

TerraQSAR™ - LOGP

Octanol/Water Partition Coefficient Estimation Software, vs. 2.1

User Manual

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Purpose

TerraQSAR™ - logP is a holistic, probabilistic-algorithm-based neural network software program, designed and optimized solely for the computation of *n*-octanol/water partition coefficients, commonly referred to as logP or K_{ow} of organic (carbon-containing) substances with a defined chemical structure.

Table of Contents

Purpose	1
Table of Contents	1
Introduction.....	2
Theory.....	2
Computation Process	2
Data Set.....	2
Fragments.....	3
Input Query	3
Computation.....	3
Results.....	3
SMILES Notation.....	4
Literature.....	5
Acknowledgement.....	8
Security Features	8
Legal	9
License Agreement	9
Trademarks and Copyrights	14
Program Interface	15
Technical Requirements	22
Installation Instructions	22
Part 1. Installation of the Accelrys software.....	22
Part 2. Installation of TerraQSAR.....	22
Customer Support.....	22

Introduction

Welcome to **TerraQSAR™**, a breakthrough development in toxicity estimation software, developed by [TerraBase Inc.](#)

TerraQSAR™ toxicity estimation software is based on the probabilistic neural network methodology using the molecular structure of the substances under investigation. The **TerraQSAR™ - logP** program estimates the n-octanol/water partition coefficients of organic compounds.

TerraQSAR modules use as input a 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.

The **TerraQSAR™ - logP** module computes the partition coefficient and its base-10 logarithmic derivative, commonly known as logP or logK_{ow}, as well as the molecular weight (MW) of substances entered.

Theory

The field of artificial intelligence and neural network application is experiencing rapid growth in all aspects of technology. From elevator control to drug design, neural network methods have lots to contribute to product development, operating improvements, and frequently enable the customer to tackle problems, which were inaccessible hitherto.

The **TerraQSAR** products exploit the neural network methodologies developed in recent years by researchers and programmers both within and outside the company. In contrast to linear methodologies, such as simple regression methods, principal components analysis and others, neural networks make use of non-linear relationships, which makes them particularly useful for chemical/biological problems where different and/or unknown modes of action are known or likely to be present, in addition to linear relationships.

Important information on both the theory and specific aspects of this software can be found in the references given in the [Literature](#).

Computation Process

Data Set

The **TerraQSAR™ - logP** octanol/water partition coefficient computation program is based on a data set of measured values for 4,000+ organic (carbon-containing) compounds. These data are available from TerraBase Inc.'s **TerraTox™ - Explorer** database.

Fragments

Major fragments used in the **TerraQSAR** modules have been described in detail in several publications listed in the [Literature](#), especially the works by Kaiser *et al.* An overview of basic fragment types considered is given in Table 1 below.

Table 1. Examples of fragments used in **TerraQSAR**.

Fragment type	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

Input Query

All **TerraQSAR** modules use the SMILES string code as input. For additional comments about the SMILES code, refer to the paragraph on [SMILES Notation](#).

Computation

The computer evaluates the number and type of [fragments](#) present in the query string and computes the resulting estimate on the basis of the same types of fragments present in a data set of 4000+ compounds for which measured values have been published in the literature. Computation time varies with the complexity of the query structure and speed of the computer. Typically, for compounds without chiral centers, and a molecular weight of <200, computation time on a 2 GHz machine takes <5 seconds.

Results

Figure 1 shows the measured vs. predicted values for all 4,000+ compounds used in the development of the **TerraQSAR – logP** estimation program, as obtained from the program. The data cover approximately fourteen orders of magnitude, ranging from approximately $\log P = -4$ to $\log P = 10$.

