TerraQSAR™ - SKIN

Skin Irritation Estimation Software, vs. 1.1

User Manual

Purpose

TerraQSAR™ - SKIN is a holistic, probabilistic-algorithm-based neural network software program, designed and optimized solely for the computation of the skin irritation potential for the rabbit, as measured with the Draize test, of organic (carbon-containing) substances with a defined chemical structure.

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Introduction

Welcome to **TerraQSAR™**, a breakthrough development in toxicity and effect 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 - SKIN** program computes the dermal irritation potential of organic compounds to the rabbit (Draize test).

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 - SKIN** module computes the skin irritiation potential in scalar, 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 - SKIN** dermal irritation estimation program is based on a data set of measured values 1936 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** or **TerraTox™ - SKIN** databases.

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	C(=O)O, S(=O)(=O)O
Aliphatic ring fragment	C1CCCCC1, C1CCCC1
Aromatic ring fragment	c1ccccc1, c1ccccn1
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	C(C)(C)C, CCCC
Ionization fragment	[O-], [Na+]
Polarity fragment	O=N(=O)CC(O)
Reactivity fragment	C=CC=O
Stereo fragment	Cl[C@H](C)N, Cl[C@@H](C)N
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 all 1936 compounds used in the development of the **TerraQSAR - SKIN** dermal irritation (Draize test) estimation program, as obtained from the program. The experimental data are usually given as MILD, MODERATE, and SEVERE irritants. We have assigned the values of 0 to the MILD, 1 to the MODERATE, and 2 to SEVERE irritants. Consequently, all predicted values lie in the range of 0.00 to 2.00. The computed values can roughly be acribed as non-irritating or weak irritants at values below 0.5, weak to moderate irritants at values in the range o 0.5 to 1.5, as as strong irritants when the values exceed 1.5.

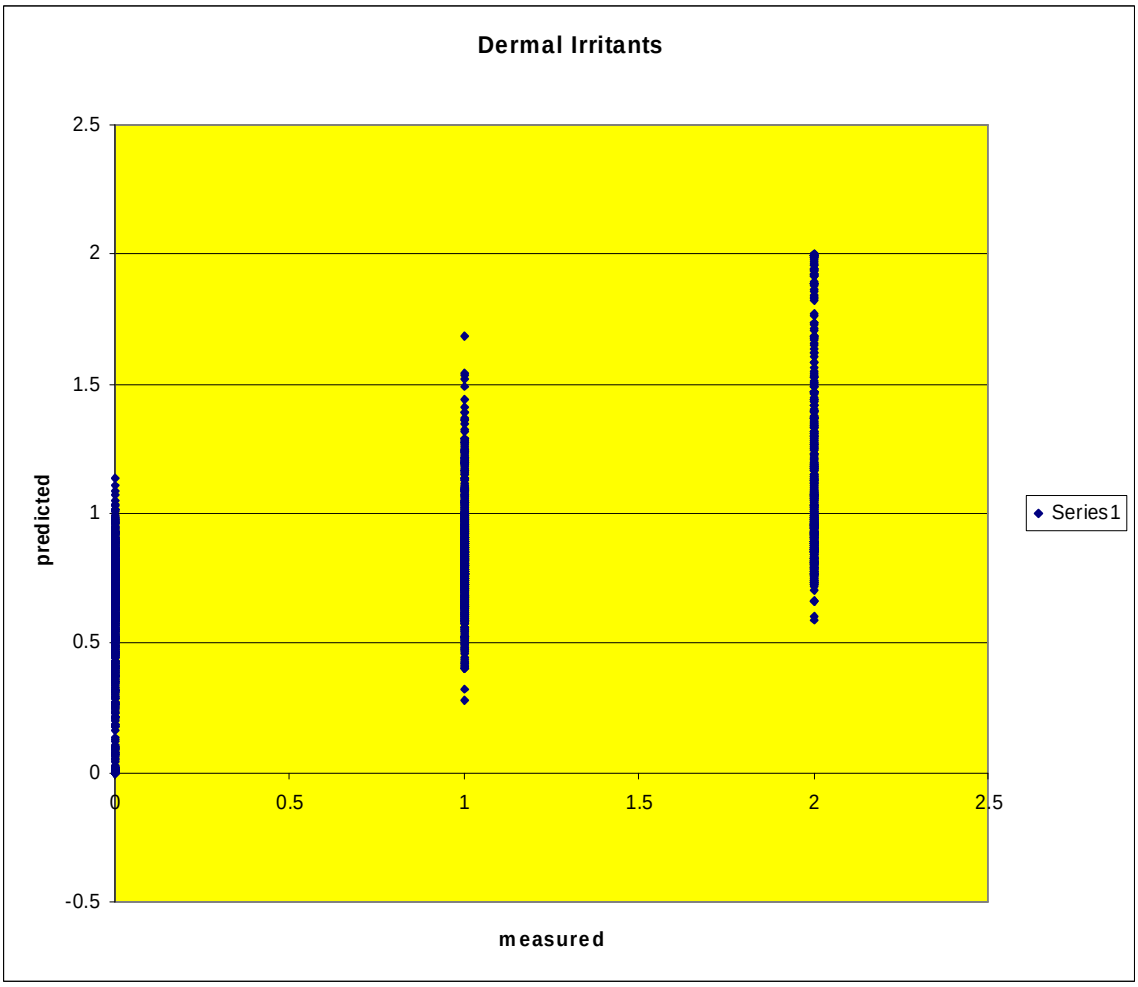

Fig. 1. Plot of the measured vs. predicted skin irritation values for all 1936 compounds in the training set; units are scalar between 0.00 and 2.00, see text.

