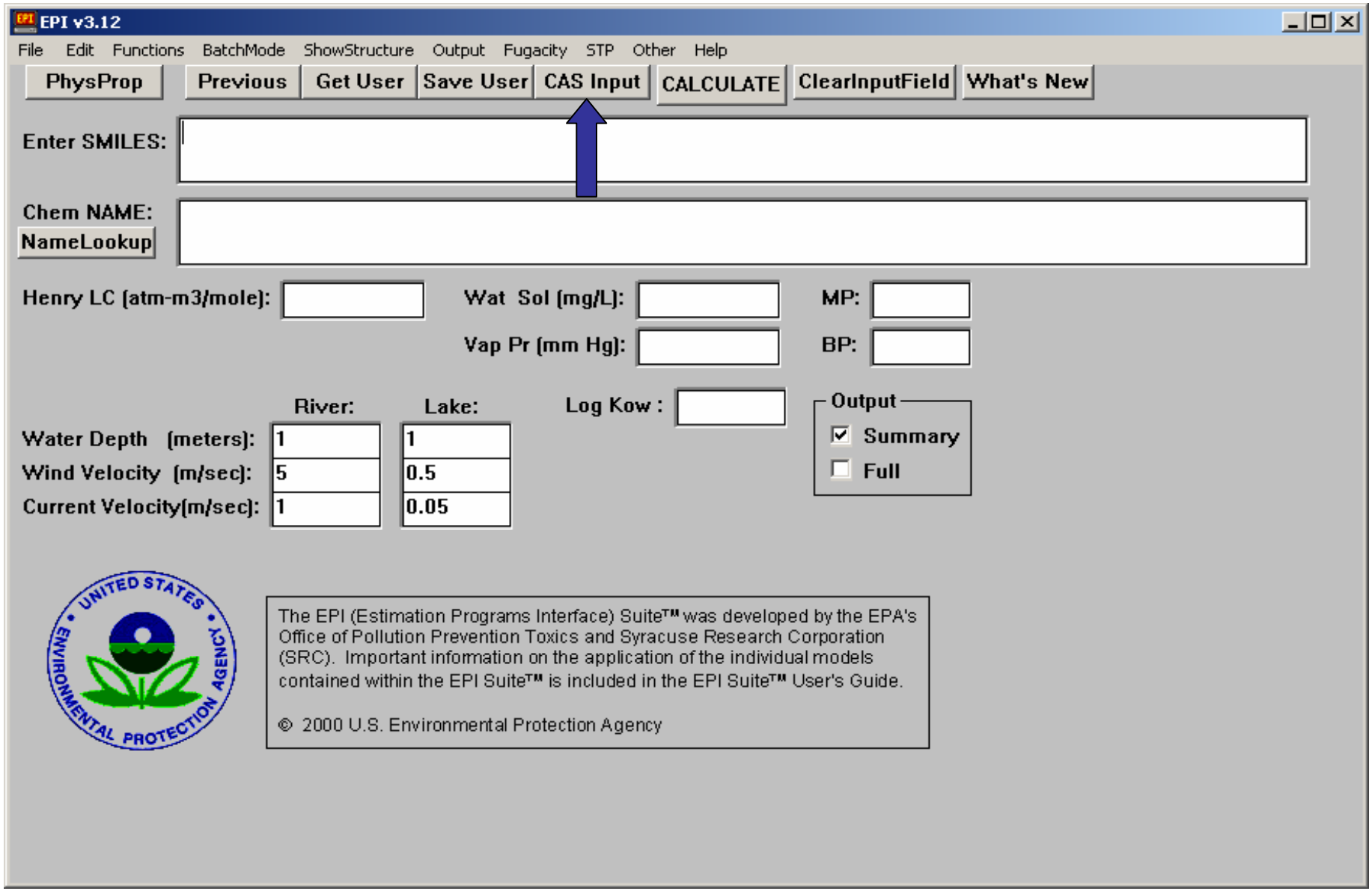
2-Propenoic acid, isodecyl ester

MP = -100 °C

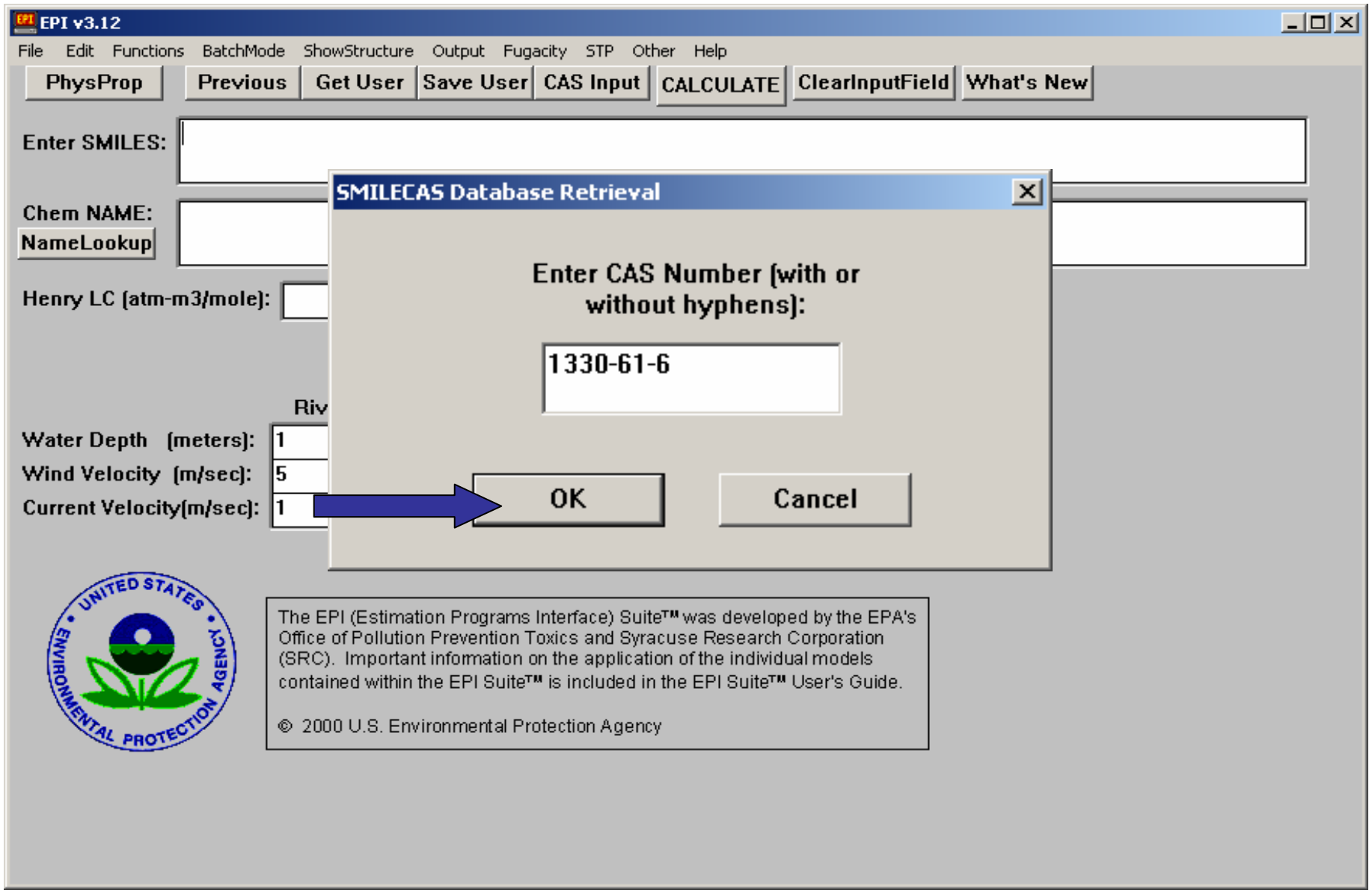



My Documents
Microsoft Office Acc...
My Computer
Microsoft Office Ex...
My Network Places
Microsoft Office P...
Recycle Bin
Microsoft Office Publi...
Internet Explorer
Microsoft Office W...
