

# Neural Network Programs for the Estimation of Toxicity and Receptor Binding

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by

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# TerraQSAR™

stand-alone,  
probabilistic neural network (PNN) -  
based  
toxicity/effect computation programs for  
PCs



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## Principle of Method

**TerraQSAR™** toxicity estimation software is based on the **probabilistic neural network (PNN)** methodology, using the molecular structure of the substance under investigation as the sole input.



## *Purpose*

**TerraQSAR™ - FHM** is a specialized, neural network-based software program, designed and optimized solely for the computation of acute (96-hr) median lethal concentrations (LC50) of organic (carbon-containing) substances with a defined chemical structure to the **fish fathead minnow** (*Pimephales promelas*).



## *Purpose*

**TerraQSAR™ - RMIV** is a specialized, neural network-based software program, designed and optimized solely for the computation of the **intravenous lethal dose (LD50)** of organic (carbon-containing) substances with a defined chemical structure to **rat and mouse**.



## *Purpose*

**TerraQSAR™ - E2-RBA** is a specialized, neural network-based software program, designed and optimized solely for the computation of **estrogen receptor binding affinity (E2-RBA)** of organic (carbon-containing) substances with a defined chemical structure relative to that of *17beta-estradiol (E2)*.



## *Purpose*

**TerraQSAR™ - HIV** is a specialized, neural network-based software program, designed and optimized solely for the computation of human immunodeficiency (HIV-1) effect concentrations (EC50) of organic (carbon-containing) substances with a defined chemical structure to the **HIV-1 virus** [fall 2003].



## Input

**TerraQSAR** modules use as input only the chemical's **SMILES** code (2-D or 3-D), which is an international code for the representation of chemical structures and amenable to computer analysis.

**SMILES** = acronym for  
**Simplified Molecular Line Entry System**



## Output

The TerraQSAR™ programs typically compute the **LC50, LD50, or EC50** in both mg/L or mg/kg b.w. (body weight) and in pT (log [L/mmole] or log ([kg b.w.]/mmole) units, as well as the molecular weight (MW) of substances entered, directly from the compound's structure.

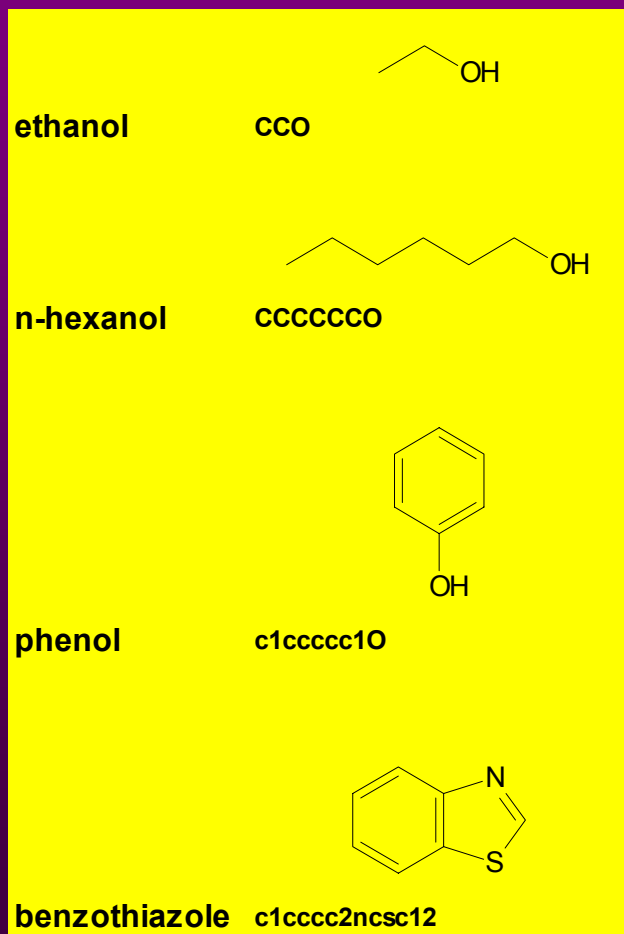


## *Data Set*

The **TerraQSAR™ - FHM** fathead minnow toxicity estimation program is based on a data set of measured 96-hr LC50 values for fathead minnow for 886 organic (carbon-containing) compounds. These data are widely available, both from non-commercial sources, such as the US Environmental Protection Agency's Ecotox database, or from commercial sources, such as TerraBase Inc.'s **TerraTox™ - Explorer** database.



# *SMILES string examples and structures (hydrogen atoms omitted)*



## *Note regarding the SMILES notation*

TerraBase Inc. uses the Accelrys Corp. system of the SMILES notation, which is not fully compatible with the Daylight Corp. system.

This is not to be considered as a value or preference statement, but merely an acknowledgement of the use of Accelrys software.



**Table 2. Valid and invalid examples of SMILES code.**

Substance	SMILES not valid	SMILES valid
cyclopentadiene <sup>a</sup>	<chem>c1cccC1</chem>	<chem>C1=CC=CC1</chem>
coumarin <sup>a</sup>	<chem>c1cc2OC(=O)ccc2cc1</chem>	<chem>c1cc2OC(=O)C=Cc2cc1</chem>

<sup>a</sup> The SMILES strings shown as “not valid” are valid *per se*, however, the interpretation of these codes are different between Daylight and Accelrys chemistry engines, the latter interpreting these as the hydrogen-saturated compounds cyclopentane and 3,4-dihydrocoumarin, respectively.



