Use of HPV Challenge Data and the EPI Suite™ Model

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Characterizing Chemicals in Commerce: Using Data on High Production Volume Chemicals
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Physical/Chemical Properties

- Provides basic information on the nature and characteristics of a chemical substance
  - Molecular weight
  - Melting point
  - Octanol/Water partitioning coef. (Kow)
  - Water solubility
  - Vapor pressure
  - Boiling point
  - Hydrolysis half-life

Physical/Chemical Properties

- Gives insight into
  - Partitioning in the environment
  - Potential for environmental exposure
  - Potential routes of human exposure
  - Toxicity and biological effects

Physical/Chemical Properties

- Used to assess human and environmental health effects
  - Absorption thru skin, lungs and GI tract
  - Skin irritation
  - GI tract stability
  - Lung irritation, overload and toxicity
  - Probability of skin sensitization
  - Probability of pulmonary sensitization

Environmental Fate Properties

- Molecular weight
- Melting point
- Octanol/Water partitioning coef. (Kow)
- Water solubility
- Vapor pressure
- Boiling point
- Hydrolysis half-life
- Henry's Law constant
- Biodegradability
- Koc
- Fish BCF
- Atmospheric oxidation rate

Environmental Fate Properties

- Give insight on
  - Chemical behavior in environment
  - Partitioning between air, water, soil, and sediment
  - Environmental persistence
  - Human and environmental exposure

Environmental Fate Properties

- Used to assess environmental behavior and effects
  - predict acute and chronic toxicity to aquatic organisms
  - PBT potential
  - global warming potential
  - ozone depletion potential
  - smog potential
  - predict probability of acute and chronic risk aquatic organisms

Use of HPV Data

Screening and Prioritazation

- Tier I - prioritization by applying screening criteria to a subset of data
- Tier II – In- depth review and characterization of HPV chemicals

Model Development and Improvement

- EPISUITE
- Others

HPV Data Process Flow and Screen

Tier I Screening

- Prioritization assigns HPV chemicals into THREE GROUPs based on Sponsor's data as submitted for human health and/or environmental effects (ecotoxicity)

- Environmental fate data are used to further modify review group assignments

HPV Data Process Flow and Screen

Environmental Fate

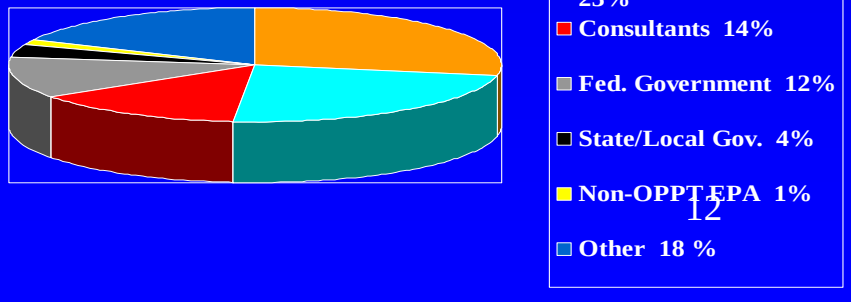
	Final Review Group After Applying Environmental Fate Criteria		
Preliminary Review Group Based on Toxicity ↓	**Fails Log K_{ow} Criterion Only (Log Kow >4)**	**Fails Biodeg. Criterion Only**	**Fails Both Log K_{ow} AND Biodeg. Criteria**
1st	1st	1st	1st
2nd	1st	1st	1st
3rd	2nd	2nd	1st or 2nd

Data

- Reliable experimental data are always preferred over estimated data
- For some parameters estimated or modeled data acceptable
  - log $K_{OW,}$
  - Photodegradation (atmospheric oxidation)
  - Transport/Distribution
  - Stability in water
  - BP, VP and water solubility estimates may be acceptable under certain conditions

Estimation Programs Interface (EPI Suite™)

- Estimates physical/chemical properties and environmental fate and transport
- EPI Suite™ developed by EPA and Syracuse Research Corporation for use in EPA's New Chemicals Program
- Widely used in other EPA programs and externally



Estimation Programs Interface (EPI Suite™)

