

# TerraQSAR<sup>TM</sup> - RMIV

## Rat / Mouse *intravenous* LD50 Estimation Software, vs. 3.1

### User Manual

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#### Purpose

TerraQSAR<sup>TM</sup> - RMIV is a holistic, probabilistic-algorithm-based neural network software program, designed and optimized solely for the computation of single dose, *intravenous* route of exposure, median lethal concentrations (LD50) of organic (carbon-containing) substances with a defined chemical structure to the rat and mouse.

#### 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 .....	24
Installation Instructions .....	24
Part 1. Installation of the supporting software .....	24
Part 2. Installation of TerraQSAR .....	24
Customer Support.....	24

## Introduction

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

**TerraQSAR** prediction software is based on the probabilistic neural network methodology using the molecular structure of the substances under investigation. The **TerraQSAR - RMIV** program computes the *intravenous* lethal dose of organic compounds to 50% of a population (*iv.* LD50) of the rat (*Rattus norvegicus*) or mouse (*Mus musculus*).

**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 - RMIV** module computes the LD50 in both mg/kg and pT (log [kg body weight]/mmole) units, 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 - RMIV** rat / mouse LD50 toxicity estimation program is based on a data set of measured values for over 6000 organic (carbon-containing) compounds. These data are widely available, both from non-commercial sources, such as the US National Institute of Health's database, or from commercial sources, such as 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** programs.

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

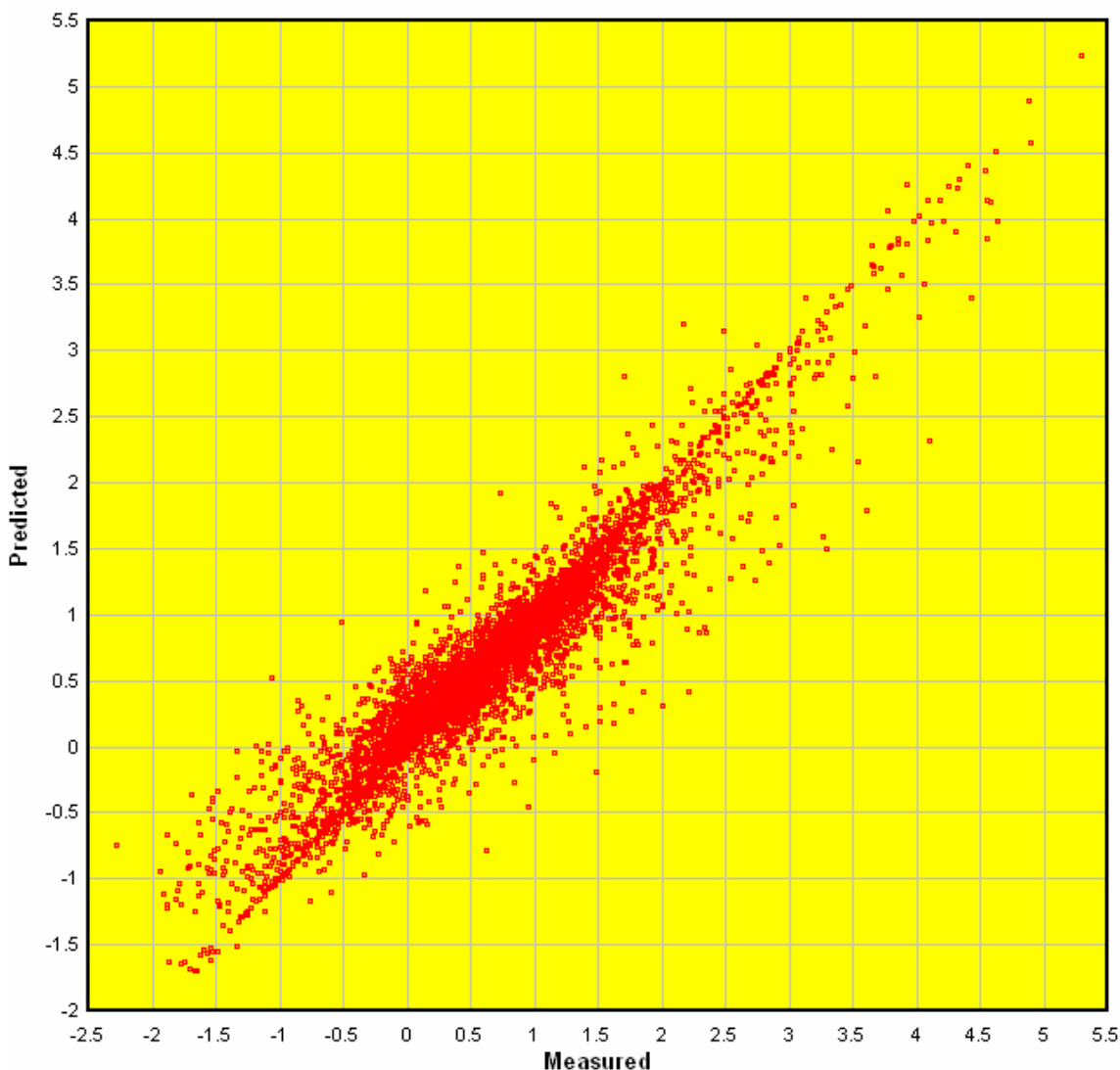
All **TerraQSAR** modules use the SMILES string code as input. For additional comments about the SMILES code, refer to the paragraph on [SMILES Notation](#).