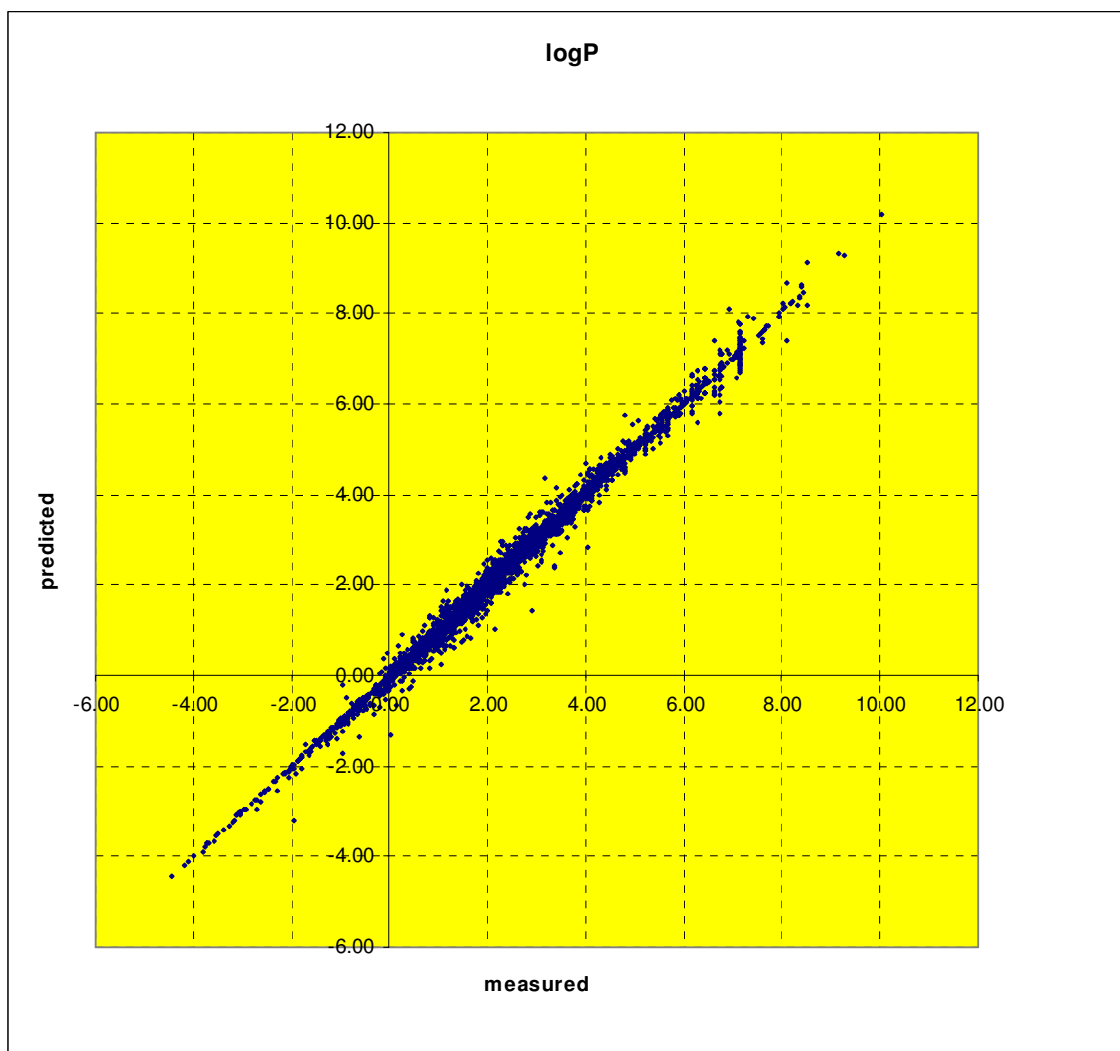


Fig. 1. Plot of the measured vs. predicted octanol/water partition coefficient values for all 4,000+ compounds in the training set; units are logP. LOO-RMSE = 0.11

SMILES Notation

The Simplified Molecular Input Line Entry System (SMILES) has been developed by D. Weininger at the beginning of the 1980's. It is far superior to the previously used Wiswesser Line Notation (WLN) for coding and depicting chemical structures, by being simple, intuitive, and machine readable. For an excellent tutorial on the SMILES notation, refer to the [Daylight Corp.](#) web site.

Recently, [Accelrys Inc.](#) introduced a variety of software modules allowing the visualization of SMILES codes as chemical structure drawings. In this process, Accelrys introduced changes to the common (Daylight Corp.) interpretation of SMILES codes by their software. As a result, lower case "c", formerly only interpreted as sp^2 carbon, is now interpreted as either as sp^2 or sp^3 carbon, depending on its surrounding and connections to other atoms. The determinant here is whether or not the carbon atom is part of an aromatic

ring, as defined by the Hueckel rules. This has ramifications for the correct interpretation of SMILES strings by the **TerraQSAR** programs, as they are built on the backbone of the Accelrys software. Therefore, all users are cautioned to ascertain that their SMILES codes follow the rules of the Accelrys software, i.e., to ascertain that only sp^2 carbons in ring systems which satisfy Hueckel conditions for aromaticity are given in lower case “c”; all other sp^2 carbons, whether in rings or not, must be entered as capital “C”. Some examples of valid and not valid SMILES strings are listed below in Table 2.

Table 2. Valid and not valid examples of Accelrys’ SMILES code.

Substance	SMILES not valid	SMILES valid
cyclopentadiene ^a	c1cccC1	C1=CC=CC1
coumarin ^a	c1cc2OC(=O)ccc2cc1	c1cc2OC(=O)C=Cc2cc1

^a The SMILES strings shown as “not valid” are valid *per se*, however, the interpretation of these codes are the hydrogen-saturated compounds cyclopentane and 3,4-dihydrocoumarin, respectively.

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Acknowledgement

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Program Interface

The program interface of the **TerraQSAR** toxicity prediction modules is shown in Figure 2. It is simple, intuitive, and highly functional.