## *Fragments*

Fragments used in the **TerraQSAR** modules have been described in detail in several publications listed in the literature, especially in the works by Kaiser *et al.* An overview of basic fragment types considered is given in **Table 1**.



## Table 1. Fragment types used in TerraQSAR

Fragment Types	Examples
Acidity fragment	<chem>C(=O)O</chem> , <chem>S(=O)(=O)O</chem>
Aliphatic ring fragment	<chem>C1CCCCC1</chem> , <chem>C1CCCC1</chem>
Aromatic ring fragment	<chem>c1ccccc1</chem> , <chem>c1cccn1</chem>
Atom fragment	C, H, N, O
Bond fragment	C-C, C=C, C#C
Group fragment	C-O-H, C-O-C, O=C-O-C
Hydrophobicity fragment	<chem>C(C)(C)C</chem> , <chem>CCCC</chem>
Ionization fragment	[O-], [Na+]
Polarity fragment	<chem>O=N(=O)CC(O)</chem>
Reactivity fragment	<chem>C=CC=O</chem>
Stereo fragment	<chem>Cl[C@H](C)N</chem> , <chem>Cl[C@@H](C)N</chem>
Weight fragment	molecular weight



## *Computation*

The computer evaluates the number and types of bonds and fragments present in the compound and computes the toxicity estimate on the basis of the same types of bonds and fragments present in the training data set.

**Computation time** varies with the complexity of the query structure and speed of the computer. Typically, for compounds without chiral centers, and molecular weights of <200, computation time on a 2 GHz machine takes **<5 seconds**.



## *Results*

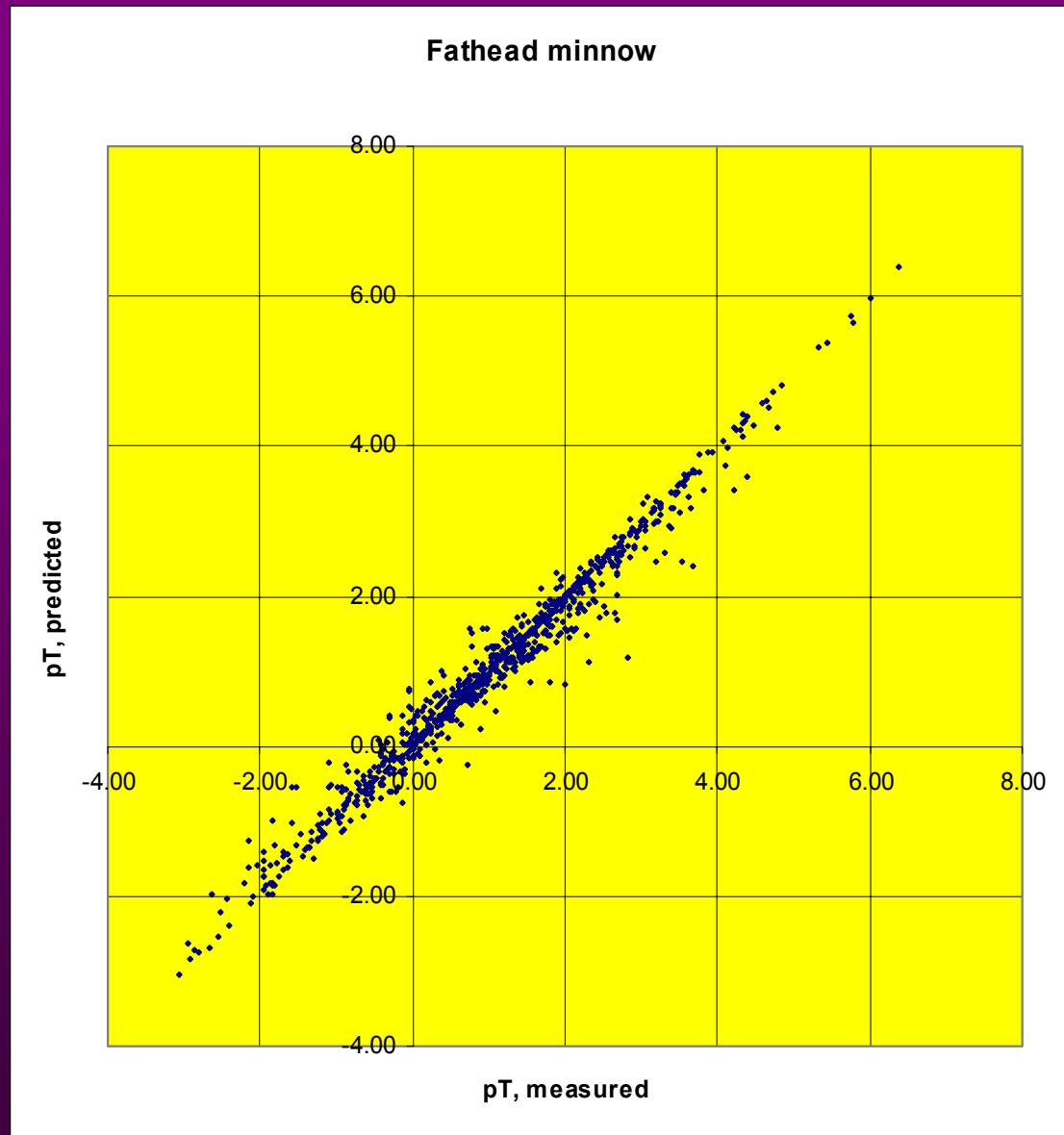
Figure 1 shows the measured vs. predicted values for all 886 compounds fathead minnow values used in the development of the **TerraQSAR - FHM** estimation program, as obtained from the program.