Application Explorer
OncoLogic Program
Adobe Acrobat ...
Scantrip
Burn CD & DVDs w...
SF December - Chicago
Accessories
Cisco IPTV Viewer
CrossEyes
Energy Star
Lotus Applications
Microsoft Office
Novell (Common)
Roxio Easy CD Creator 5
Startup
Symantec Client Security
WinZip
Acrobat Distiller 7.0
Adobe Acrobat 7.0 Professional
Adobe Designer 7.0
Burn CD & DVDs with Roxio
Internet Explorer
Remote Assistance
Scantrip
Windows Media Connect
Windows Media Player
Windows Movie Maker
ZENworks for Desktops 4
WordPerfect Office 12 - Home Edition
Corel Photobook
ACDLABS 8.0
EPI Suite
EFAST V 2.0
OncoLogic
Aopwin
Bcfwin
Biowin
Dermwin
Ecosar
EPI Suite v3.12
EPI User Guide
Henrywin
Hydro
Kowwin
Mpbpvp
Pckoc
SMILES Help Doc
Uninstall EPI Suite
WaterFrag
Wskowwin
New Office Document
Open Office Document
Program Updates
Programs
Favorites
Documents
Settings
Search
Help and Support
Run...
Shut Down...
Windows XP Professional
IP: 161.80.97.74
Start
> Emailing: Experimental...
Example Chemical 1 - BL...
Example Chemical 3 - BL...
SF Example Chemicals - ...
Microsoft PowerPoint - [...
12:27 PM

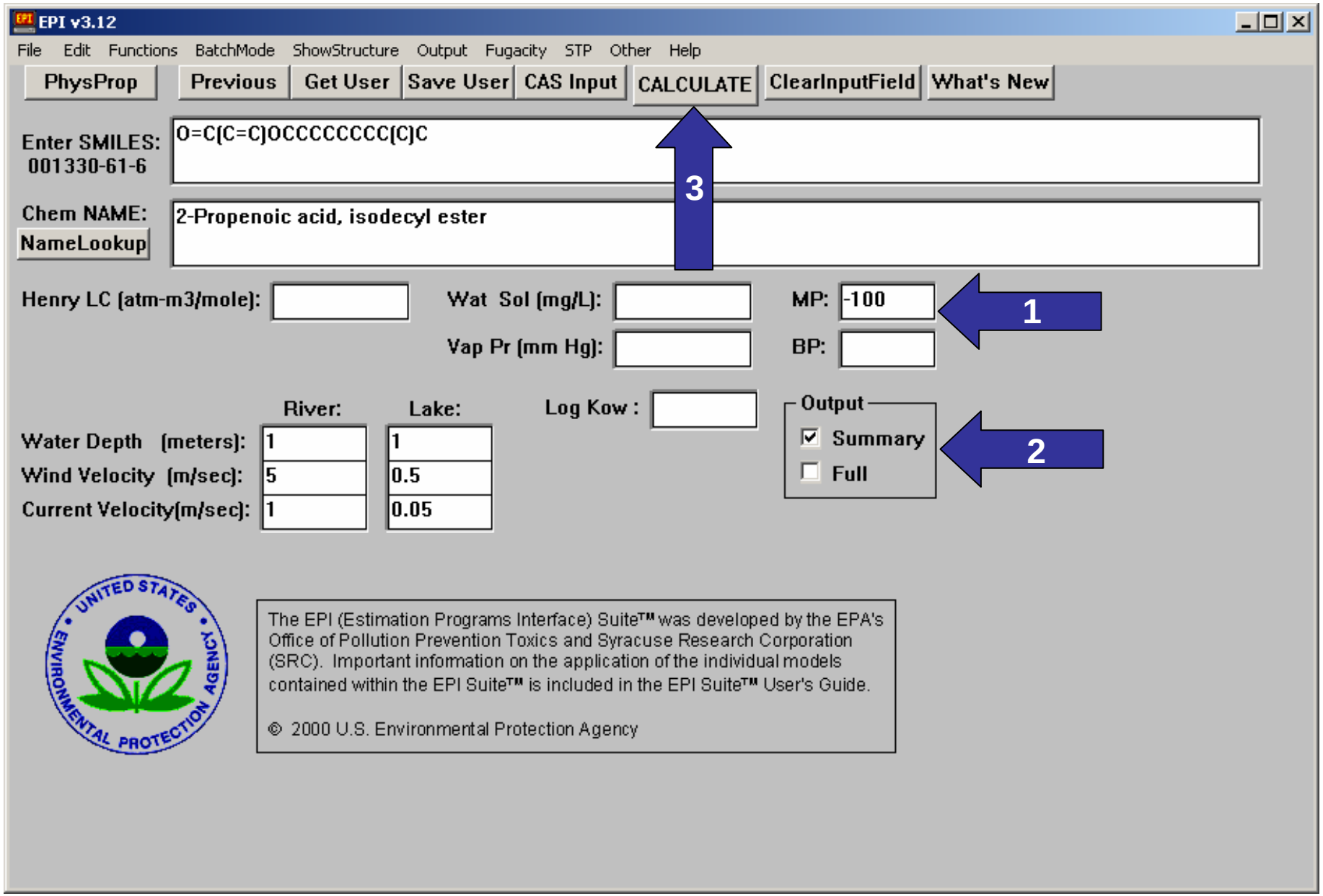
EPISuite™ – Input Screen