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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Program Interface

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

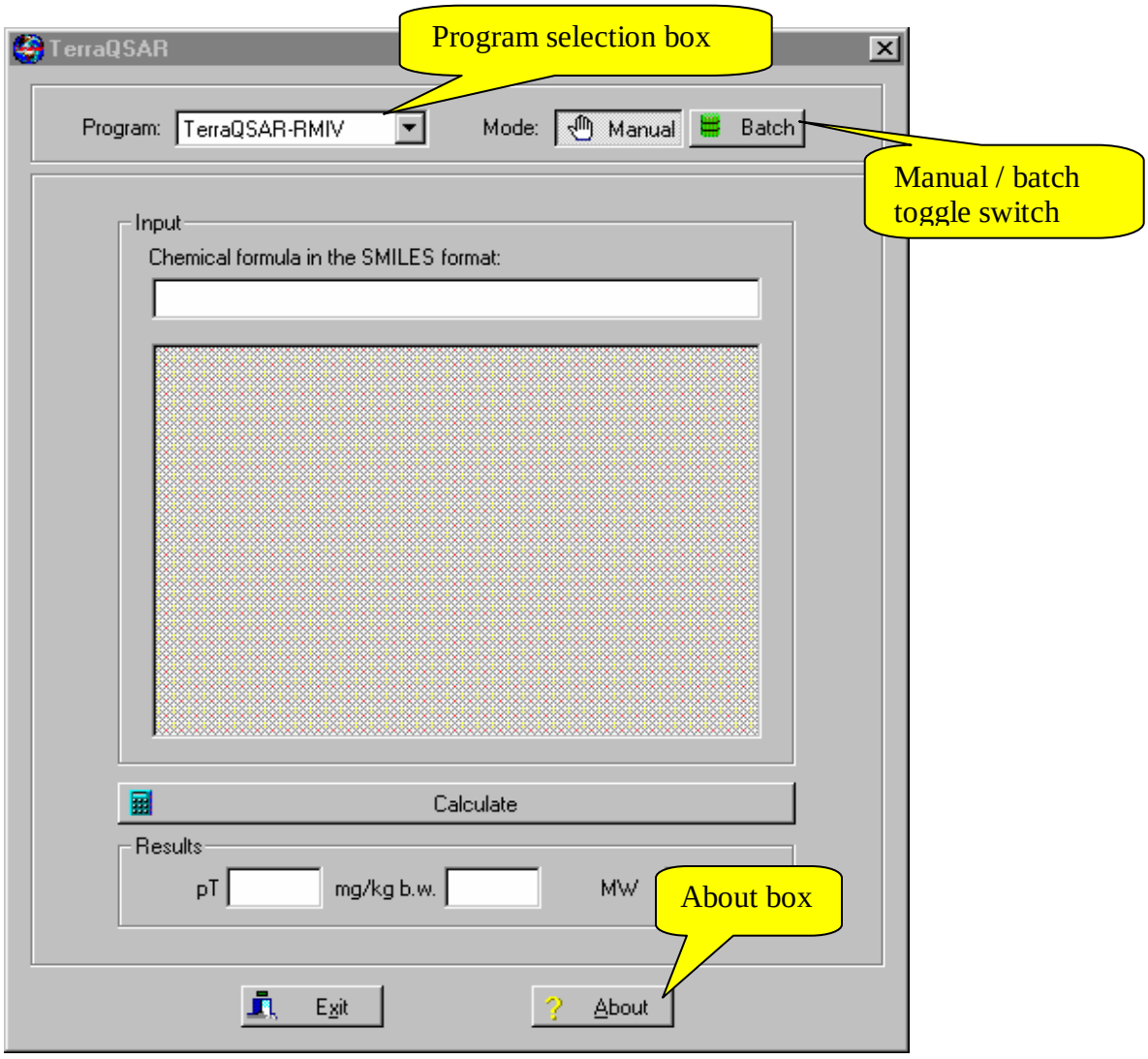


Fig. 2. The Program Interface as it appears on startup. Note: The field names in the Results panel vary, depending on the Program Module used; the example shown is for TerraQSAR-RMIV.

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 program versions 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.