The data cover approximately ten orders of magnitude, ranging from  $pT = -3$  to  $pT = 7$ , where  $pT$  is the negative logarithm of the millimolar LC50 concentration,  $pT = \log (L/\text{mmol})$ .



# Figure 1

## FHM



**Table 3. Statistical indicators for TerraQSAR - FHM**

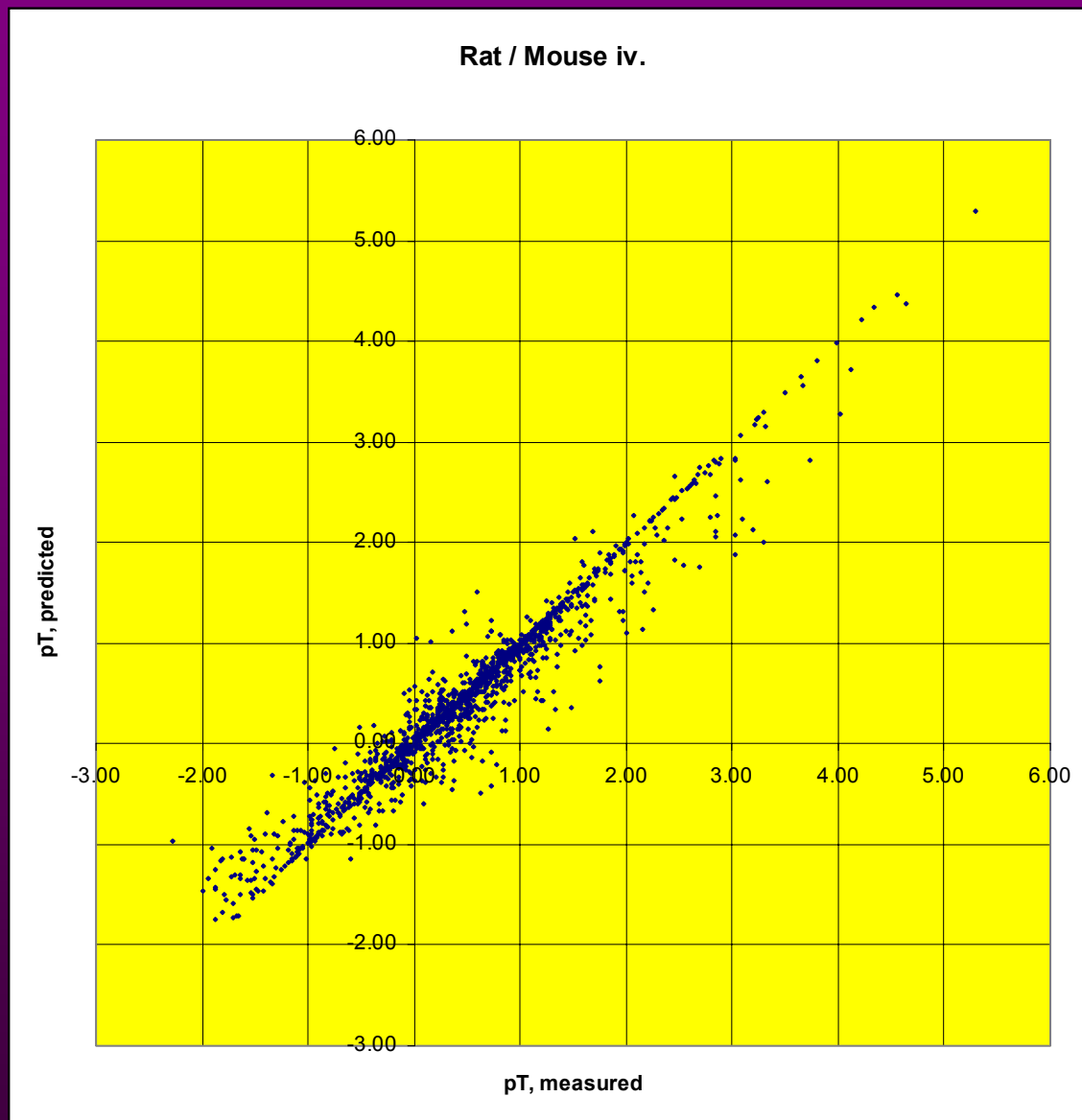
<b>Program Module</b>	<b>Indicator</b>	<b>Variable</b>
<b>FHM</b>	<b>Number of compounds</b>	<b>886</b>
	<b>Range (log units)</b>	<b>10.5</b>
	<b>Correl. coeff. (<math>r^2</math>)</b>	<b>0.979</b>
	<b>Slope</b>	<b>1.064</b>
	<b>Intercept</b>	<b>-0.061</b>
	<b>RMS* error (leave-out 33%)</b>	<b>0.192</b>
	<b>RMS error (full training set)</b>	<b>0.063</b>