## 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 2457 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 molecular weight of <200, computation time on a 2 GHz machine takes <5 seconds.

## Results

Figure 1 shows the measured vs. predicted values for the 6000+ compounds used in the development of the **TerraQSAR - RMIV** rat /mouse LD50 estimation program, as obtained from the program. The data cover approximately eight orders of magnitude, ranging from approximately  $pT = -2$  to  $pT = 7$ , where  $pT$  is the negative logarithm of the millimolar LD50 value per kg body weight (b.w.).



**Fig. 1.** Plot of the measured vs. predicted rat / mouse *iv.* LD50 values for 6000+ compounds in the training set; units are pT, equal to  $\log([\text{kg b.w.}]/\text{mmol})$ . The cross-validation leave-one-out (LOO) root mean square error (RMSE) = 0.12.

## 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  $\text{sp}^2$  carbon, is now interpreted as either as  $\text{sp}^2$  or  $\text{sp}^3$  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 Hückel 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 Hückel 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 <b>not valid</b>	SMILES <b>valid</b>
cyclopentadiene <sup>a</sup>	c1cccC1	C1=CC=CC1
coumarin <sup>a</sup>	c1cc2OC(=O)ccc2cc1	c1cc2OC(=O)C=Cc2cc1

<sup>a</sup> 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.

## Literature

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## **Acknowledgement**

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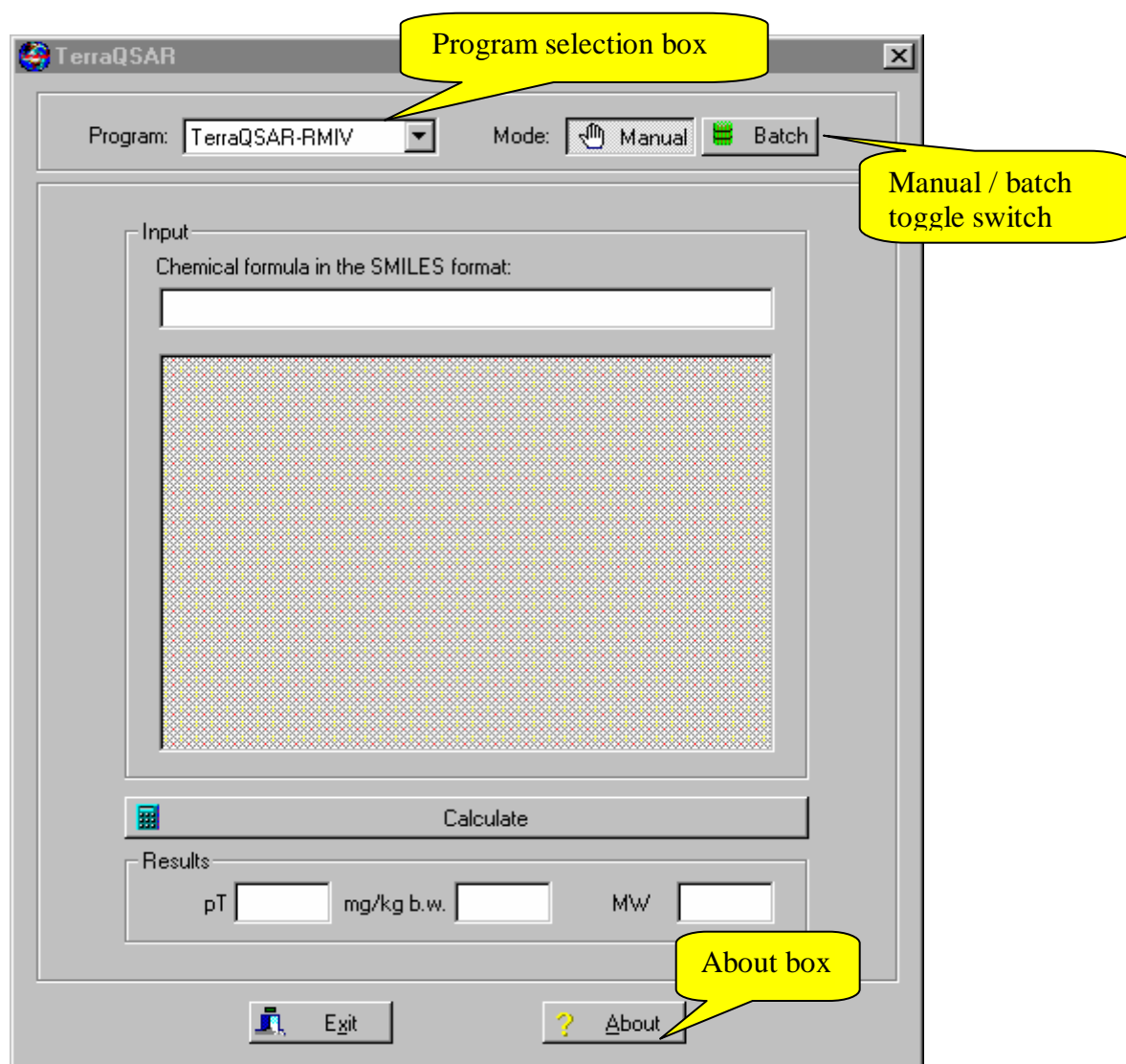
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## Program Interface