EPISuite™ – Chemical Entry



EPISuite™ – Calculations



EPISuite™ – Summary Output

```
SMILES : O=C(C=C)OCCCCCCCC(C)C
CHEM   : 2-Propenoic acid, isodecyl ester
CAS NUM: 001330-61-6
MOL FOR: C13 H24 O2
MOL WT : 212.34
------------------------------ EPI SUMMARY (v
 Physical Property Inputs:
    Water Solubility (mg/L):    ------
    Vapor Pressure (mm Hg) :    ------
    Henry LC (atm-m3/mole) :    ------
    Log Kow (octanol-water):    ------
    Boiling Point (deg C)  :    ------
    Melting Point (deg C)  :    -100.00

 Log Octanol-Water Partition Coef (SRC):
    Log Kow (KOWWIN v1.67 estimate) =  5.07

 Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPWIN v1.41):
    Boiling Pt (deg C):  253.36  (Adapted Stein & Brown method)
    Melting Pt (deg C):  11.48  (Mean or Weighted MP)
    VP(mm Hg,25 deg C):  0.0227  (Mean VP of Antoine & Grain methods)
    MP  (exp database):  -100 deg C
    BP  (exp database):  158 @ 50 mm Hg deg C

 Water Solubility Estimate from Log Kow (WSKOW v1.41):
    Water Solubility at 25 deg C (mg/L):  3.034
       log Kow used: 5.07 (estimated)
       melt pt used: -100.00 deg C

 Water Sol Estimate from Fragments:
    Wat Sol (v1.01 est) =  2.3895 mg/L
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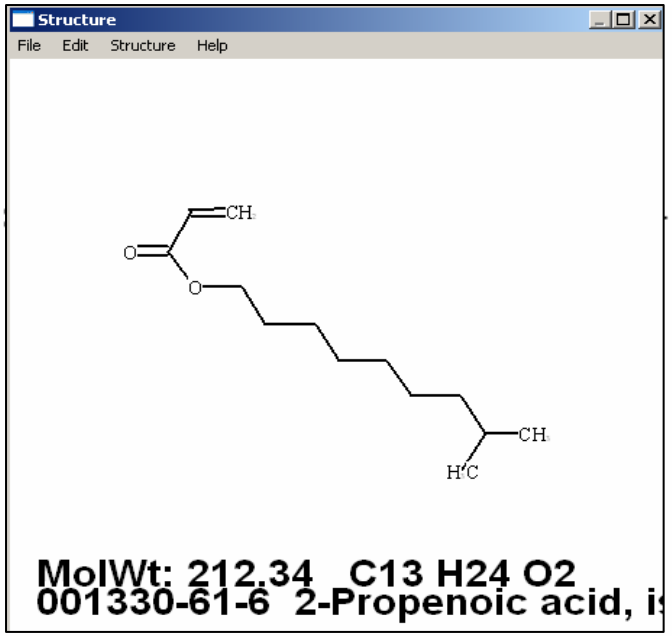


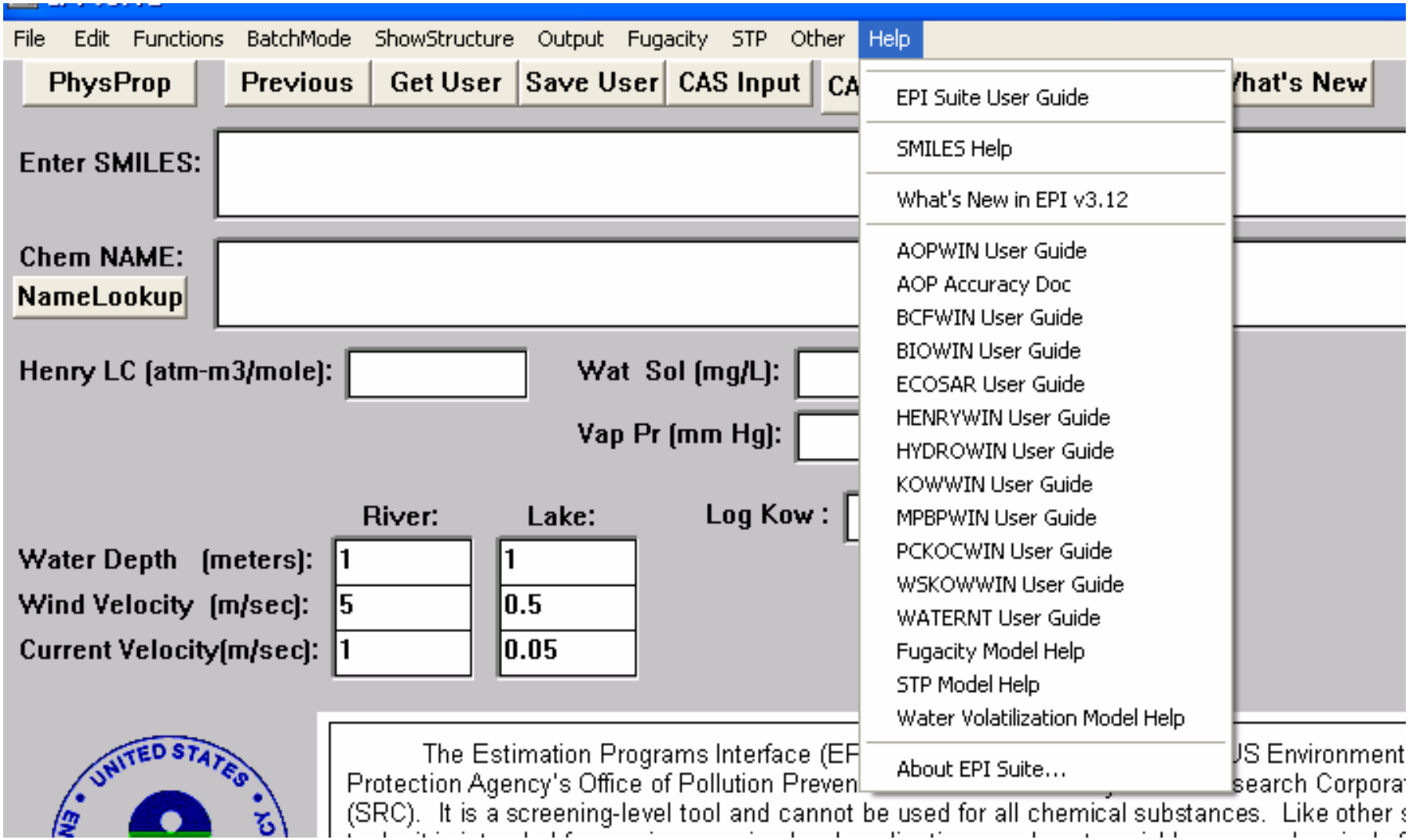
EPISuite™ - “Full Mode” Output

```
KOWWIN Program (v1.67) Results:
===============================

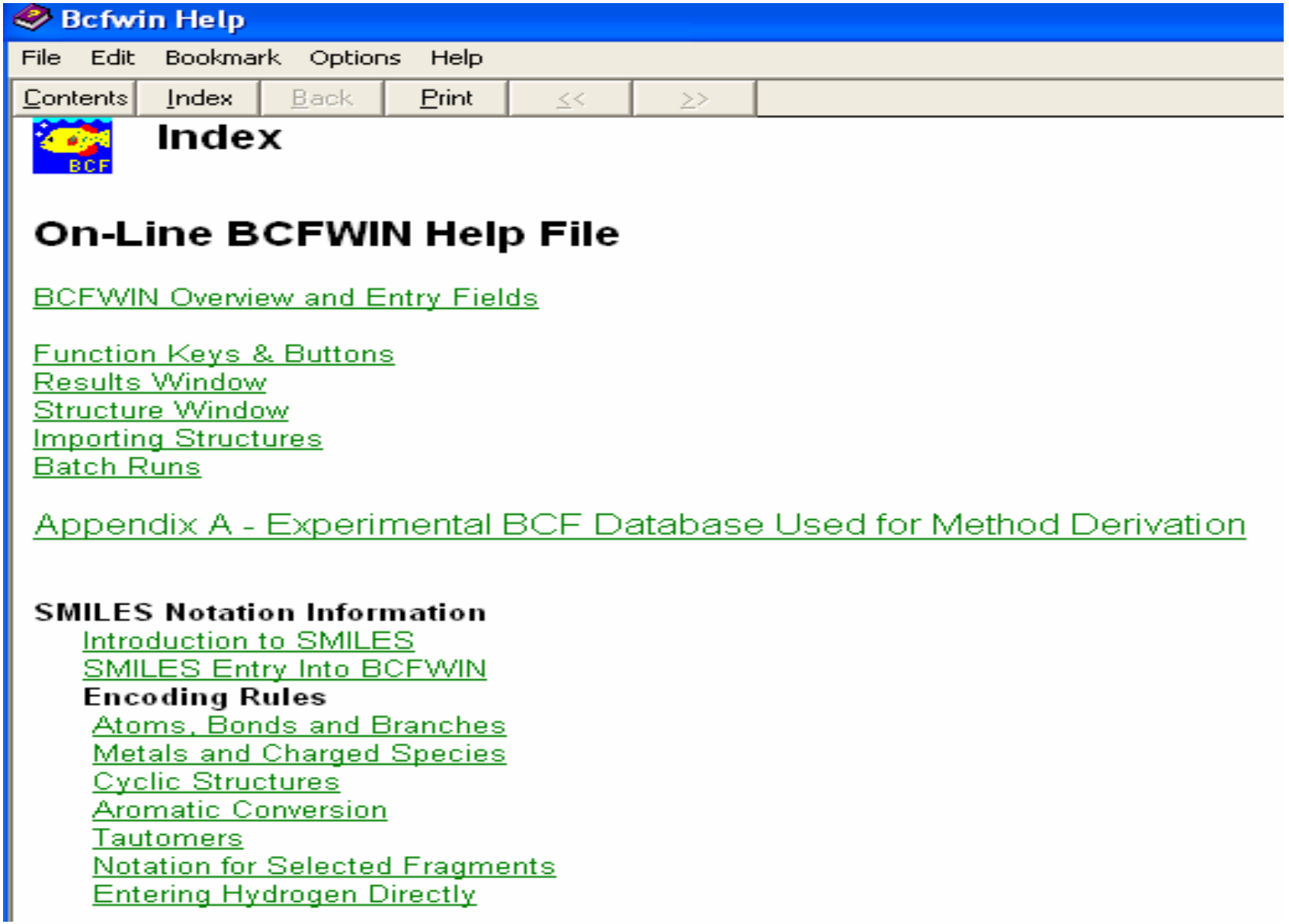
                  Log Kow(version 1.67 estimate): 5.07

SMILES : O=C(C=C)OCCCCCCCC(C)C
CHEM   : 2-Propenoic acid, isodecyl ester
MOL FOR: C13 H24 O2
MOL WT : 212.34
-------+-----+-----------------------------------------+---------+--------
 TYPE  | NUM |        LOGKOW FRAGMENT DESCRIPTION      |  COEFF  |  VALUE
-------+-----+-----------------------------------------+---------+--------
 Frag  |  2  |  -CH3    [aliphatic carbon]             | 0.5473  |  1.0946
 Frag  |  7  |  -CH2-   [aliphatic carbon]             | 0.4911  |  3.4377
 Frag  |  1  |  -CH     [aliphatic carbon]             | 0.3614  |  0.3614
 Frag  |  1  |  =CH2    [olefinic carbon]              | 0.5184  |  0.5184
 Frag  |  1  |  =CH- or =C<  [olefinc carbon]          | 0.3836  |  0.3836
 Frag  |  1  |  -C(=O)O  [ester, aliphatic attach]     |-0.9505  | -0.9505