\* RMS: root mean square error



## Figure 2

## RMIV



**Table 4. Statistical indicators for TerraQSAR - RMIV**

<b>Program Module</b>	<b>Indicator</b>	<b>Variable</b>
<b>RMIV</b>	<b>Number of compounds</b>	<b>1497</b>
	<b>Range (log units)</b>	<b>7.5</b>
	<b>Correl. coeff. (<math>r^2</math>)</b>	<b>0.969</b>
	<b>Slope</b>	<b>1.057</b>
	<b>Intercept</b>	<b>0.005</b>
	<b>RMS* error (leave-out 33%)</b>	<b>0.199</b>
	<b>RMS error (full training set)</b>	<b>0.076</b>

\* RMS: root mean square error



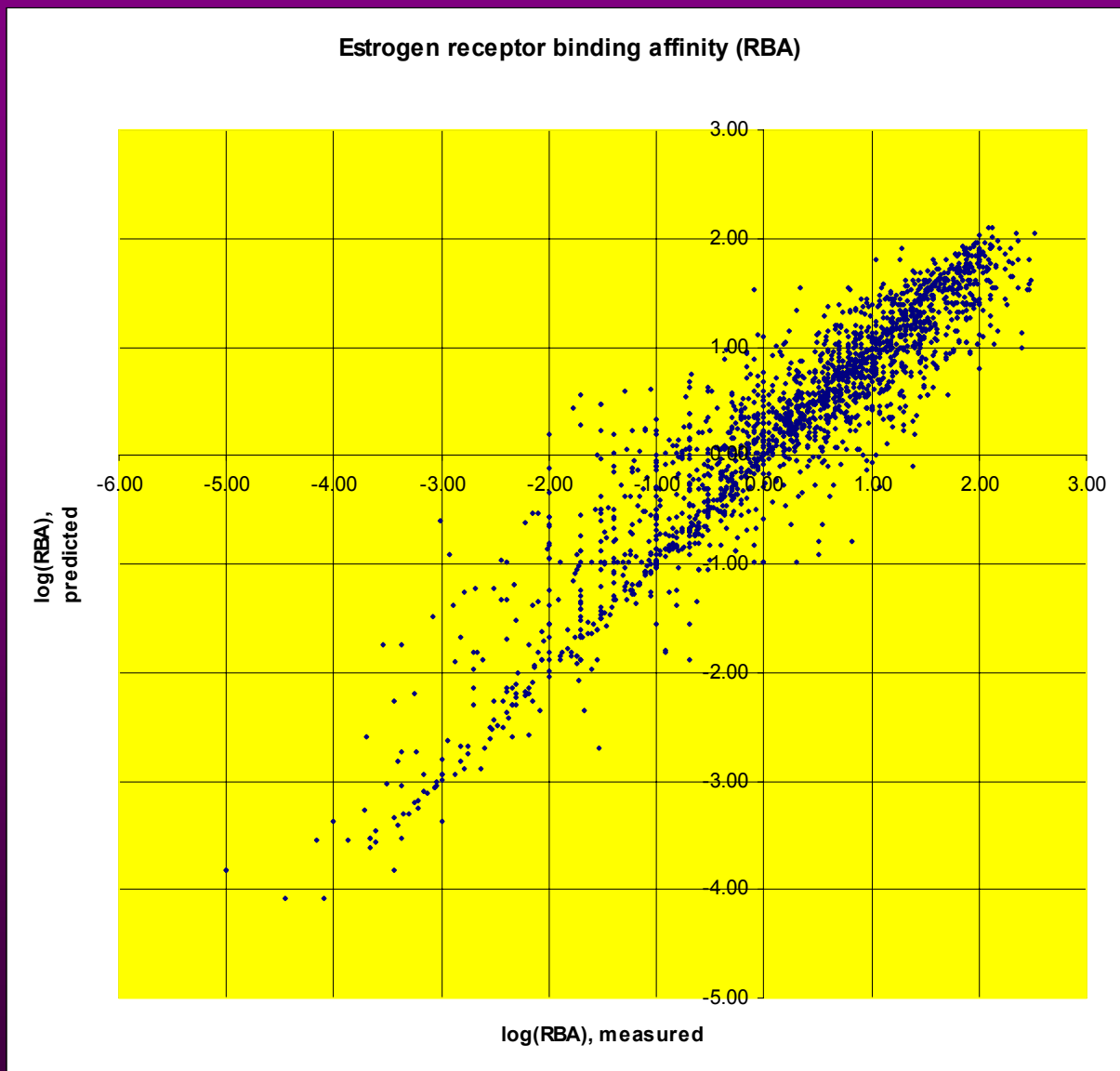
## *Note regarding the E2-RBA data*

The measured data available for this program (>2000 compounds) show a non-normal distribution with more than twice the numbers of compounds in the log(RBA) range 0 to +3 range than in the -4 to 0 range.