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



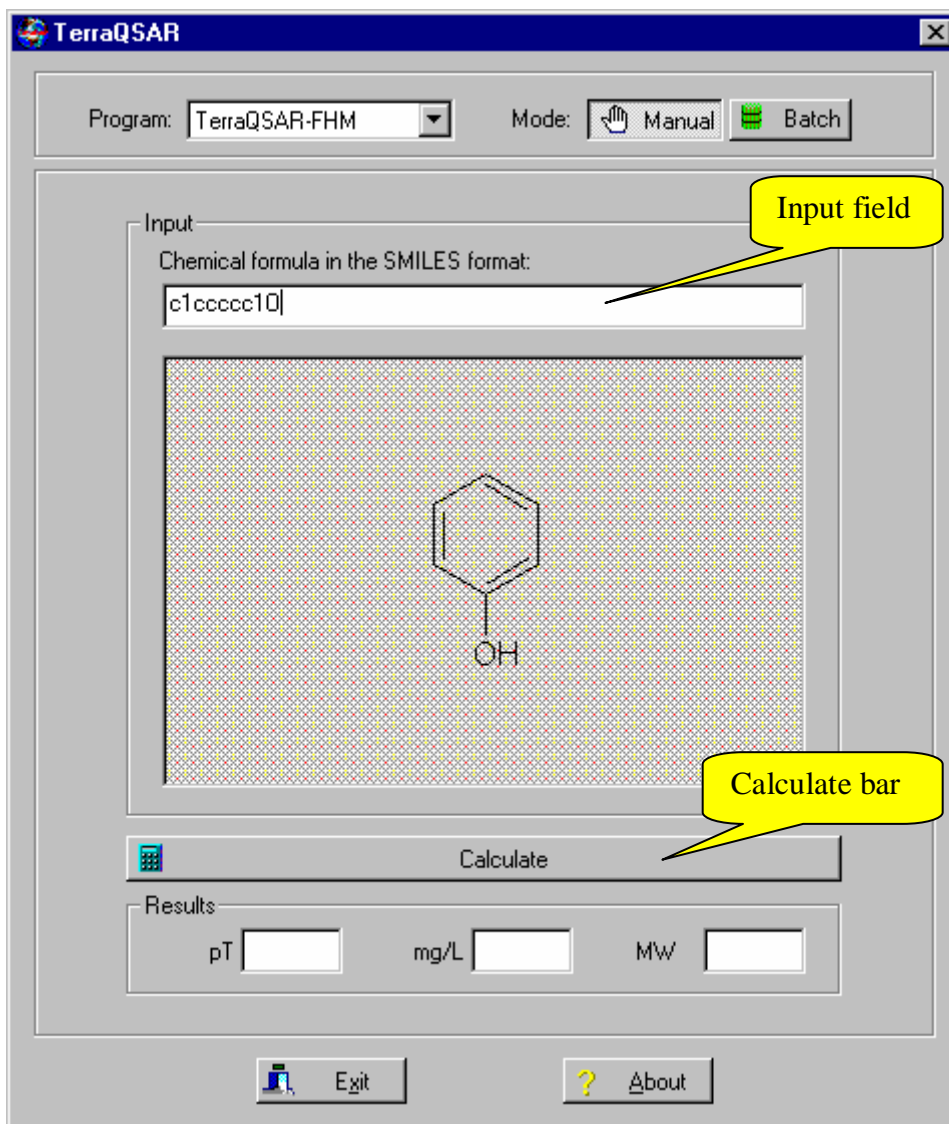
**Fig. 2.** The Program Interface as it appears on startup.

The Program selection box allows the user to the selected program, e.g. “TerraQSAR-FHM” for the TerraQSAR - fathead minnow LC50 estimation module, “TerraQSAR-RMIV” for the TerraQSAR - rat / mouse *iv.* LD50 module, etc. The second box provides a toggle switch between switch between Manual mode and Batch mode (the latter is 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.