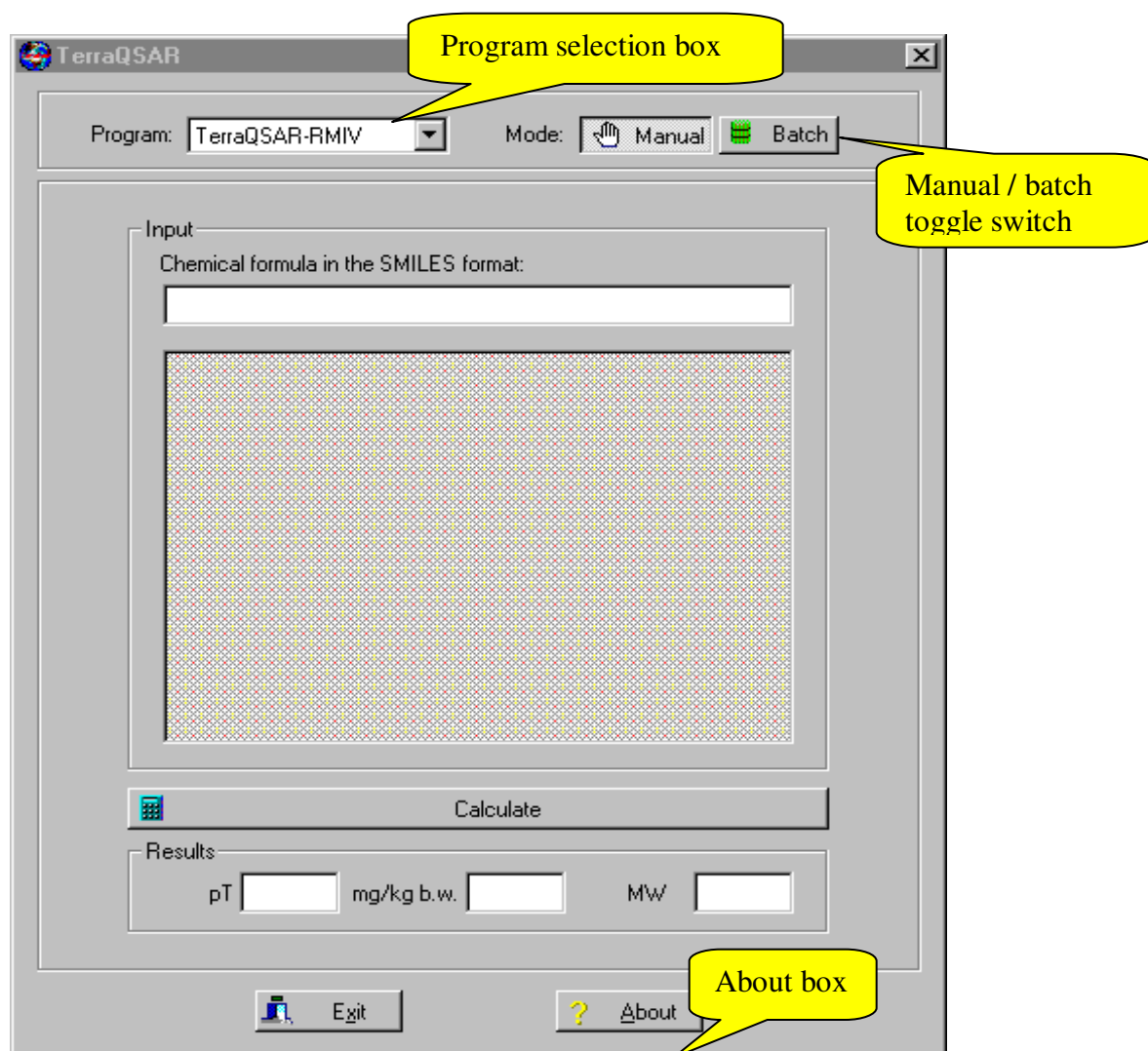


Fig. 2. The Program Interface as it appears on startup.

The Program selection box allows the user to switch between purchased program modules, e.g., “FHM” for fathead minnow 96-hr LC50, “E2-RBA” for estrogen receptor binding relative to 17 β -estradiol, “RMIV” for rat / mouse *iv.* LD50, etc. The second box provides a toggle switch between Manual mode and Batch mode (available in the Professional version only). The About box contains important user information.

In the Manual mode, the user enters a SMILES (Simplified Molecular Input Line Entry System) string, either by typing it into the Input field, or by pasting it from memory, when copied into memory from another source, such as a TerraBase Inc. database output. Please consult the section on [SMILES Notation](#) for important advice.

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 Figure 3.