# Figure 3

## E2-RBA



**Table 5. Statistical indicators for TerraQSAR – E2-RBA**

<b>Program Module</b>	<b>Indicator</b>	<b>Variable</b>
<b>E2-RBA</b>	<b>Number of compounds</b>	<b>&gt; 2000</b>
	<b>Range (log units)</b>	<b>7.5</b>
	<b>Correl. coeff. (<math>r^2</math>)</b>	<b>0.930</b>
	<b>Slope</b>	<b>1.082</b>
	<b>Intercept</b>	<b>-0.068</b>
	<b>RMS* error (leave-out 33%)</b>	<b>0.250</b>
	<b>RMS error (full training set)</b>	<b>0.120</b>

\* RMS: root mean square error

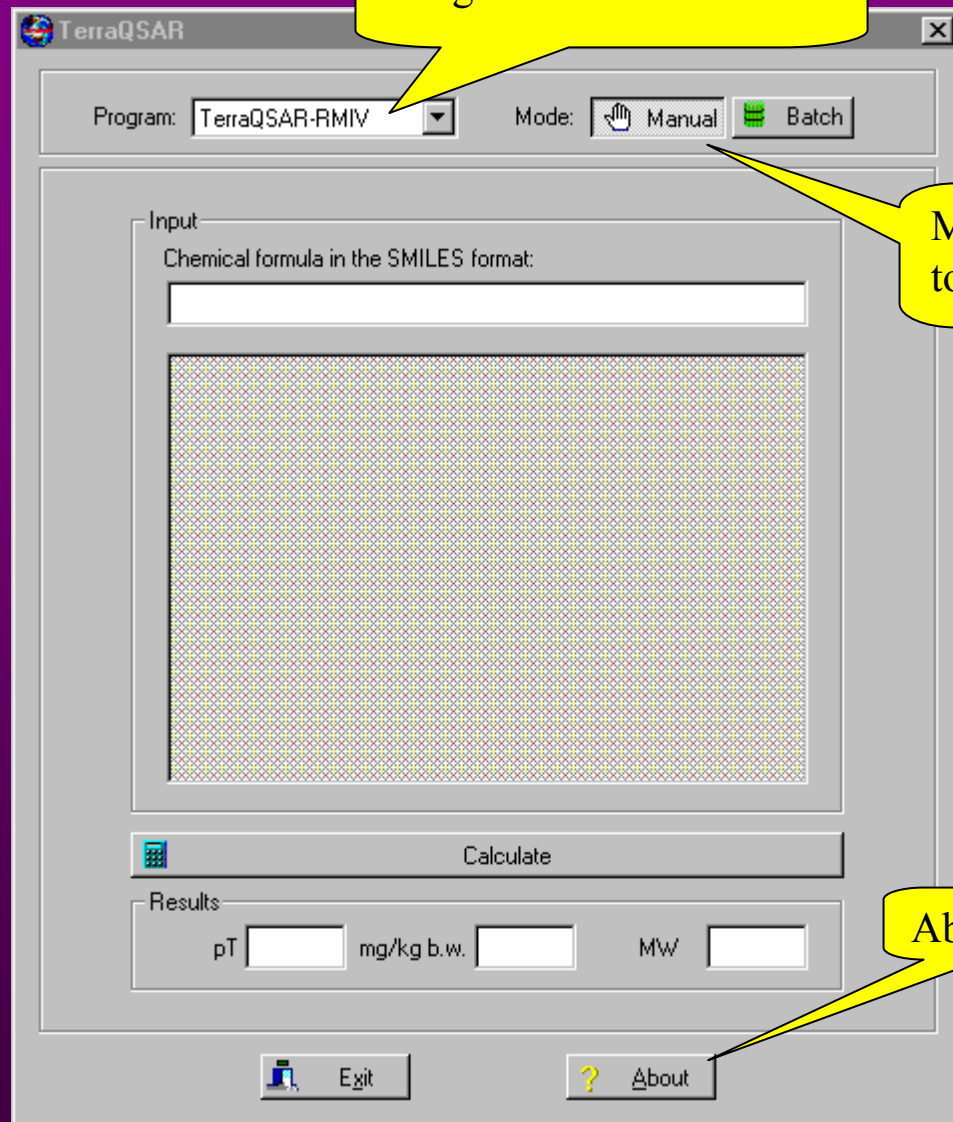


## Program Interface

The program interface of the **TerraQSAR** toxicity prediction modules is shown in the next slide.

It is simple,  
intuitive, and  
highly functional.





Program selection box

Manual / batch toggle switch

About box



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## *Example 1:*

Phenol has the SMILES string “c1ccccc1O”.

Copying this string into memory, for example from this text (making sure the quotation marks are omitted), and pasting it into the **Input field** will result in the appearance of the chemical structure of phenol in the shaded, rectangular field below, as shown in the next slide.



TerraQSAR

Program: TerraQSAR-FHM Mode: Manual Batch

Input

Chemical formula in the SMILES format:

c1ccccc1O

Calculate

Results

pT	0.510	mg/L	29.0837	MW	94.1
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Exit About



TerraBase Inc.

Once the user has ascertained that the structure of the compound is that of the desired chemical, a simple click of the **Calculate bar** below the structure field will result in the three fields below the bar to be filled with the predicted values for the compound, as shown in the next slide.