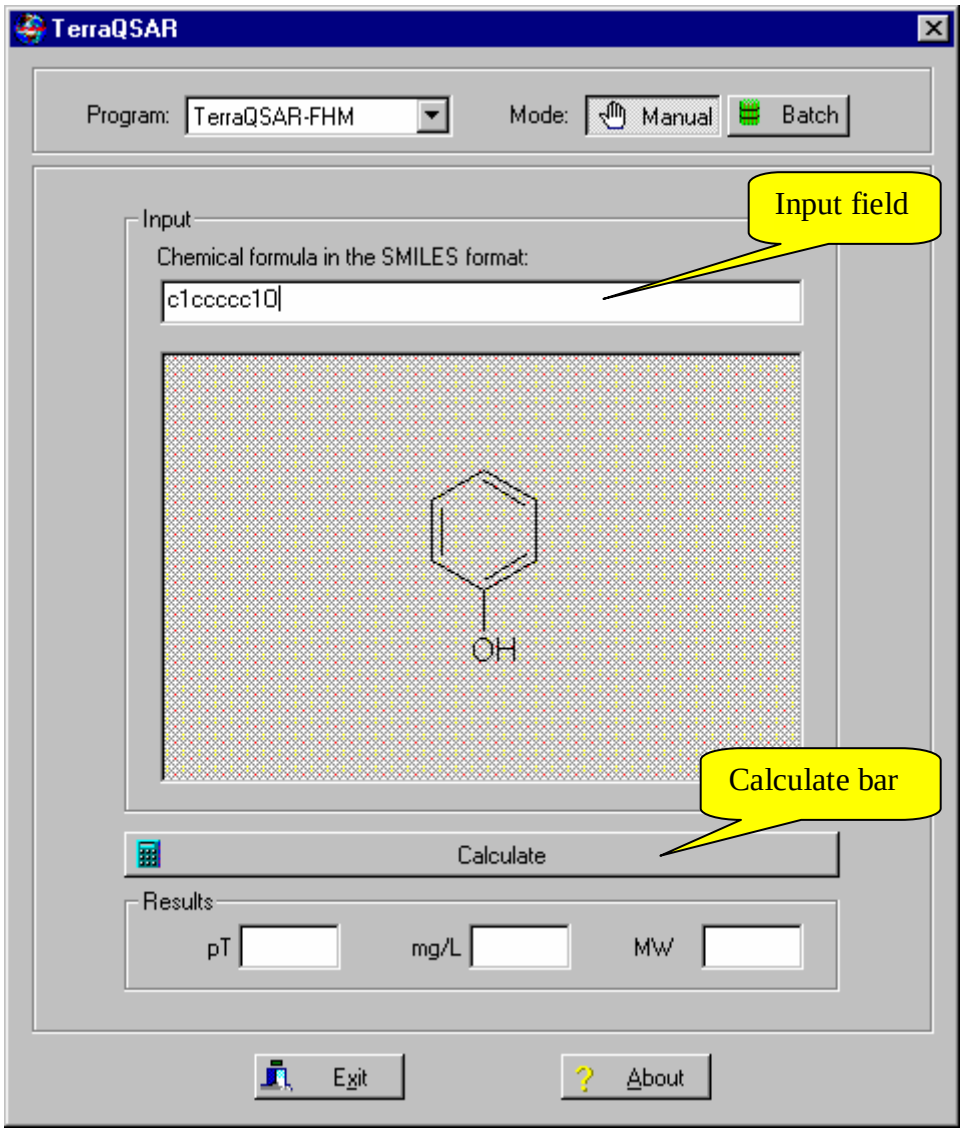


Fig. 3. Result of entering or pasting the SMILES string for phenol (c1ccccc1O) into the input field: the structure of phenol (excluding hydrogen atoms) will appear in the field below (example shows the TerraQSAR - FHM program module).

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 is the SKIN-irritation potential (in units between 0.00 and 2.00, as detailed above), field 2 remains empty, 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.