 Const |     |  Equation Constant                      |         |  0.2290
-------+-----+-----------------------------------------+---------+--------
                                                 Log Kow   =   5.0742
```

Help Menu and Additional Model Information Available



Model (Endpoint) Information



Appendix A - Experiemental Database Used for Method Derivation

Initially, all 694 compounds in the experimental BCF database were used in a single regression. However, it bec
behave differently. Therefore, the database was divided into a non-ionic group (610 compounds) and an ionic grou
carboxylic acids, (2) sulfonic acids, (3) sodium, potassium and other salts of sulfonic acids, and (4) compounds h
ammoniums). The tables belows list the compounds in the inoic and non-ionic groups.

The table headings are as follows:

LogP: log octanol-water partition coefficeint
LogBCF: recommended log BCF
Calc: log BCF calculated by BCFWIN
Error: difference between recommended and calculated log BCF

Ionic Compound Dataset

CAS	NAME	LogP	LogBCF	Calc	Error
000946-30-5	SODIUM 4-NITROCHLOROBENZENE SULFONATE	-0.70	0.48	0.50	0.02
001934-21-0	ACID YELLOW-23	-0.02	0.48	0.50	0.02
000086-87-3	NAPHTHALENEACETIC ACID	2.24	0.43	0.50	0.07
000090-51-7	2-AMINO-8-NAPHTHOL-6-SULFONIC ACID	-1.39	0.43	0.50	0.07
005460-09-3	1-AMINO-8-NAPHTHOL-3,6-DISULFONIC ACID MONOSODIU	-2.33	0.46	0.50	0.04
042615-29-2	LINEAR ALKYL SULFONATE	4.78	1.79	1.85	0.06
005835-26-7	ISOPIMARIC ACID	6.45	1.66	1.75	0.09
050925-42-3	DIRECT YELLOW-86	5.30	0.74	0.75	0.01
000471-74-9	SANDARACOPIMARIC ACID	6.45	1.75	1.75	0.00
056113-42-9	TETRACHLOROPHTHALIC ACID MONOAMIDE	1.36	0.49	0.50	0.01
000127-20-8	DALAPON (SODIUM SALT)	1.68	0.33	0.50	0.17
000075-98-9	TRIMETHYLACETIC ACID	1.48	0.36	0.50	0.14
000115-28-6	CHLORENDIC ACID	3.14	0.32	0.50	0.18
056776-29-5	DASC-4	4.79	0.32	0.50	0.18
056776-28-4	BSB	4.71	0.32	0.50	0.18
000051-44-5	3,4-DICHLOROBENZOIC ACID	3.25	0.36	0.50	0.14
010541-83-0	P-(METHYLAMINO) BENZOIC ACID	1.01	0.38	0.50	0.12
000087-02-5	7-AMINO-4-HYDROXY-2-NAPHTHALENESULFONIC ACID	-1.39	0.38	0.50	0.12

More Information on EPISuite™

- Latest Version
  - EPISuite v. 3.20
    - Deployed in February 2007
  - http://www.epa.gov/oppt/exposure/pubs/episuite.htm

- Points of Contact
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    e-mail: mayo.kelly@epa.gov