Field 1 (**pT**) is the  $-\log$  **LC50** [mmol/L];

Field 2 (**mg/L**) is the **LC50** in mg/L (FHM module);

Field 3 (**MW**) shows the **molecular weight** of the compound.



***Example 1 (continued):*** phenol “c1ccccc1O”

The fields show the following values:

- field 1 (pT) is the LC50 value in log(L/mmol): 0.51
- field 2 (mg/L) is the LC50 value in mg/L: 29.08
- field 3 shows the mol. weight of the compound: 94.1

Computation time ~ 2 sec at 2 GHz



# FHM: Erythromycin

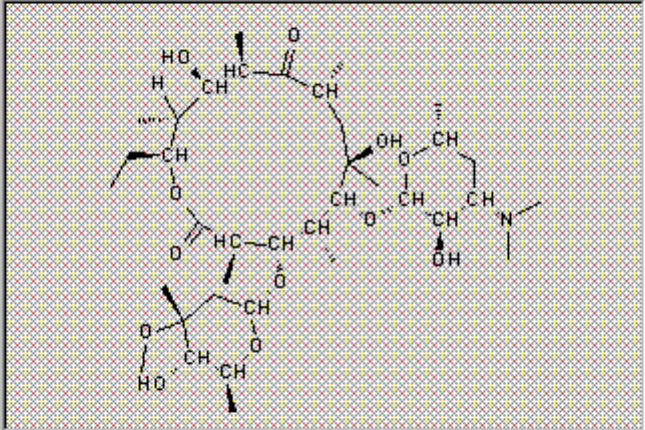
TerraQSAR

Program: TerraQSAR-FHM Mode: Manual Batch

Input

Chemical formula in the SMILES format:

```
C[C@H]1[C@H](O)[C@@](OC)(C)C[C@H](O1)O[C@H]2[C@
```



Calculate

Results

pT	2.422	mg/L	2.7182	MW	717.9
----	-------	------	--------	----	-------

Exit About



# FHM: Methoxychlor

TerraQSAR

Program: TerraQSAR-FHM Mode: Manual Batch

Input

Chemical formula in the SMILES format:

```
c1cc(OC)ccc1C(C(Cl)(Cl)Cl)c2ccc(OC)cc2
```

Calculate

Results

pT	4.660	mg/L	0.0076	MW	345.7
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Exit About



# FHM: anthraquinone dye

TerraQSAR

Program: TerraQSAR-FHM Mode: Manual Batch

Input

Chemical formula in the SMILES format:

```
[c1cccc2C(=O)c3c(cccc3C(=O)c12)Nc4cccc5C(=O)c6cc(ccc6C(=O)c45)]
```

Calculate

Results

pT	2.416	mg/L	2.4987	MW	650.6
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Exit About



# RMIV: 2-aminothiazole

The screenshot shows the TerraQSAR software interface. At the top, the window title is "TerraQSAR". Below the title bar, there is a "Program:" dropdown menu set to "TerraQSAR-RMIV" and a "Mode:" section with "Manual" selected and "Batch" as an alternative. The main area is divided into "Input" and "Results" sections. In the "Input" section, a text box contains the SMILES string "s1c(N)ncc1". Below this, a large window displays the chemical structure of 2-aminothiazole, which consists of a five-membered ring with a sulfur atom at the bottom, a nitrogen atom at the top-right, and an amino group (H<sub>2</sub>N) attached to the carbon atom at the top-left. A "Calculate" button is located below the structure. The "Results" section at the bottom shows the following values: pT: -0.760, mg/kg b.w.: 576.2628, and MW: 100.1. At the very bottom of the window, there are "Exit" and "About" buttons.

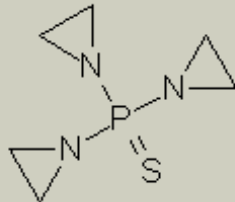


# RMIV: 2-aminothiazole

TerraQSAR

Program: TerraQSAR-RMIV Mode: Manual Batch

Input  
Chemical formula in the SMILES format:  
S=[P](N1CC1)(N2CC2)N3CC3



Calculate

Results  
pT 1.210 mg/kg b.w. 11.6673 MW 189.2

Exit About



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# RMIV: 2-aminothiazole

The screenshot shows the TerraQSAR software interface. At the top, the window title is "TerraQSAR". Below the title bar, there is a "Program:" dropdown menu set to "TerraQSAR-RMIV" and a "Mode:" section with "Manual" selected and "Batch" as an alternative. The main area is divided into "Input" and "Results" sections. In the "Input" section, a text box contains the SMILES string "s1c(N)ncc1". Below this, a large window displays the chemical structure of 2-aminothiazole, which consists of a five-membered ring with a sulfur atom at the bottom, a nitrogen atom at the top-right, and an amino group (H<sub>2</sub>N) attached to the carbon atom at the top-left. A "Calculate" button is located below the structure. The "Results" section at the bottom contains three input fields: "pT" with the value "-0.760", "mg/kg b.w." with the value "576.2628", and "MW" with the value "100.1". At the very bottom of the window, there are "Exit" and "About" buttons.