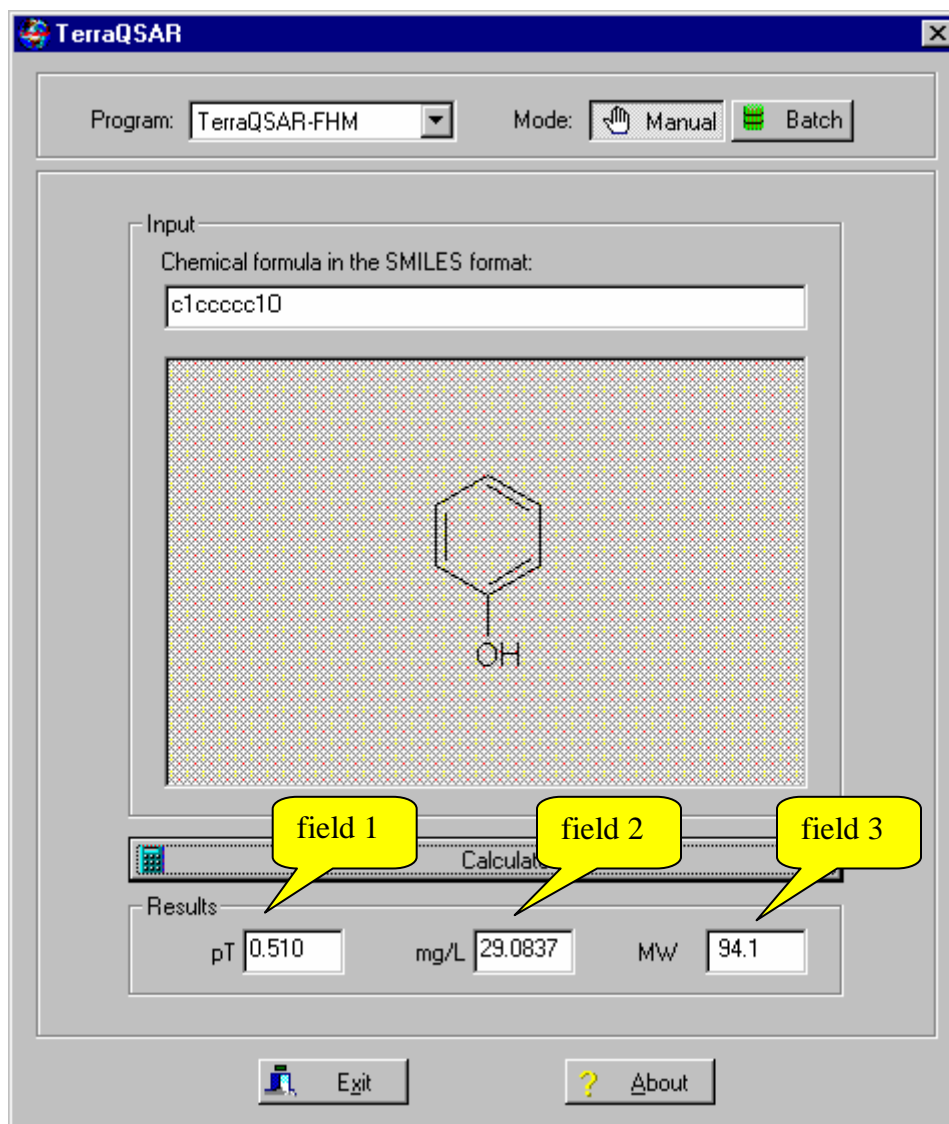
**Example 1:**

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 (example shows the TerraQSAR - FHM program module).

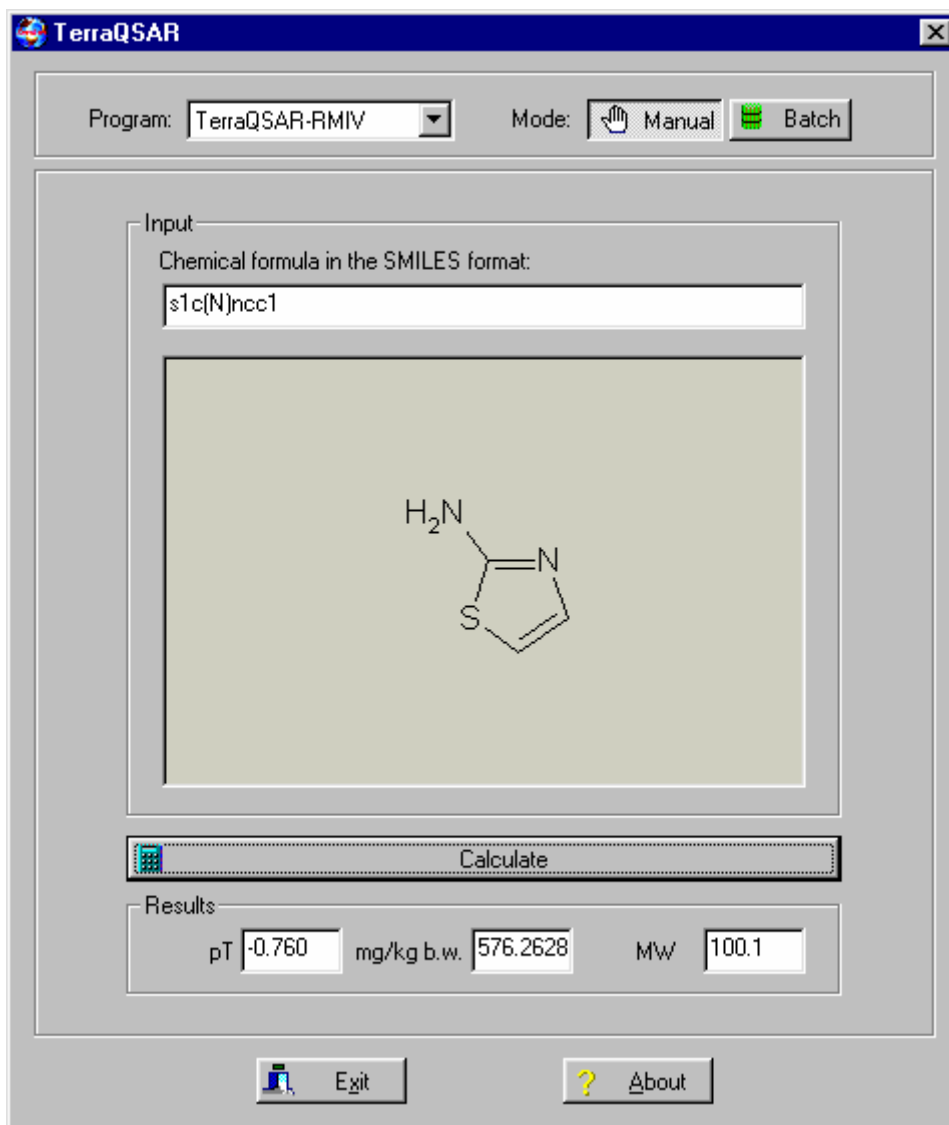
Once the user has ascertained that the structure of the compound is that of the desired chemical, a simple click of the Calculate bar below the structure field will result in the three fields below the bar to be filled with the predicted values for the compound, as shown in Figure 4. Field 1 (pT) is the negative logarithm of the LC50 concentration in mmol/L; field 2 (mg/L in TerraQSAR – FHM program module) is the LC50 value in mg/L (in TerraQSAR – FHM program module); 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 shows the TerraQSAR - FHM program module).