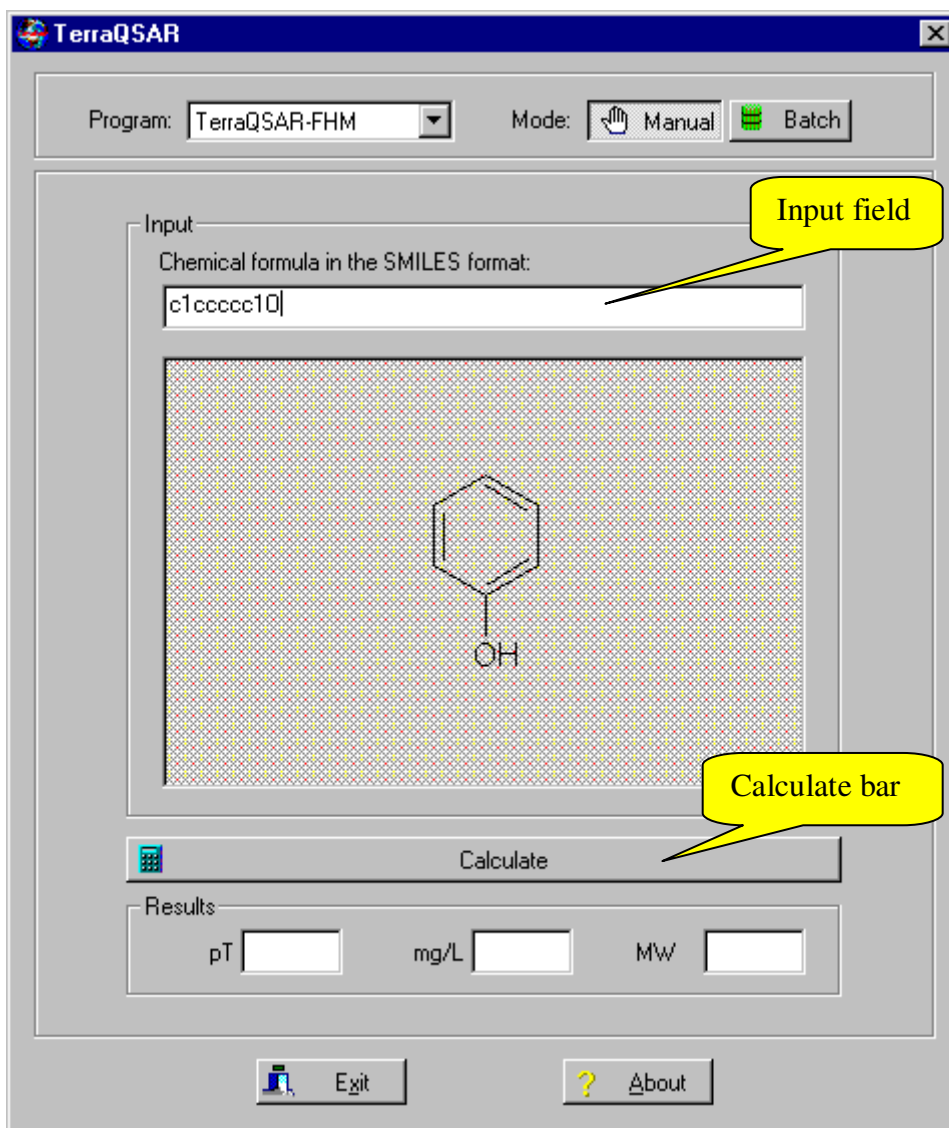


Fig. 3. Result of entering or pasting the SMILES string for phenol (c1ccccc1O) into the input field: the structure of phenol (excluding hydrogen atoms) will appear in the field below.

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 Figure 4. Field 1 (pT) is the negative logarithm of the LC50 concentration in mmol/L; field 2 (mg/L) is the LC50 value in mg/L; and field 3 (MW) shows the molecular weight of the compound. Computation time varies with the complexity of the structure and the computer specifics, ranging from a nearly instantaneous result (~1 sec) for small structures to minutes for large molecules with highly complex structures.