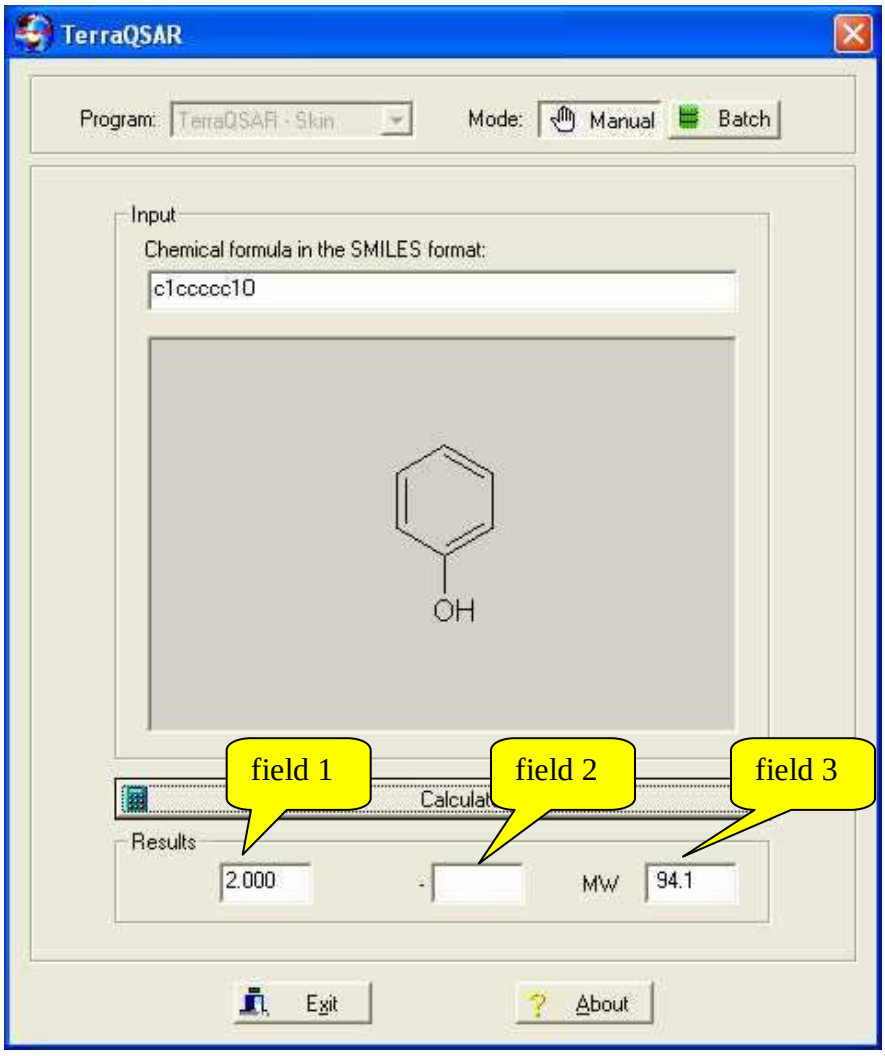


Fig. 4. Result of the execution of "Calculate". The fields show the following values: Field 1 (without label) is the skin irritation potential as described above. Field 2 is unused, and field 3 shows the molecular weight of the compound. Example shows the computed value for phenol (2.00), indicating a strong dermal irritant.

Example 2:

A low complexity molecule, the chemical 2-aminothiazole, CAS 96-50-4, with the SMILES and structure shown in Figure 5, has a computed skin irritation potential of 0.93; computation time <5 sec.