# RMIV: Rotenone

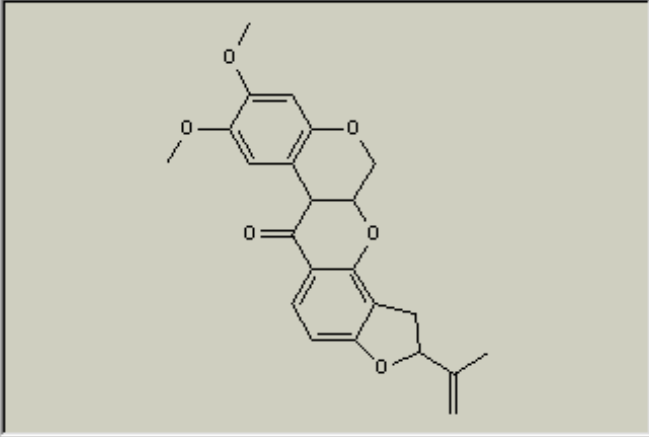
TerraQSAR

Program: TerraQSAR-RMIV Mode:  Manual  Batch

Input

Chemical formula in the SMILES format:

```
COc5cc4OCC3Oc2c1CC(Oc1ccc2C(=O)C3c4cc5OC)C(C)=C
```



Calculate

Results

pT	3.290	mg/kg b.w.	0.2023	MW	394.4
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# RMIV: Antimycin A

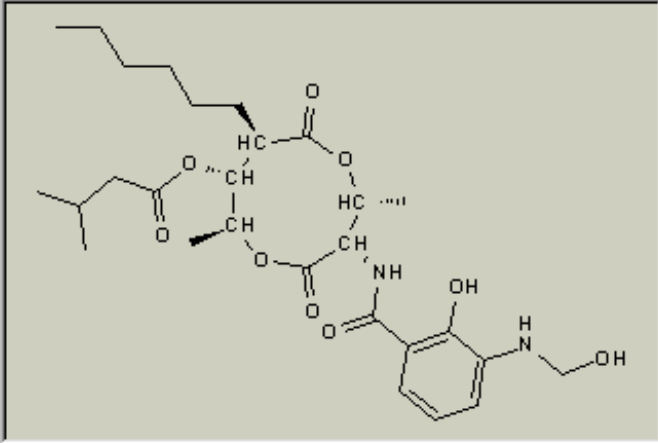
TerraQSAR

Program: TerraQSAR-RMIV Mode: Manual Batch

Input

Chemical formula in the SMILES format:

```
OCNc1cccc(c1O)C(=O)N[C@@H]2C(=O)O[C@@H](C)[C@H](OC(=O)C)C[C@@H](O)C(=O)Nc3cc(O)c(NCO)cc3
```



Calculate

Results

pT	2.790	mg/kg b.w.	0.8930	Mw	550.6
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Exit About



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## *Examples 5-8:*

The following examples of more complex molecules demonstrate the versatility of the TerraQSAR - FHM program:

- methoxychlor (pesticide),
- hexadecylphenol deriv. (surfactant),
- synthetic steroid with chiral centres (drug),
- diazo compound sulfonic acid salt (azo-dye).



# RMIV: Alcuronium dichloride

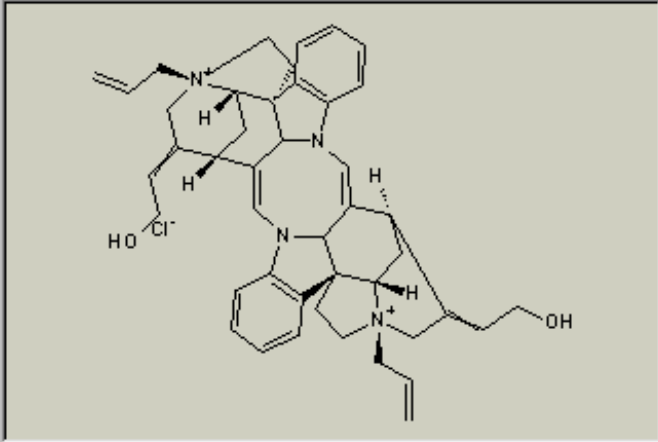
TerraQSAR

Program: TerraQSAR-RMIV Mode: Manual Batch

Input

Chemical formula in the SMILES format:

```
3[C@@]47CC[N@+]5(CC=CCO)[C@@]([H])([C[C@@]45[H]])C(C67)=
```



Calculate

Results

pT	3.490	mg/kg b.w.	0.2388	MW	737.8
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Exit About