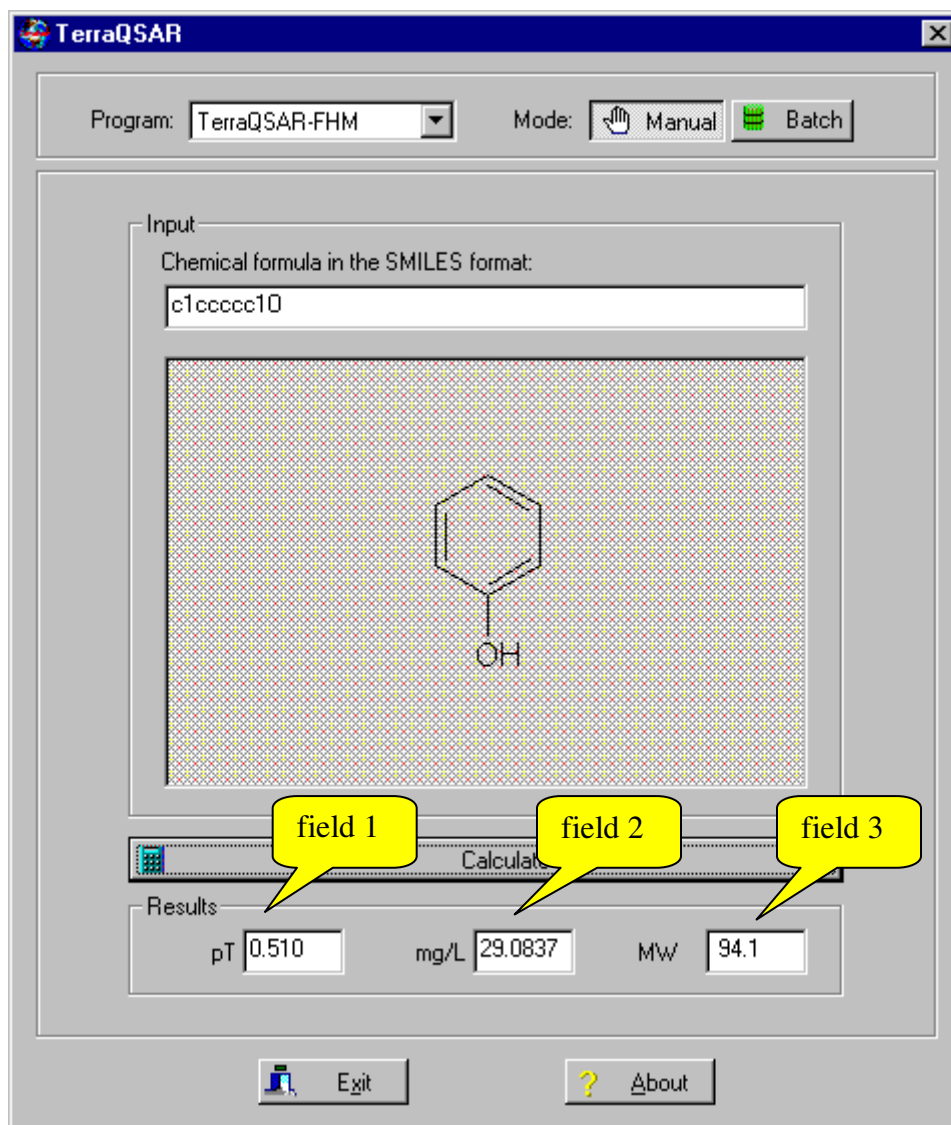


Fig. 4. Result of the execution of “Calculate”. The fields show the following values: Field 1 (pT) is the negative logarithm of the millimolar LC50 concentration, field 2 (mg/L) is the LC50 value in mg/L, and field 3 shows the molecular weight of the compound. Computation time ca. 2 sec at 2 GHz.

Example 2: A more complex molecule, the insecticide p,p'-Methoxychlor, with the SMILES and structure shown in Figure 5, has a computed LC50 value of 0.0076 mg/L, as shown in Figure 5.