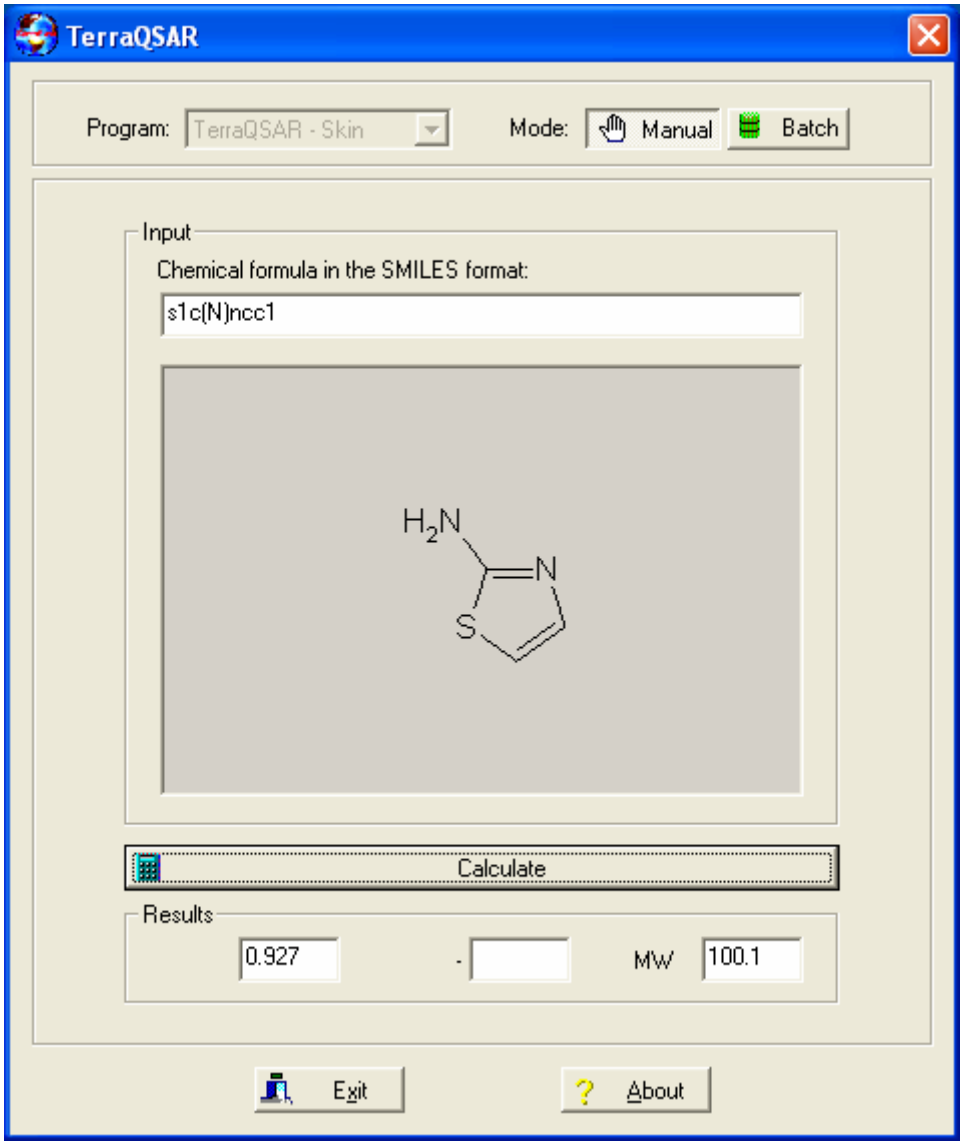


Fig. 5. Result of computation for the insecticide 2-aminothiazole, SMILES string shown in the input field, depicting the compound 2-aminothiazole, with its computed skin irritation potential in rabbit Draize test of 0.93, indicating moderate skin irritation.

Example 3:

The chemo-sterilant Thiotepa, tris(1-aziridinyl)phosphine sulfide, CAS 52-24-4, has a predicted skin irritation of 0.95, as shown in Figure 6.

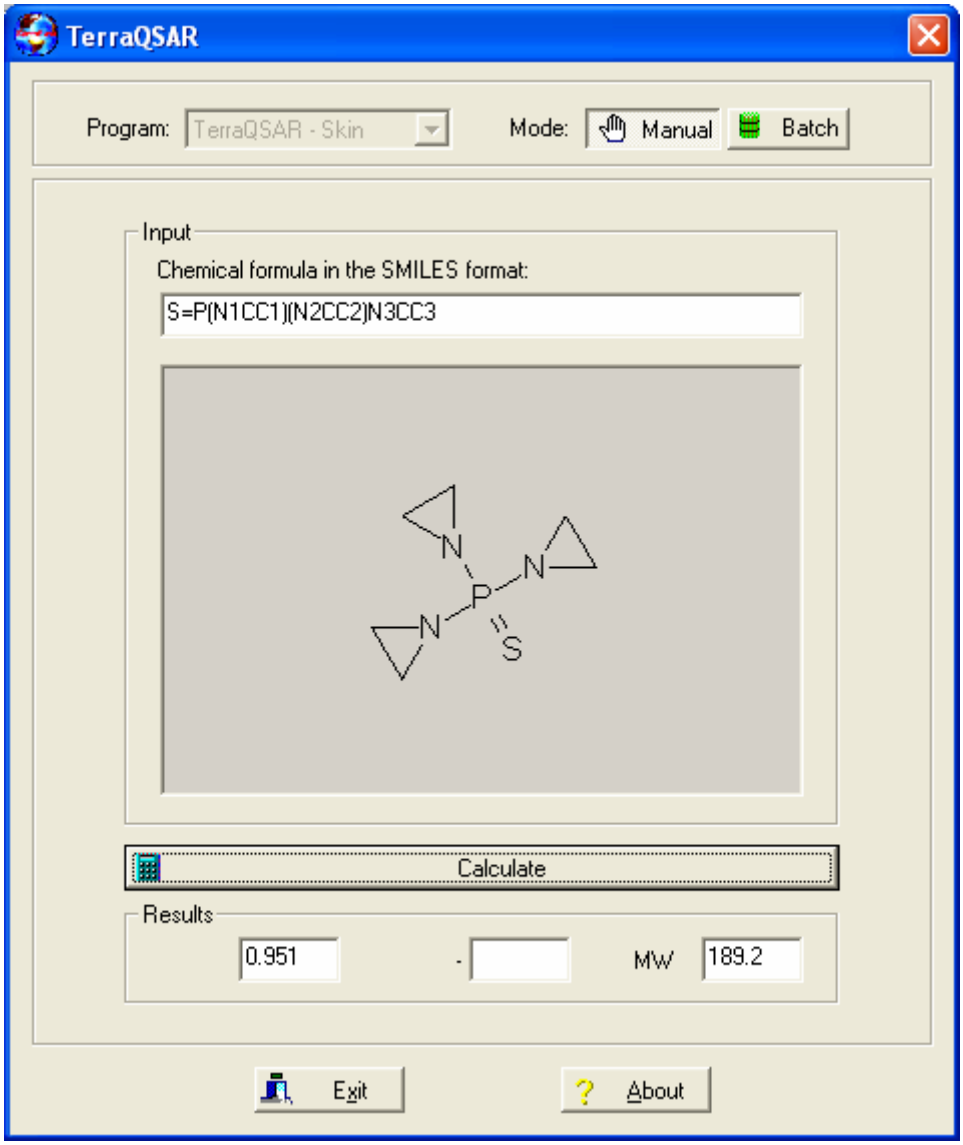


Fig. 6. Result of computation for the SMILES string shown in the input field, depicting the chemo-sterilant Thiotepa, with its computed skin irritation potential of 0.95, indicating moderate irritation.