- Intended as a screening level tool
- Intended for use only in absence of measured values
- Not applicable to all chemicals

Chemical Property and Fate Programs in EPI Suite™

AOPWIN	atmospheric oxidation
BCFWIN	bioconcentration factor (BCF)
BIOWIN	biodegradability
HENRYWIN	Henry's law constant
HYDROWIN	aqueous hydrolysis
KOWWIN	octanol-water partition coefficient
MPBPVP	melting point, boiling point, vapor pressure
PCKOC	soil sorption coefficient (Koc)
WSKOW	water solubility from log Kow
WATERNT	water solubility from fragments
STPWIN	removal in activated sludge treatment
LEVEL III	transport/distribution by fugacity
WVOLWIN	volatilization from water

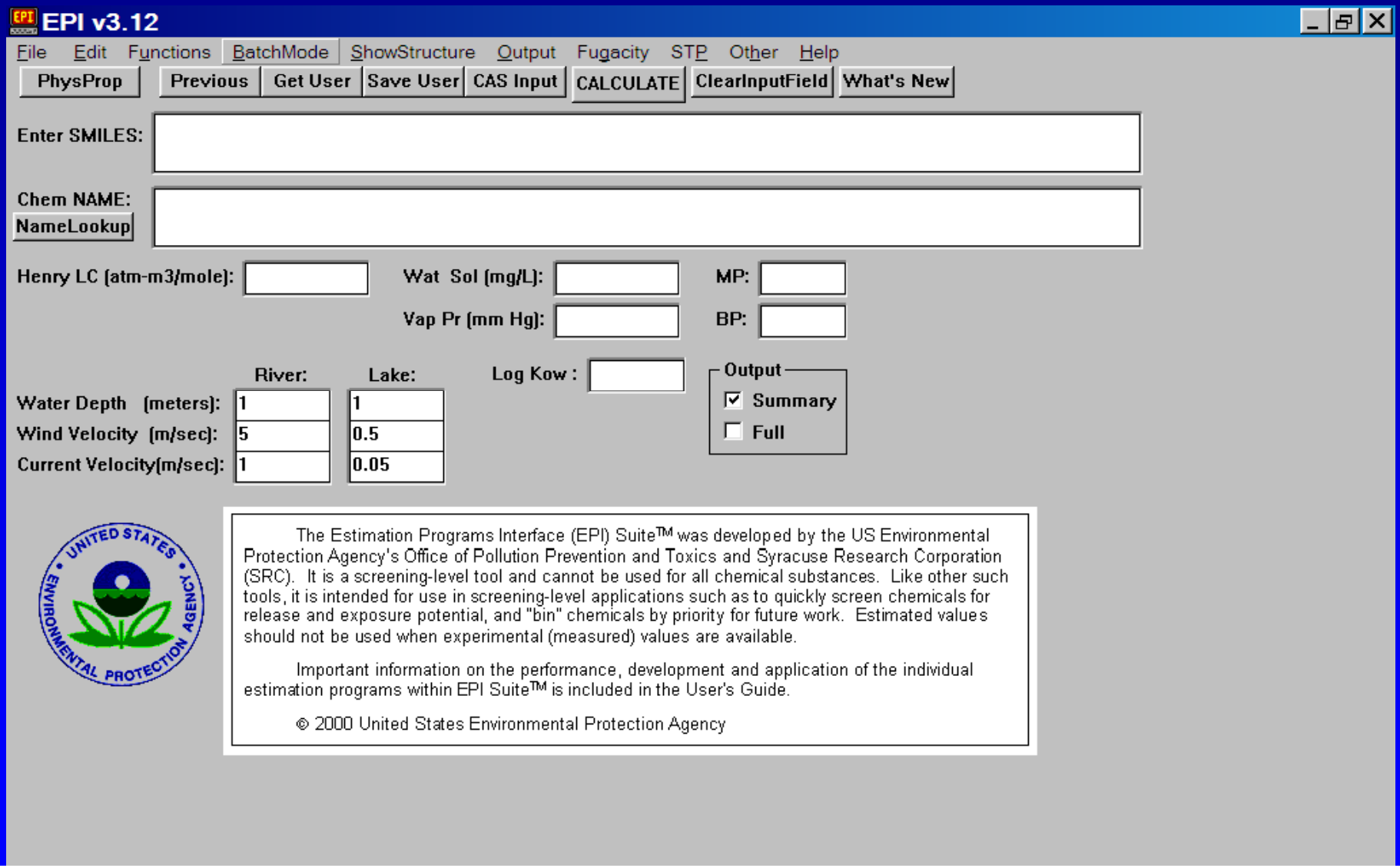
Estimation Programs Interface (EPI Suite™)