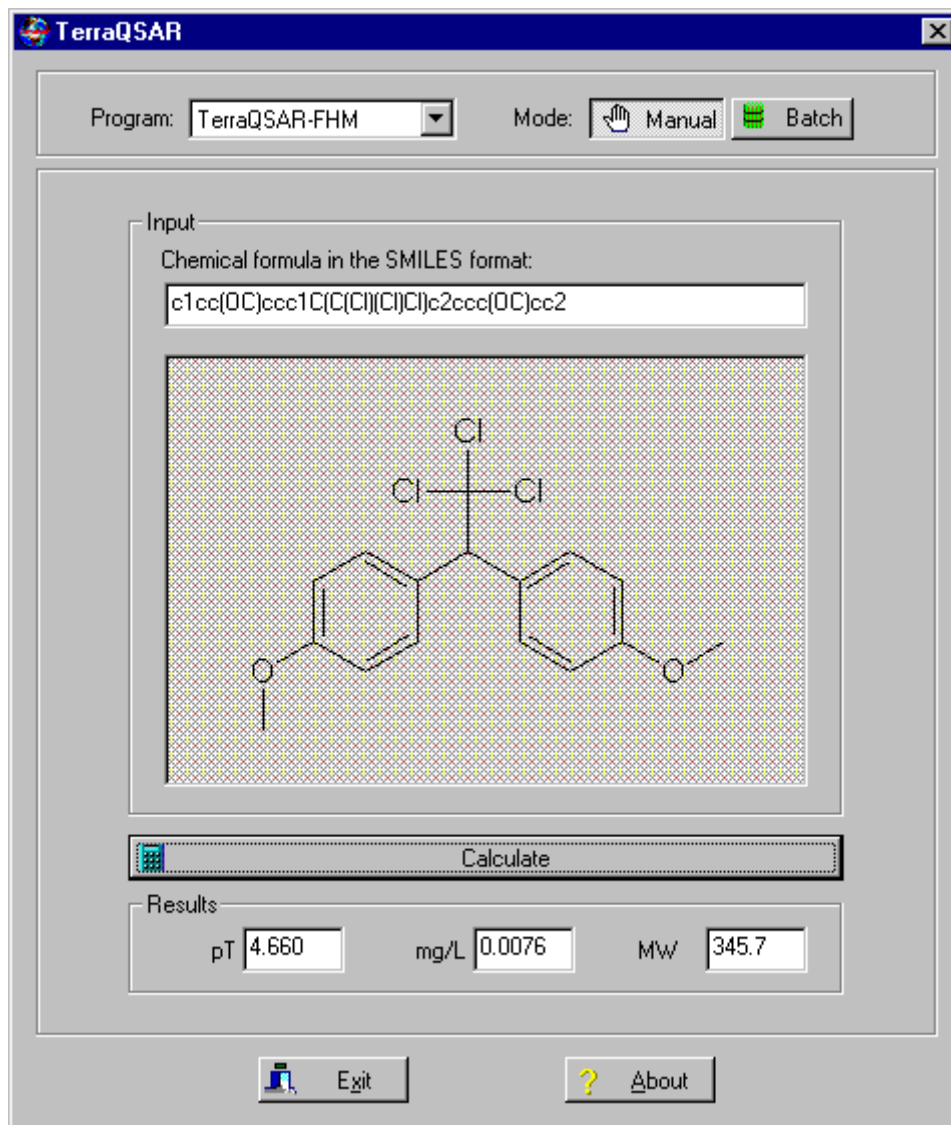


Fig. 5. Result of computation for the insecticide p,p'-Methoxychlor, SMILES string shown in the input field, depicting the compound p,p-Methoxychlor, with its computed 96-hr LC50 value for fathead minnow of 0.0076 mg/L.

Example 3: The insecticide Noviflumuron, CAS 121451-02-3, has a predicted fathead minnow 96-hr LC50 of 0.89 mg/L, as shown in Figure 6.

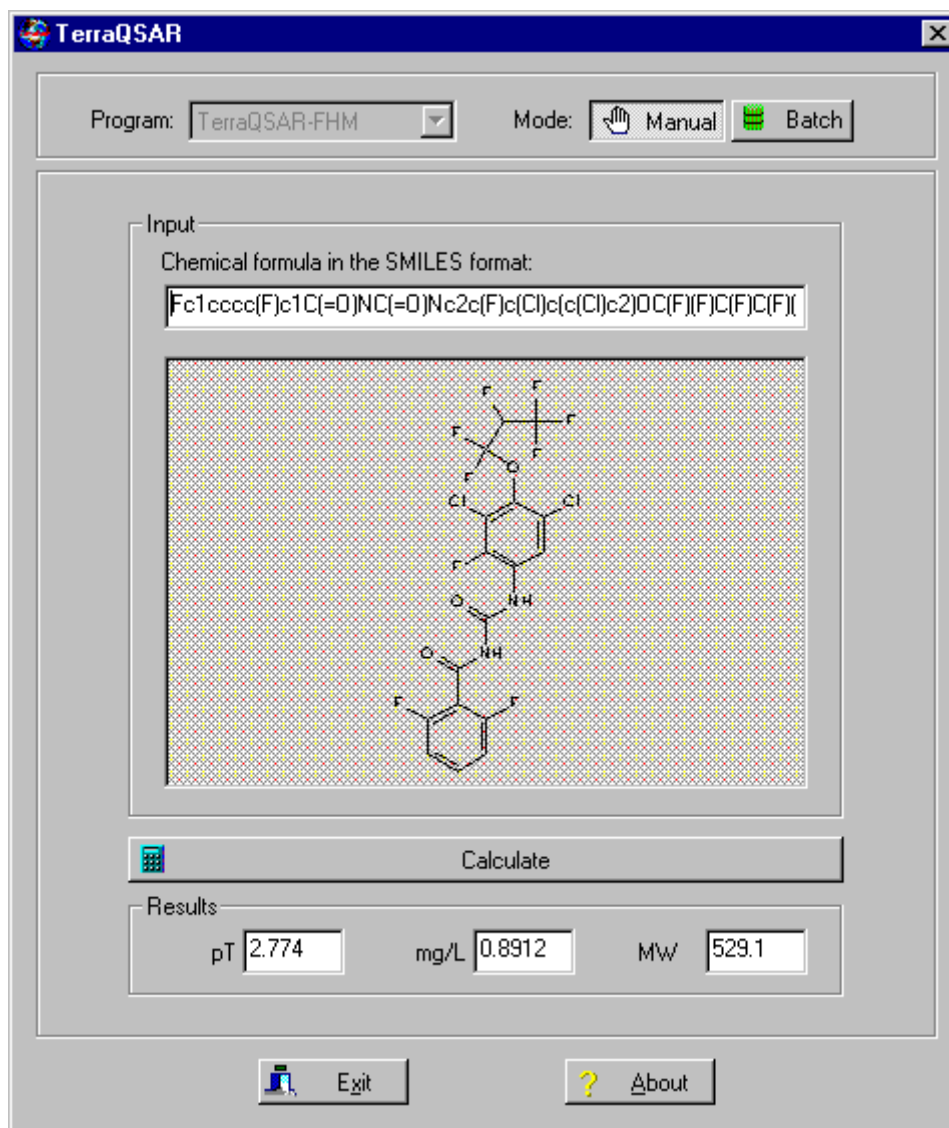


Fig. 6. Result of computation for the SMILES string shown in the input field, depicting the insecticide Noviflumuron, with its computed 96-hr LC50 value for the fathead minnow of 0.89 mg/L.