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](CCCCCC)C(=O)O[C@@H]2C
(only a part of the SMILES code is visible in the Input field) has a predicted skin irritation potential of 0.73, as shown in Figure 7; computation time ca. 20 sec at 2 GHz.

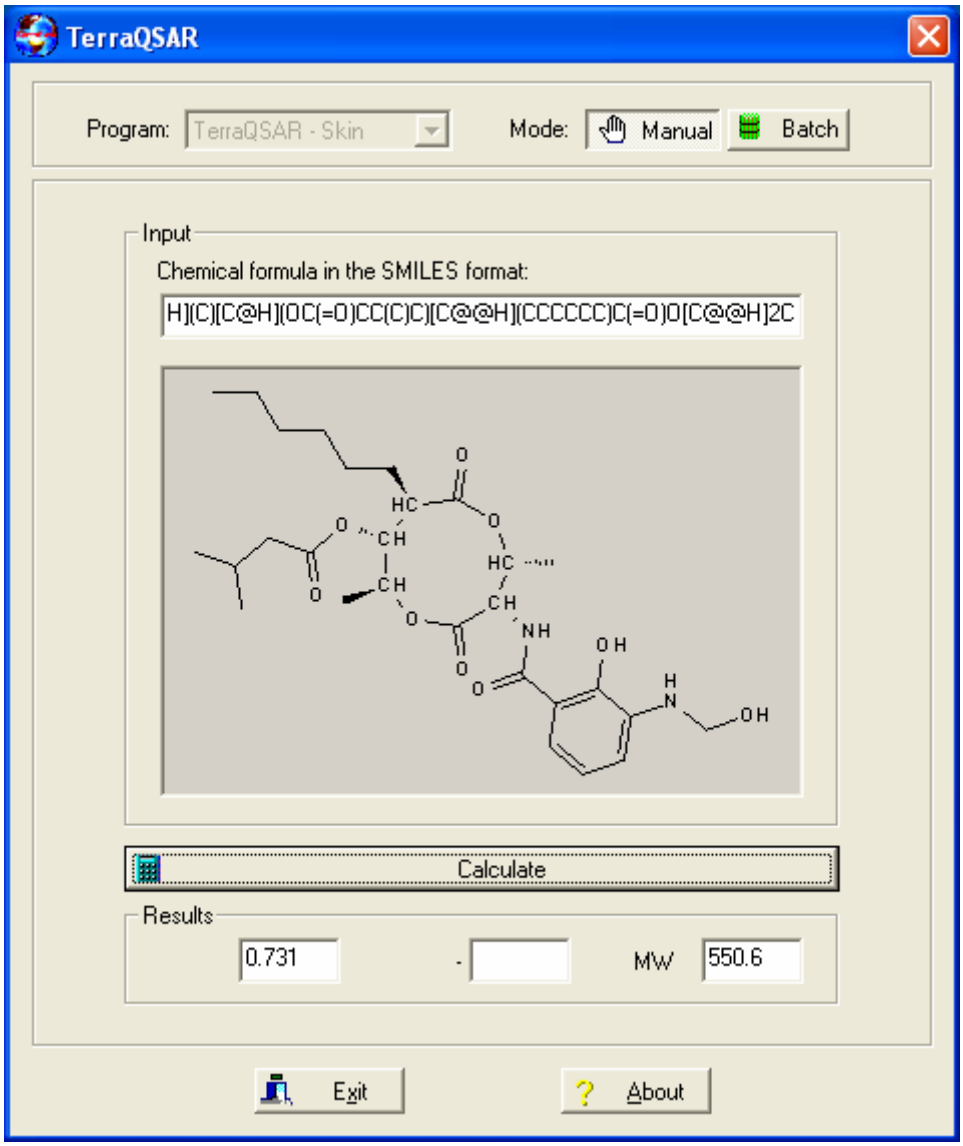


Fig. 7. Result of computation for the SMILES string shown in the input field, depicting the antibiotic Antimycin A, with the computed rabbit skin irritation potential (Draize test) of 0.73.

Example 5:
The diisopentyltin oxide, CAS 63979-62-4, with the SMILES code: CC(C)CC[Sn](=O)CCC(C)C and the structure shown in Figure 8, has the predicted skin irritation value of 1.68, indicating a strong irritant.