**Example 2:**

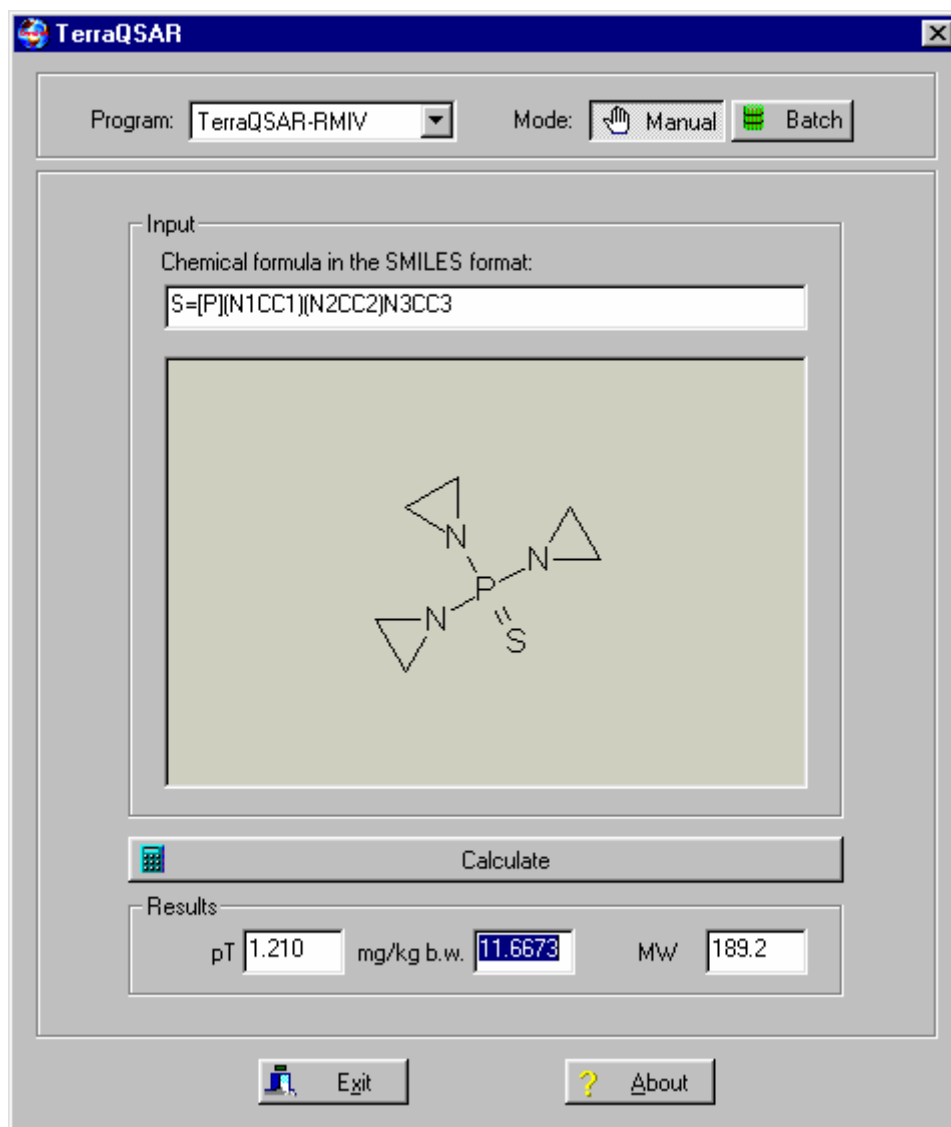
A low complexity molecule, the chemical 2-aminothiazole, CAS 96-50-4, with the SMILES string "s1c(N)ncc1" and structure shown in Figure 5, has a computed *iv.* LD50 value of 576 mg/kg b.w. (pT: -0.76), as shown in Figure 5; computation time <5 sec.



**Fig. 5.** Result of computation for the insecticide 2-aminothiazole, SMILES string shown in the input field, depicting the compound 2-aminothiazole, with its computed *iv.* LD50 value for rat / mouse of 576 mg/kg b.w. (pT: -0.76).

**Example 3:**

The chemo-sterilant Thiotepa, tris(1-aziridinyl)phosphine sulfide, CAS 52-24-4, SMILES string “S=P(N1CC1)(N2CC2)N3CC3” has a predicted rat / mouse *iv.* LD50 of 11.67 mg/kg b.w. (pT: 1.21), as shown in Figure 6.