Example 4: The antibiotic compound Erythromycin B, CAS 527-75-3, with the 3D-SMILES code
C[C@H]1[C@H](O)[C@@](OC)(C)C[C@H](O1)O[C@@H]2[C@@H](C)C(=O)O[C@@H](CC)[C@@](C)([H])[C@@H](O)[C@@H](C)C(=O)[C@H](C)C[C@](O)(C)[C@@H]([C@@H]2C)O[C@@H]3O[C@H](C)C[C@H](N(C)C)[C@H]3O
(only a part of the SMILES code is visible in the Input field) has a predicted octanol/water partition coefficient of -0.14, as shown in Figure 7; computation time ca. 50 sec at 2 GHz.

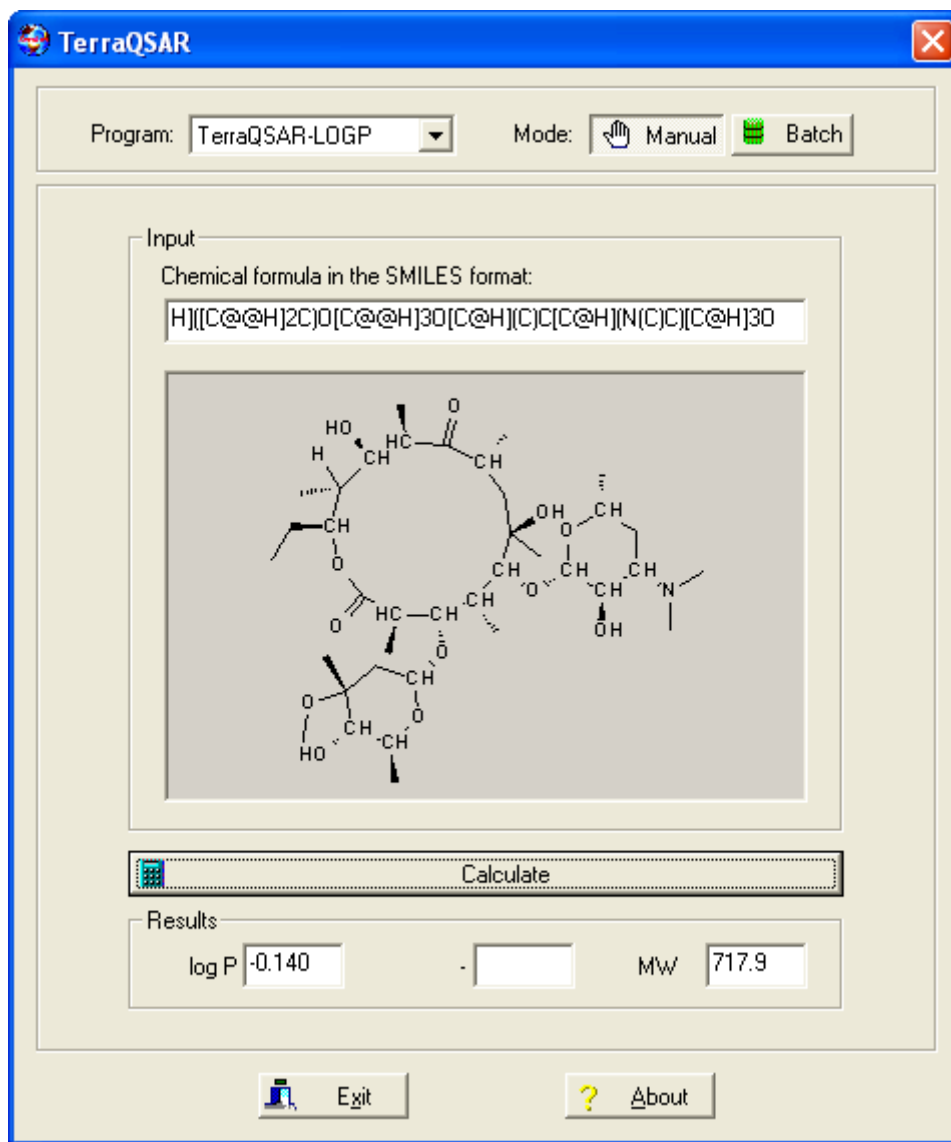


Fig. 7. Result of computation for the SMILES string shown in the input field, depicting the antibiotic Erythromycin B, with the computed octanol/water partition coefficient of -0.14.

Example 5:

An anthraquinone dye, CAS 4478-06-2, with the molecular formula C₄₂H₂₂N₂O₆, and the SMILES code:

c1cccc2C(=O)c3c(cccc3C(=O)c12)Nc4cccc5C(=O)c6cc(ccc6C(=O)c45)Nc6cccc7C(=O)c8cccc8C(=O)c67 (only a part of the SMILES code is visible in the Input field) and the

structure shown, has the predicted fathead minnow 96-hr LC₅₀ of 8.1 mg/L, as shown in Fig. 8.