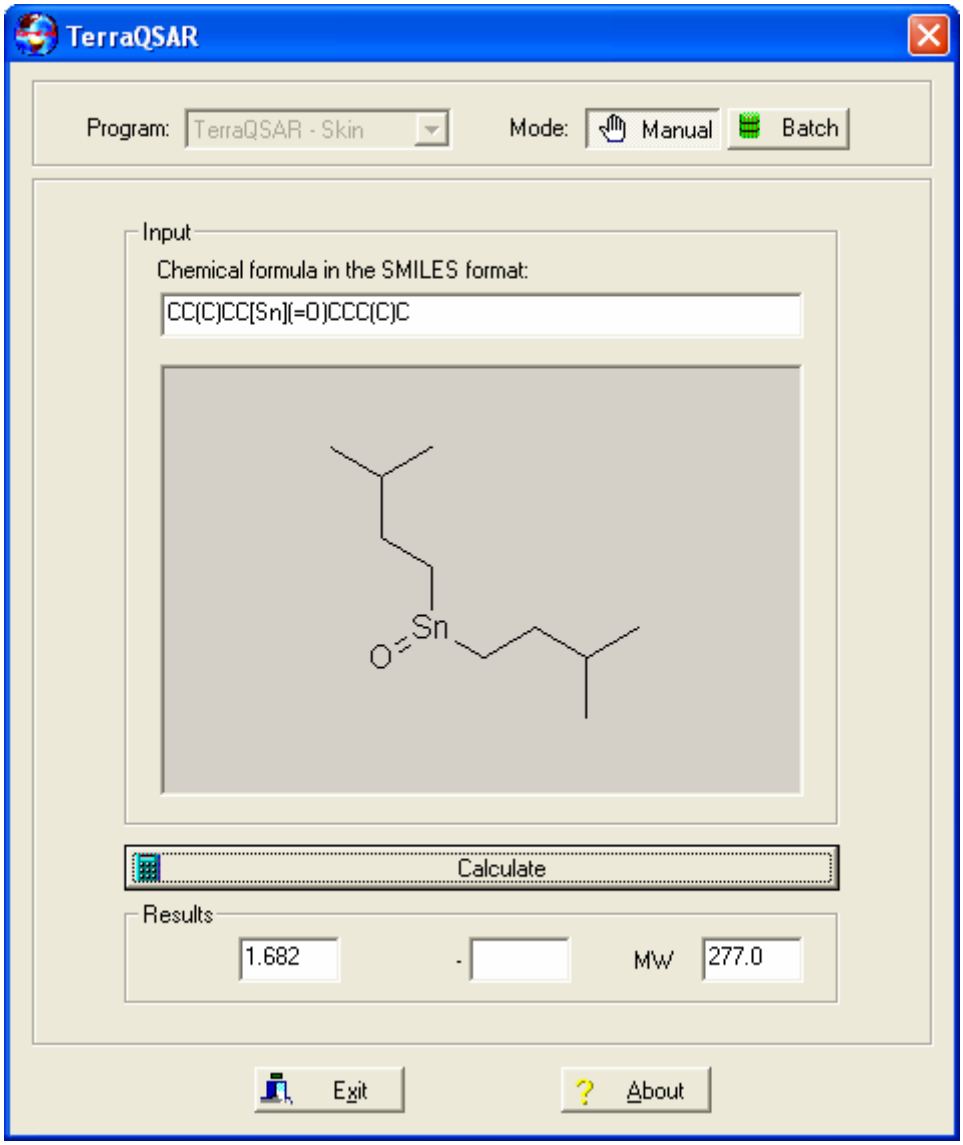
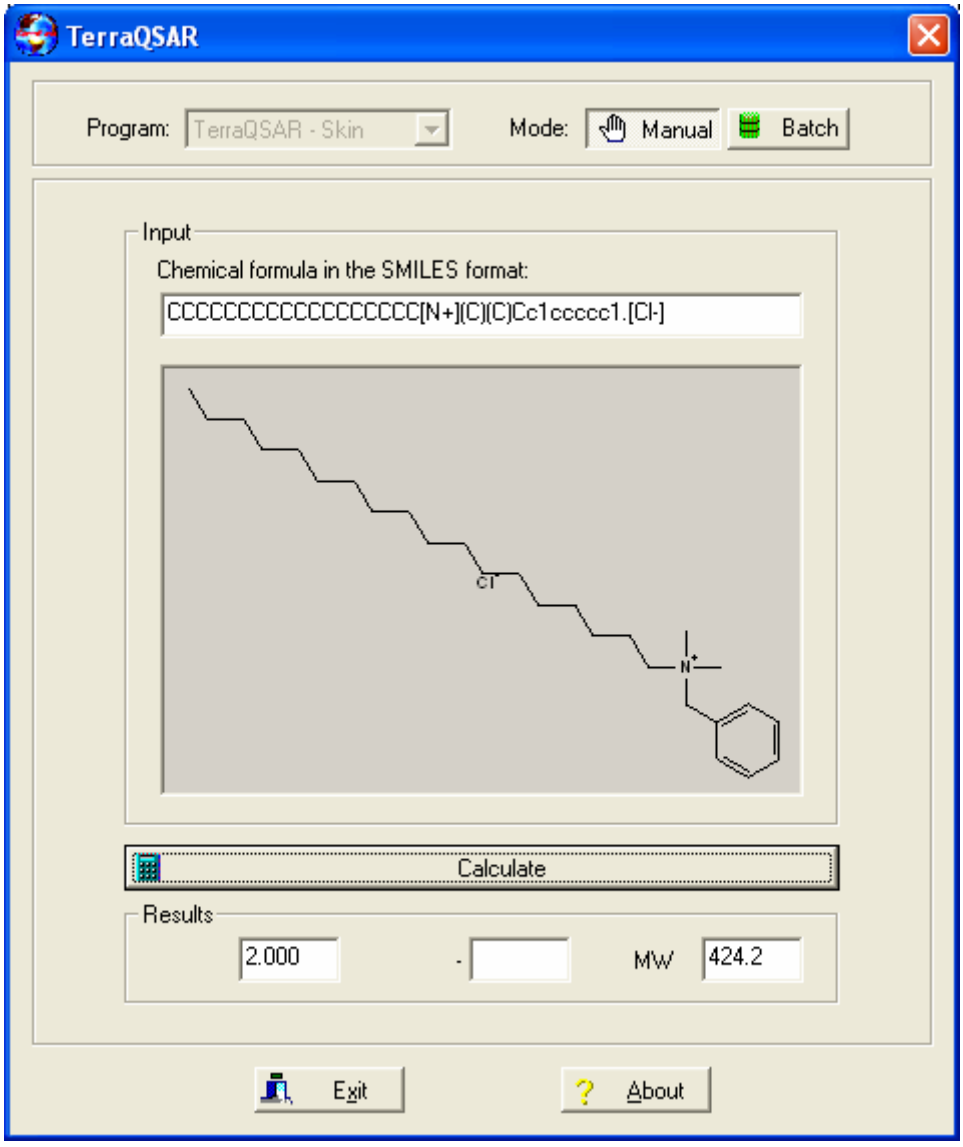