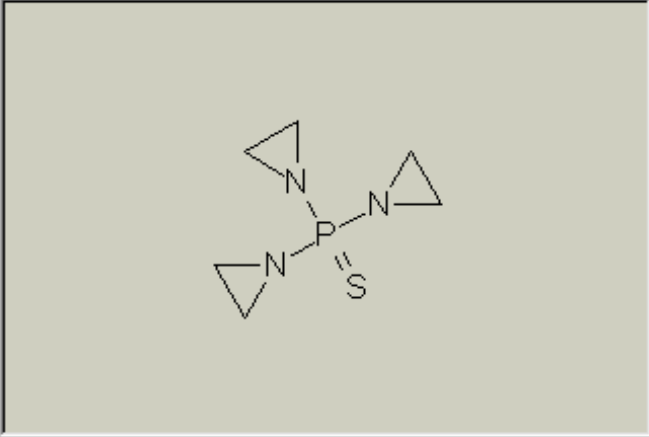


# RMIV: 2-aminothiazole

TerraQSAR

Program: TerraQSAR-RMIV Mode: Manual Batch

Input  
Chemical formula in the SMILES format:  
S=[P](N1CC1)(N2CC2)N3CC3



Calculate

Results  
pT 1.210 mg/kg b.w. 11.6673 MW 189.2

Exit About



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# RMIV: Tetrodotoxin



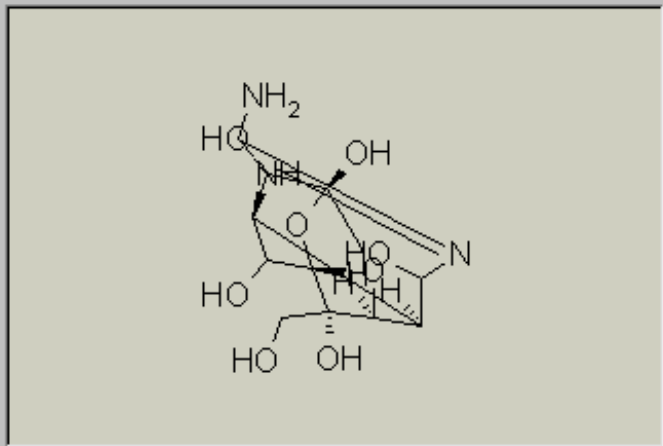
TerraQSAR

Program: TerraQSAR-RMIV Mode: Manual Batch

Input

Chemical formula in the SMILES format:

```
[C@@]23([H])[C@@]([C@]4([H])[C@]1([H])C(O)N=C(N)N[C@@]1(C
```



Calculate

Results

pT	4.640	mg/kg b.w.	0.0073	Mw	319.3
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Exit About



## *Limitations and Rules*

### *1. Metal ions*

TerraQSAR considers all metal ions equal, that is as non-toxic components of the substance. This is correct for sodium, potassium, calcium, etc. salts, but incorrect for salts of copper, cadmium, etc., The latter have their own (metal ion) toxicity, in addition to the toxicity of the organic moiety.

Therefore, the toxicity of salts of organic anions with **toxic** metal ions will be underestimated by the toxicity contribution of the metal ion and corrections will have to be applied for such.



## *Limitations and Rules*

### *2. Organo-metal compounds with covalent bonds*

TerraQSAR computes the correct values for compounds with carbon-metal covalent bonds, such as tin and silicon organo-metal compounds (e.g., diethyl-dibutyltin, CCCC[Sn](CC)(CC)CCC) with high accuracy.

Therefore, no corrections needs to be applied for these types of substances.



## *Limitations and Rules*

### *3. Organo-metal compounds with $\pi$ bonds*

Due to limitations of the Accelrys software in correctly representing organo-metal  $\pi$  bond complexes at this time (such as in **ferrocene**), TerraQSAR cannot compute values for such compounds.



## *Limitations and Rules*

### *4. Tautomers*

TerraQSAR will compute the correct value for each **tautomer**, but does not average or proportion their relative abundance.

Therefore, the user must decide which tautomer is the most important one for his purpose.

Example: **2-pyridone** (FHM module)

keto-tautomer:  $pT = -0.11$

enol-tautomer:  $pT = -0.61$



## *Technical Requirements*

### *Operating system:*

PC with W95, 98, NT, 2000, or ME OS operating systems; ready for Windows XP, subject to Accelrys software update for XP.

### *Central processor unit (CPU):*

No specific requirement, speed of computations will increase with decrease in CPU speed; 2 GHz or higher recommended.

*Mouse, or other pointing device:* required.

*Screen setting:* Variable, 800 x 640, or higher.

*Other:* CD-ROM drive.



## Literature – Neural Network Theory

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## Literature – Neural Network Applications

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## *Literature – SMILES code*

Daylight Chemical Information Systems, Inc. (2002);

[http://www.daylight.com/smiles/f\\_smiles.html](http://www.daylight.com/smiles/f_smiles.html)



**TerraBase Inc.**

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**TerraBase Inc.**

## *Future developments:*

TerraQSAR modules for other endpoints:

HIV-1

BIODEG

logP



## *TerraBase Inc. profile*

Founded in 1996, **TerraBase Inc.**, a Canadian company, produces specialty toxicity estimation programs and unique databases for scientific research in the health, pharmaceutical, pesticide, environmental risk assessment and waste management fields. TerraBase Inc. also provides toxicological and physico-chemical property estimation, data retrieval and substance classification services for scientific research and industry.

TerraBase Inc. is a leader in desktop computer software for structure-activity, structure-property and inter-species relationships. Our TerraTox™ and TerraQSAR™ products are unrivalled. They provide provide fast access to toxicity and physico-chemical data for thousands of chemicals of common interest, including pesticides, drugs, dyes, chemical intermediates, and their metabolites.

TerraBase Inc. products are used by government agencies, universities, and leading industrial R&D departments in America, Europe, Asia.



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