- EPI Suite™ can use HPV and other experimental data to improve the estimations of the other properties
- An extensive database of experimental data is included within EPI Suite™
- Includes PHYSPROP, a database of measured p/chem and fate properties for >40,000 chemicals
- HPV chemical data is included in current version and HPVC data will be used to help update and improve models

EPI Suite™ Chemical Structure Entry

- Runs from Simplified Molecular Input Line Entry System (SMILES) representation of chemical structure
- SMILES can be entered directly or using a chemical's CAS number
- Chemicals can be run batchwise
- Accepts MDL Mol files (generated by Isis Base/Draw)

EPI Suite™ v3.12 Input Screen (8 Dec 05)



EPI Suite™

- Method details
  - Estimation methods for chemical properties and degradation are based on standard regression techniques
  - Most use correction factors
  - Method details are summarized online in the Help files
  - Full reference citations are also given so that users can examine methods in more detail, if they desire

KOWWIN Program - log Kow

- KOWWIN uses a "fragment constant" methodology
  - Structure is divided into fragments (atom or larger functional groups)
  - Coefficient values of each fragment or group are summed together to yield the log Kow estimate
  - Coefficients for individual fragments and groups in KOWWIN were derived by multiple regression of more than 2400 reliably measured log Kow values
  - Also allows "Experimental Value Adjusted" (EVA) estimate based on experimental log Kow of the similar compound.

KOWWIN Program - log K_{ow} (log P)

Methodology - Atom/Fragment Contributions:

170 Fragments

290 Correction Factors

Log Kow used by:

- **BCFWIN**
- **DERMWIN**
- **ECOSAR**
- **WSKOWWIN**

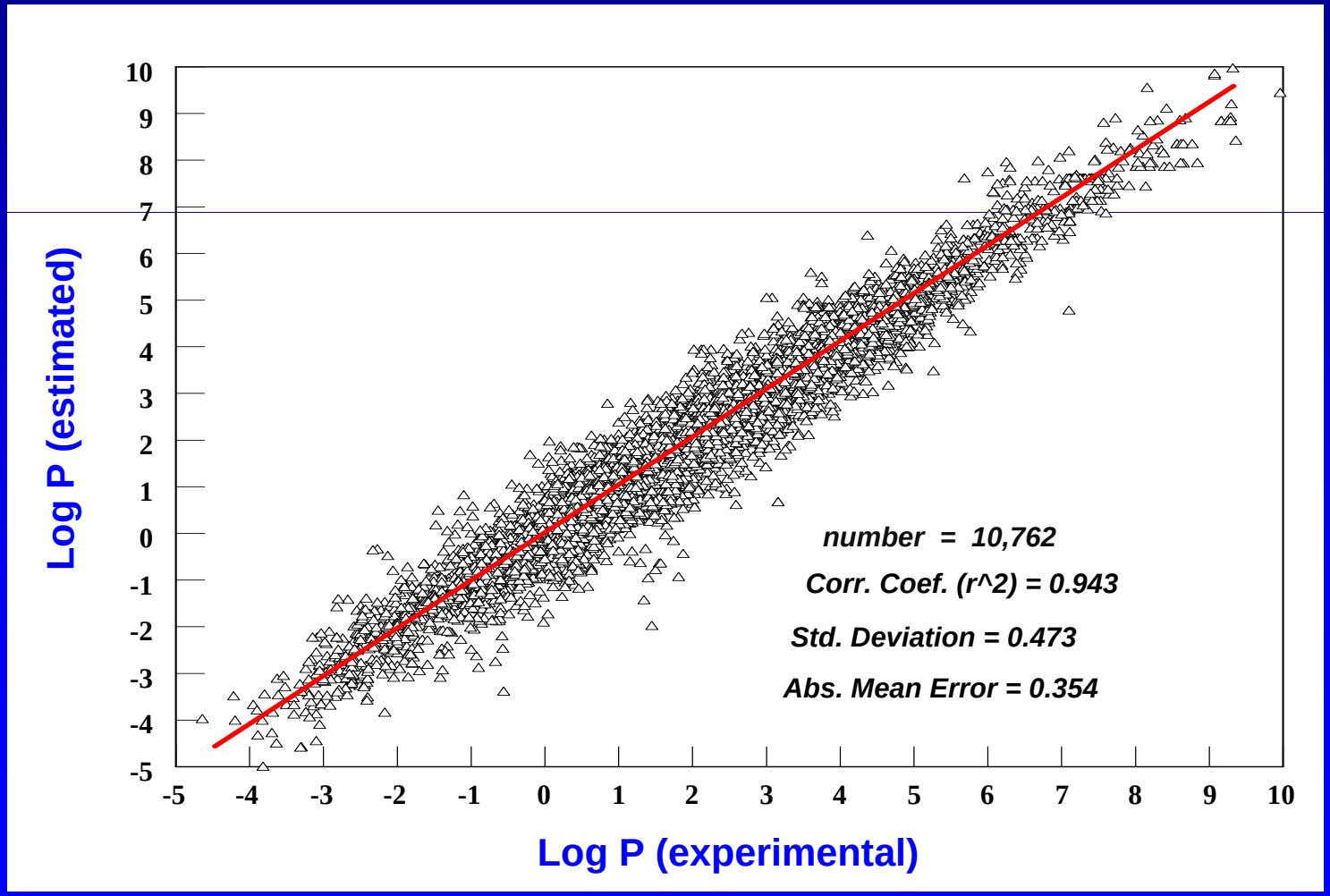
Statistical Accuracy:

	number	Corr(r^2)	Std Dev	Mean Error
Total	13229	0.954	0.436	0.316
Training	2467	0.981	0.219	0.162
Validation	10762	0.943	0.473	0.354

KOWWIN includes the experimental database of 13,229 recommended log P values

Journal Article Description: J. Pharm. Sci. 84(1): 83-92 (1995)

KOWWIN:
Validation Data Set



Example KOWWIN Output

Kowwin Results

Print Save Results Copy Remove Window Help

Log Kow(version 1.65 estimate): 0

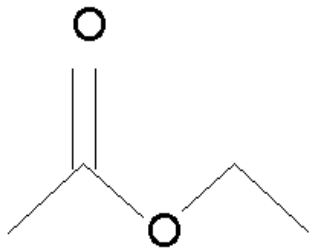
```
Experimental Database Structure Match:
  Name     :  Ethyl acetate
  CAS Num  :  000141-78-6
  Exp Log P:  0.73
  Exp Ref  :  Hansch,C et al. (1995)

SMILES : CC(=O)OCC
CHEM   : Ethyl Acetate
MOL FOR: C4 H8 O2
MOL WT : 88.11
```

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	-CH3 [aliphatic carbon]	0.5473	1.0946
Frag	1	-CH2- [aliphatic carbon]	0.4911	0.4911
Frag	1	-C(=O)O [ester, aliphatic attach]	-0.9505	-0.9505
Const		Equation Constant		0.2290
			Log Kow =	0.8642

Structure

File Edit Structure Help



Log Kow (estimated): 0.86
Ethyl Acetate

EPI Suite™

- **Accuracy**
  - EPA considers the accuracy acceptable for a screening-level tool
  - Within 1-2 orders of magnitude for most parameters
  - Information on method error is summarized online in the Help files
  - Full reference citations are also given so that users can examine the statistics in more detail, if they desire