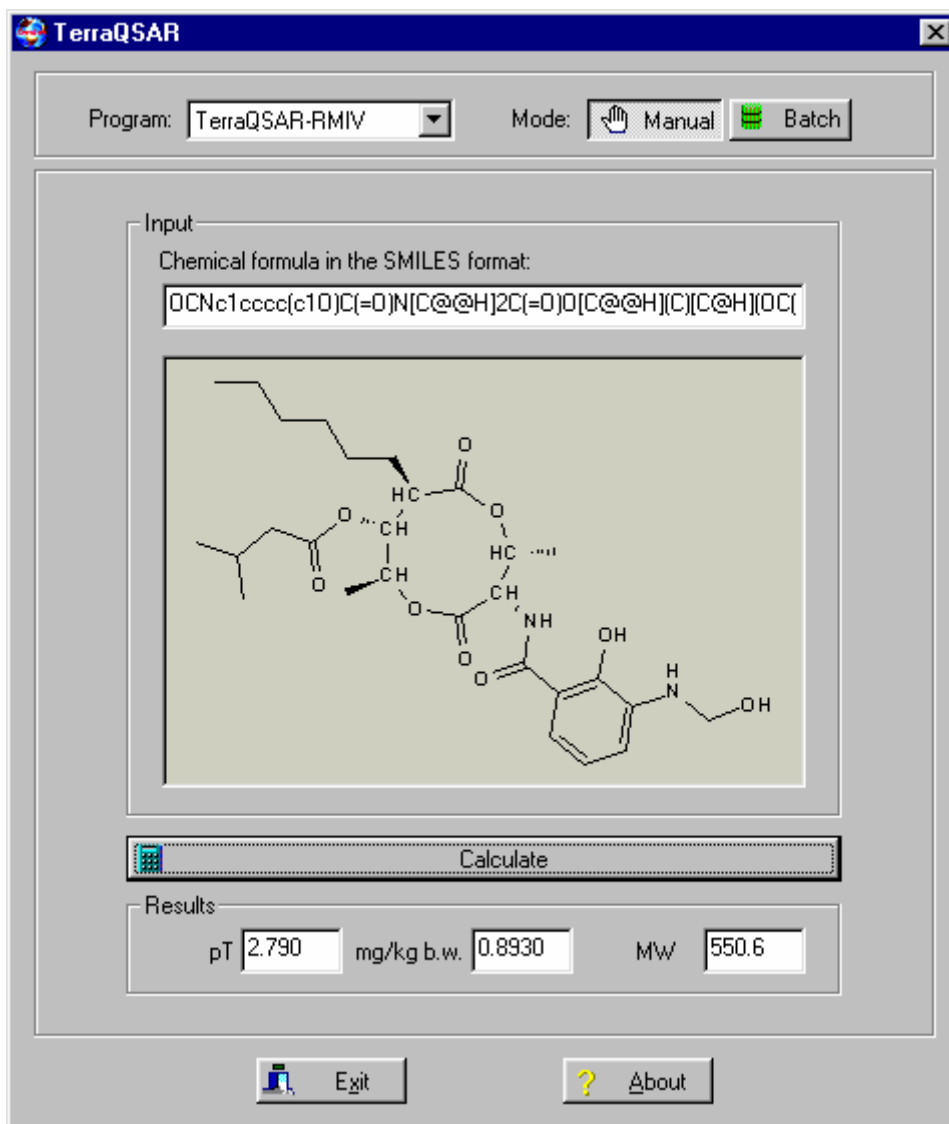


**Fig. 6.** Result of computation for the SMILES string shown in the input field, depicting the chemo-sterilant Thiotepa, with its computed *iv.* LD50 value for rat / mouse of 11.67 mg/kg b.w.

#### Example 4:

The antibiotic compound Antimycin A, CAS 1397-94-0, with the 3D-SMILES code OCNc1cccc(c1O)C(=O)N[C@@H]2C(=O)O[C@@H](C)[C@H](OC(=O)CC(C)C)[C@@H](CCCC)C(=O)O[C@@H]2C