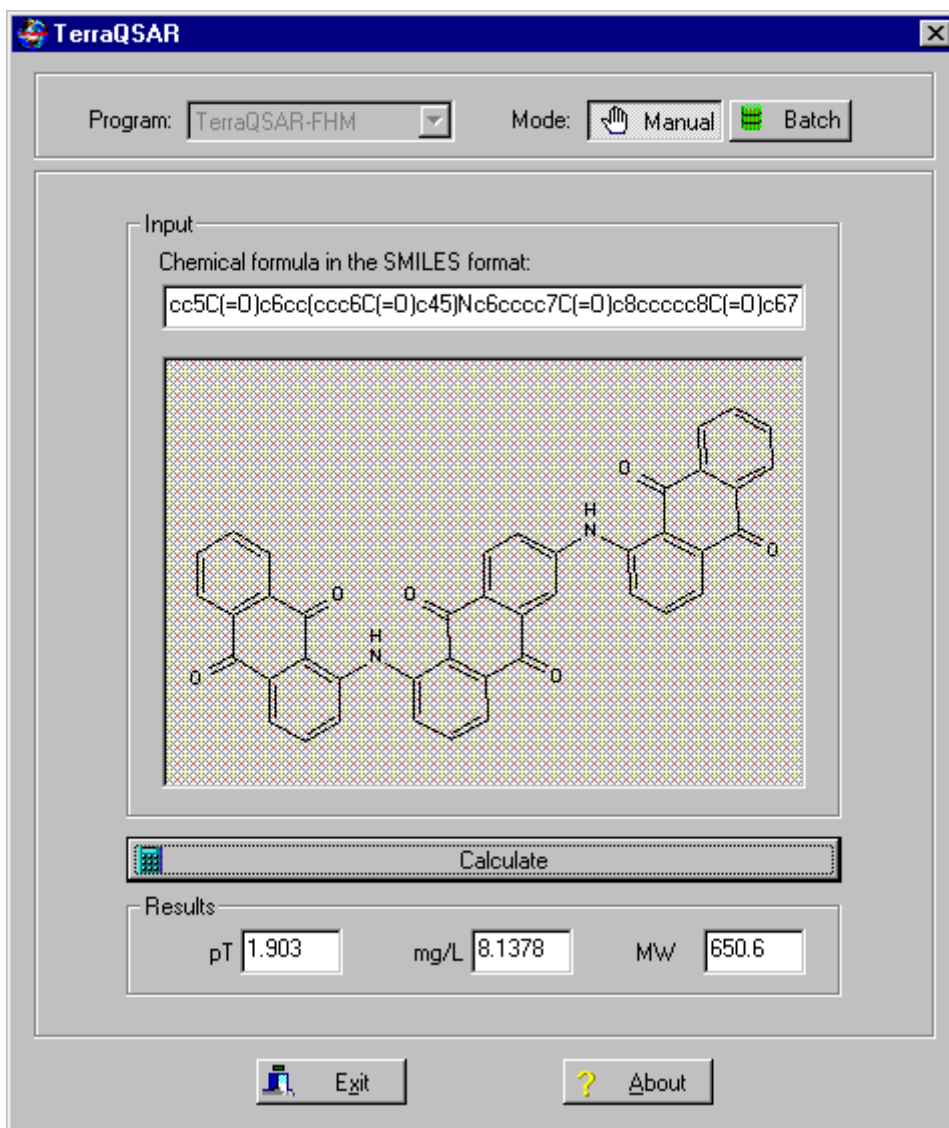


Fig. 8. Result of computation for the SMILES string shown in the input field, depicting an anthraquinone dye, with the computed 96-hr LC₅₀ value for the fathead minnow of 8.1 mg/L.

Technical Requirements

Operating system: PC with Windows 98, NT, 2000, ME, XP (SP2), or Vista, operating system.

Central processor unit (CPU): No specific requirement, duration of computations will increase with decrease in CPU speed; 1.6 GHz or higher recommended.

Mouse or other pointing device: required.

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

CD-ROM drive: required.

Other: Presence of the **TerraQSAR** CD in the CD-ROM drive is required for program execution.

Installation Instructions

The **TerraQSAR** software is a fully functional, stand-alone system, easy to install or uninstall. It consists of two installation parts; we recommend installation in the order mentioned.

Part 1. Installation of the Accelrys software

To install/un-install the Accelrys supporting software, necessary for the proper functioning of the **TerraQSAR** program, follow the instructions in the README file.

Part 2. Installation of TerraQSAR

To install **TerraQSAR**, double click on the TerraQSAR-LOGP Setup file in the root directory.

Customer Support

[TerraBase Inc.](http://www.terrabase.ca) is committed to effective customer support. With the rapid change in PC technology, operating systems and other software and hardware developments, the occasional hiccup is bound to happen. We will try our best to help customers with problems related to our products, in most cases free of charge. Contact our help department with any question and concern about our products, either by EMAIL, FAX, or MAIL.

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