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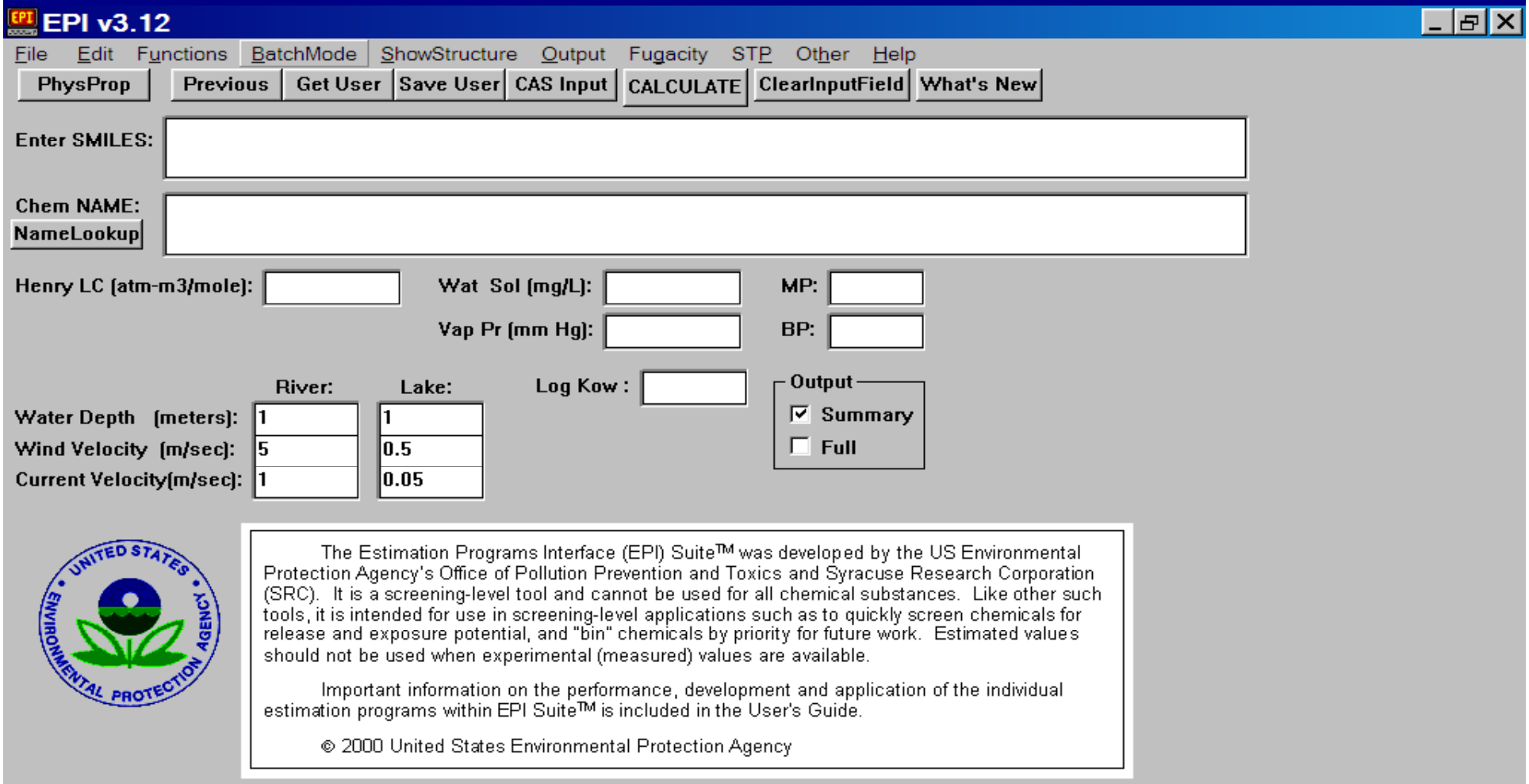
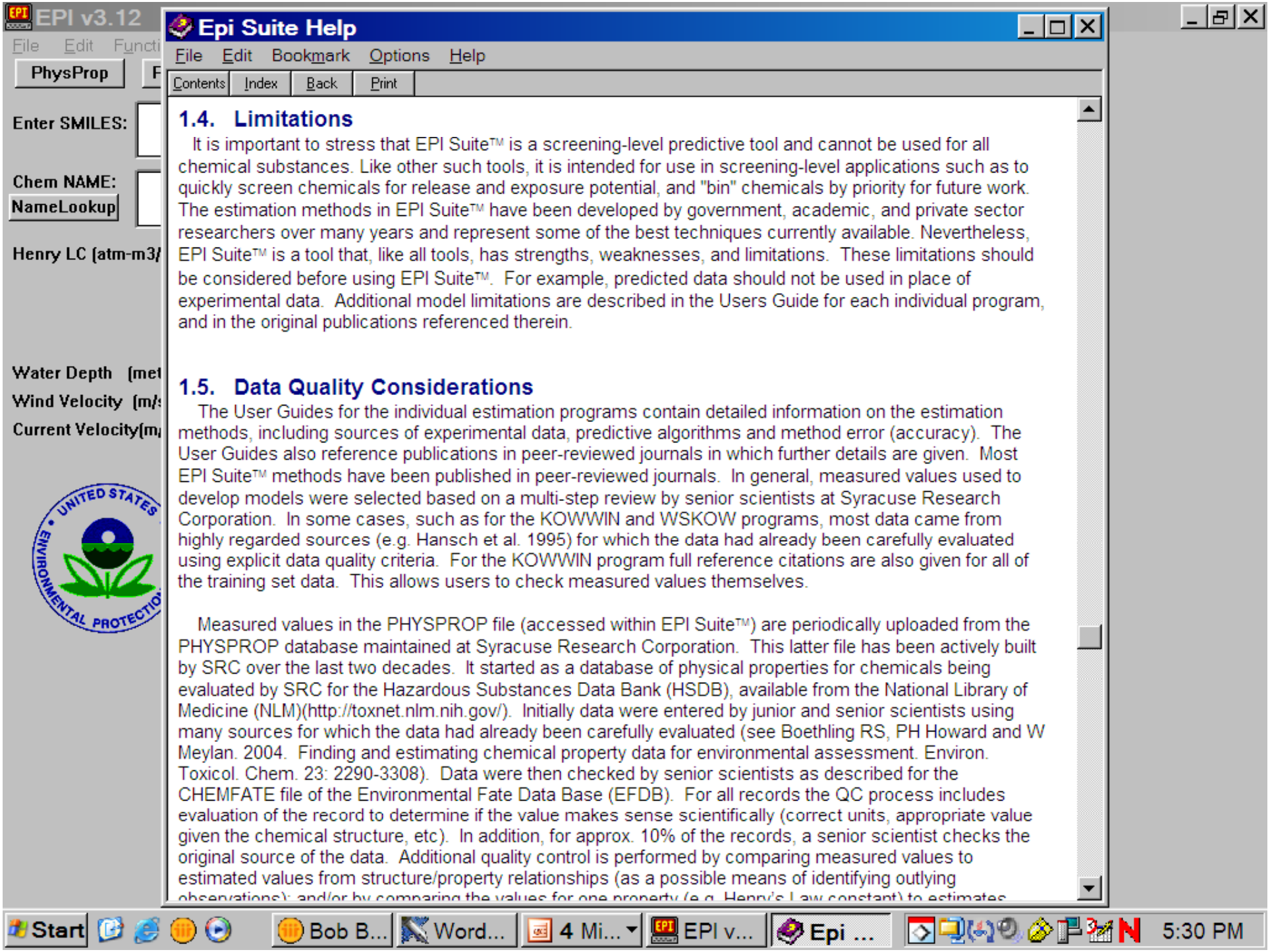
EPI Suite™ v3.12 Input Screen