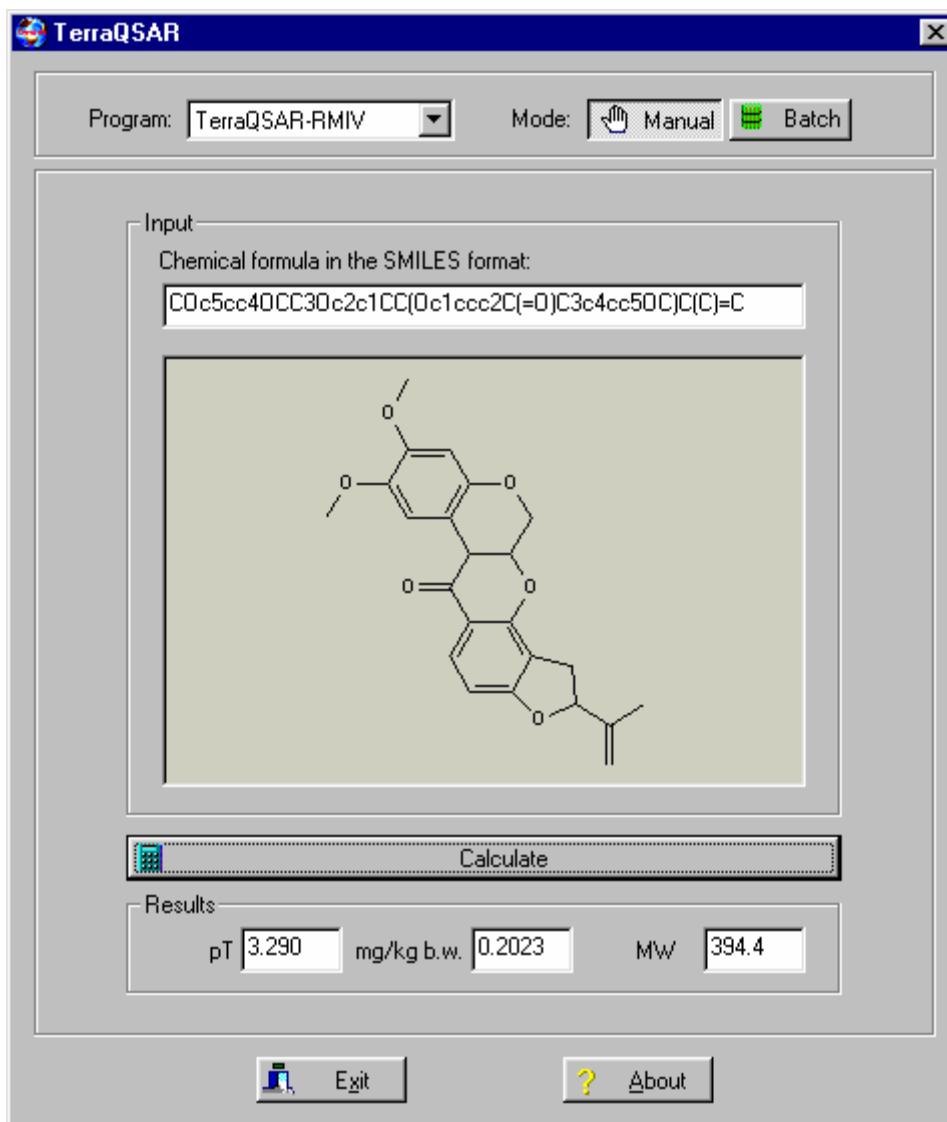
(only a part of the SMILES code is visible in the Input field) has a predicted rat / mouse *iv.* LD50 of 0.89 mg/kg b.w., as shown in Figure 7; computation time ca. 20 sec at 2 GHz.



**Fig. 7.** Result of computation for the SMILES string shown in the input field, depicting the antibiotic Antimycin A, with the computed *iv.* LD50 value for the rat / mouse of 0.89 mg/kg b.w.

**Example 5:**

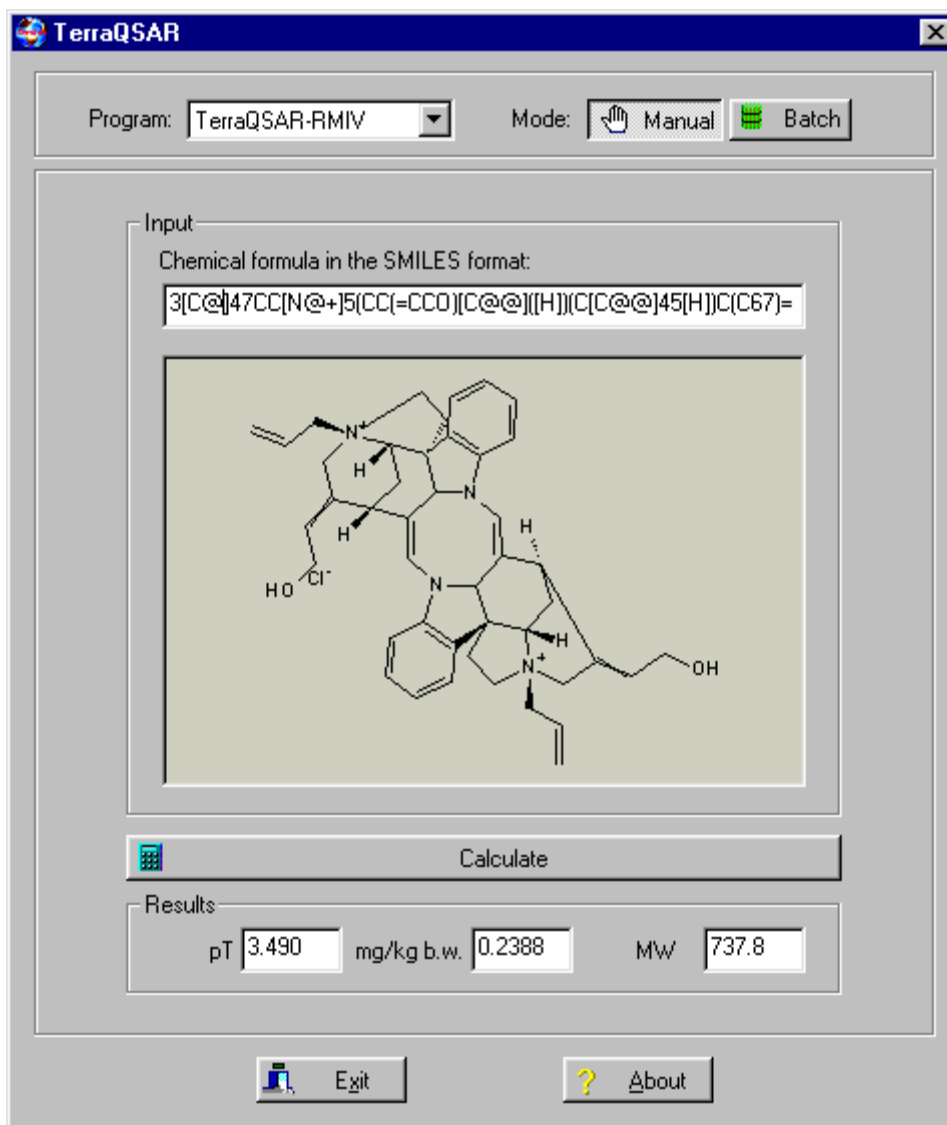
The insecticide Rotenone, CAS 83-79-4, with the SMILES code: COc5cc4OCC3Oc2c1CC(Oc1ccc2C(=O)C3c4cc5OC)C(C)=C and the structure shown in Figure 8, has the predicted rat / mouse *iv.* LD50 of 0.20 mg/kg b.w.