EPI v3.12
File Edit Functi
PhysProp
Enter SMILES:
Chem NAME:
NameLookup
Henry LC (atm-m3/
Water Depth (met
Wind Velocity (m/s
Current Velocity(m/
Epi Suite Help
File Edit Bookmark Options Help
Contents Index Back Print
1.4. Limitations
It is important to stress that EPI Suite™ is a screening-level predictive tool and cannot be used for all chemical substances. Like other such tools, it is intended for use in screening-level applications such as to quickly screen chemicals for release and exposure potential, and "bin" chemicals by priority for future work. The estimation methods in EPI Suite™ have been developed by government, academic, and private sector researchers over many years and represent some of the best techniques currently available. Nevertheless, EPI Suite™ is a tool that, like all tools, has strengths, weaknesses, and limitations. These limitations should be considered before using EPI Suite™. For example, predicted data should not be used in place of experimental data. Additional model limitations are described in the Users Guide for each individual program, and in the original publications referenced therein.
1.5. Data Quality Considerations
The User Guides for the individual estimation programs contain detailed information on the estimation methods, including sources of experimental data, predictive algorithms and method error (accuracy). The User Guides also reference publications in peer-reviewed journals in which further details are given. Most EPI Suite™ methods have been published in peer-reviewed journals. In general, measured values used to develop models were selected based on a multi-step review by senior scientists at Syracuse Research Corporation. In some cases, such as for the KOWWIN and WSKOW programs, most data came from highly regarded sources (e.g. Hansch et al. 1995) for which the data had already been carefully evaluated using explicit data quality criteria. For the KOWWIN program full reference citations are also given for all of the training set data. This allows users to check measured values themselves.
Measured values in the PHYSPROP file (accessed within EPI Suite™) are periodically uploaded from the PHYSPROP database maintained at Syracuse Research Corporation. This latter file has been actively built by SRC over the last two decades. It started as a database of physical properties for chemicals being evaluated by SRC for the Hazardous Substances Data Bank (HSDB), available from the National Library of Medicine (NLM)(http://toxnet.nlm.nih.gov/). Initially data were entered by junior and senior scientists using many sources for which the data had already been carefully evaluated (see Boethling RS, PH Howard and W Meylan. 2004. Finding and estimating chemical property data for environmental assessment. Environ. Toxicol. Chem. 23: 2290-3308). Data were then checked by senior scientists as described for the CHEMFATE file of the Environmental Fate Data Base (EFDB). For all records the QC process includes evaluation of the record to determine if the value makes sense scientifically (correct units, appropriate value given the chemical structure, etc). In addition, for approx. 10% of the records, a senior scientist checks the original source of the data. Additional quality control is performed by comparing measured values to estimated values from structure/property relationships (as a possible means of identifying outlying
Start
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Word...
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EPISUITE status and updates for

- **Modifications and additions**
  - Chemical name lookup function added
    - Type name: program gets SMILES and enters it on main screen
    - No need to know either SMILES or CAS, if the chemical name is on list
  - STPWIN
    - New option: estimate activated sludge biodeg half-lives from chemical structure via BIOWIN
    - Default mode is still no biodeg in STP

EPI Updates for v3.12

- BIOWIN
  - Ready biodegradability now estimated using a Bayesian model battery (BIOWIN3 and 5)
- WATERNT (formerly WATERFRAG)
  - Help information now available
- Level III EPI (multimedia model)
  - Default ratios of half-lives for water:soil:sediment changed from 1:1:4 to 1:2:9
  - Corrects inconsistency with PBT Profiler™

EPI Suite™: Version 3.20 enhancements

- Subcooled liquid vapor pressure
- Dimensionless Henry constant (K_{AW})
- Octanol/air partition coefficient (K_{OA})
- Fraction of airborne substance sorbed to particulates (φ)
- Anaerobic biodegradation potential
- Hydrolysis
  - All-new version of HYDROWIN

External Review

- SAB – Reviewed in 2006
- Draft Executive Summary:
  - EPI Suite is based on sound science, user friendliness, transparency, and cost-effectiveness
  - Accuracy is sufficient to support regulatory screening
  - SAB provides numerous recommendations for improvement in terms of scope, accuracy, and ease of operations

External Review

- SAB Report in final stages of Approval
- Available on EPA Website
  - Peer Review website: http://www.epa.gov/sab/panels/epi_suite_review_panel.htm
  - Draft report: http://www.epa.gov/sab/pdf/epi_suite_third_draft_03-24-06_clean_for_web.pdf

EPI Suite™ available for free download at:

www.epa.gov/oppt/exposure/pubs/episuitedl.htm