**Fig. 8.** Result of computation for the insecticide Rotenone, SMILES string shown in the input field, with the computed *iv.* LD50 value for rat / mouse of 0.20 mg/kg b.w.

**Example 6:**

The synthetic neuromuscular blocking agent Alcuronium dichloride (a curare toxin derivative), CAS 23214-96-2, and the structure shown in Figure 9 (only part of the SMILES string is visible in the TerraQSAR SMILES window), has the predicted rat / mouse *iv.* LD50 of 0.24 mg/kg b.w.

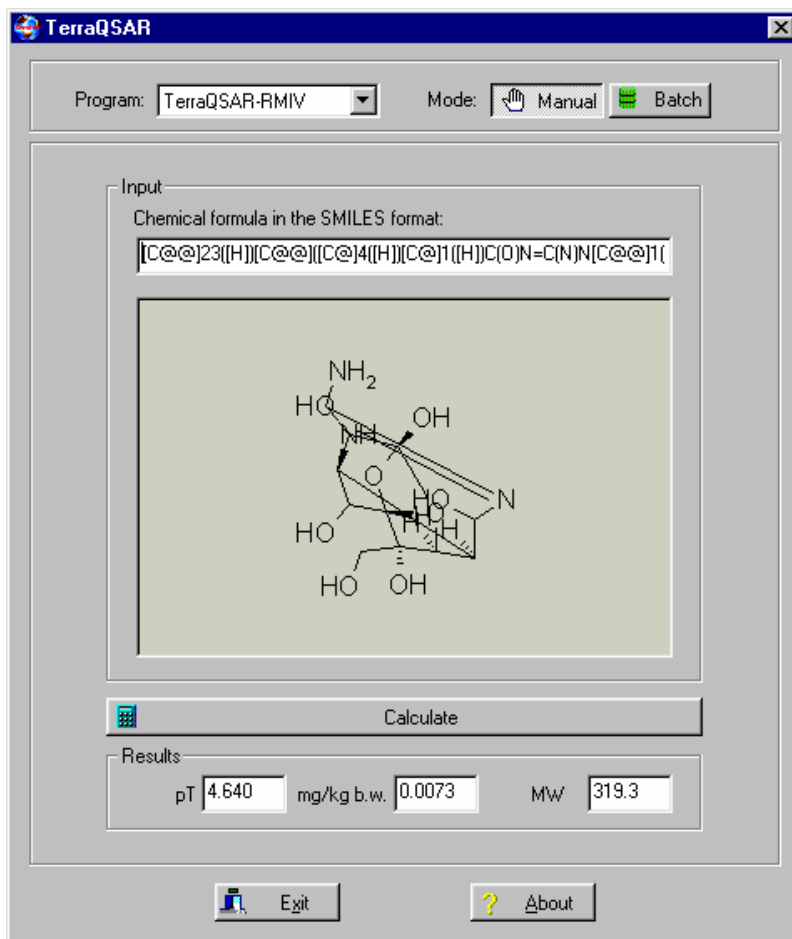


**Fig. 9.** The synthetic neuromuscular blocking agent Alcuronium dichloride, CAS 23214-96-2, (only part of the SMILES string is visible in the TerraQSAR SMILES window) results in a computed *iv.* LD50 value for rat / mouse of 0.24 mg/kg b.w.; computation time approx. 60 sec at 2 GHz.

### Example 7:

The puffer fish toxin tetrodotoxin, CAS 4368-28-9, with the SMILES code:

[C@@]23([H])[C@@]([C@]4([H])[C@]1([H])C(O)N=C(N)N[C@@]1(C2O)C(O)[C@](O3)(O)O4)(CO)O (only part of the SMILES string is visible in the TerraQSAR SMILES window) and the structure shown in Fig. 10-top (2-D) and Fig. 10-bottom (3-D), has the predicted rat / mouse LD50 of 0.0073 mg/kg b.w.



**Fig. 10.** Result of computation for the puffer fish toxin Tetrodotoxin, CAS 4368-28-9, (only part of the SMILES string is visible in the TerraQSAR SMILES window) with a computed *iv.* LD50 value for rat / mouse of 0.0073 mg/kg b.w.

## 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; 2.0 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 simple installation parts; we recommend installation in the order mentioned in the README.txt file in the root directory on the CD.

### *Part 1. Installation of the supporting software*

To install/un-install the supporting software, necessary for the proper functioning of the **TerraQSAR** program, follow the instructions given in the README.txt file in the root directory of the CD.

### *Part 2. Installation of TerraQSAR*

To install any **TerraQSAR** program module, double-click on the “TerraQSAR-Setup.exe” file using the password provided.

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