Fig. 8. Result of computation for the stannane derivative diisopentyltin oxide, SMILES string shown in the input field, with the computed skin irritation value of 1.68, indicating a strongly irritating chemical.

Example 6:

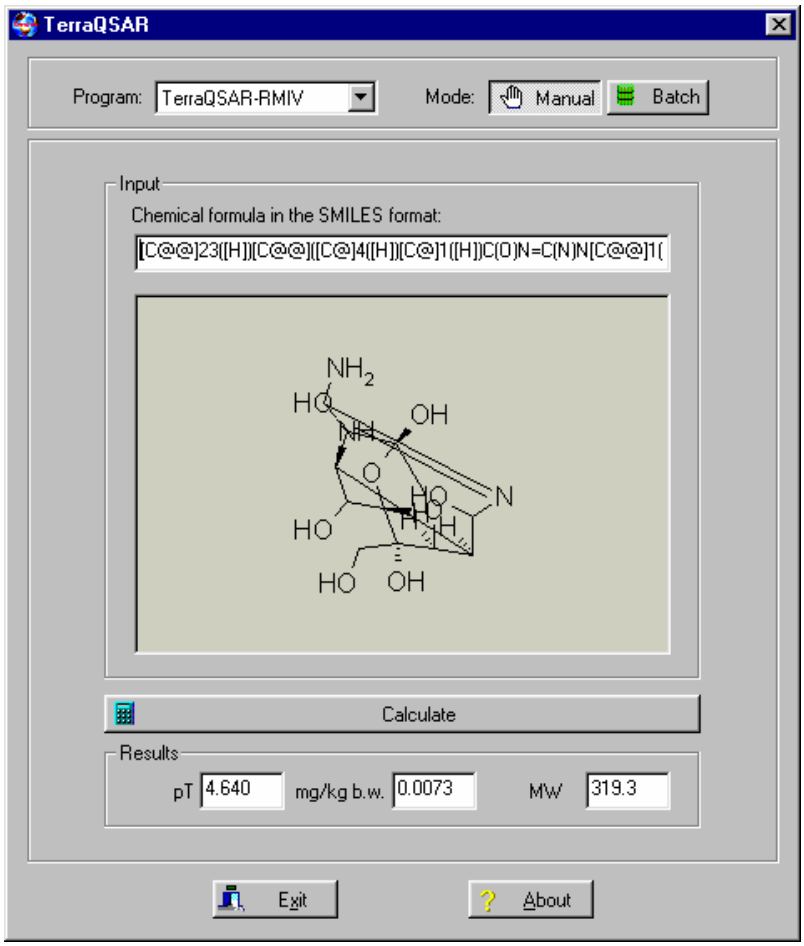
The synthetic neuromuscular blocking agent benzyldimethyloctadecylammonium chloride, CAS 122-19-0, and the structure shown in Figure 9 has the predicted skin irritation potential of 2.0, indicating a severe irritant..



<u>Fig. 9</u>. The synthetic neuromuscular blocking agent benzyldimethyloctadecylammonium chloride, CAS 122-19-0, has the predicted skin irritation potential of 2.0, indicating a severe skin irritant.

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 TerraQSAR-RMIV predicted *iv.* rat / mouse LD50 of 0.0073 mg/kg b.w.



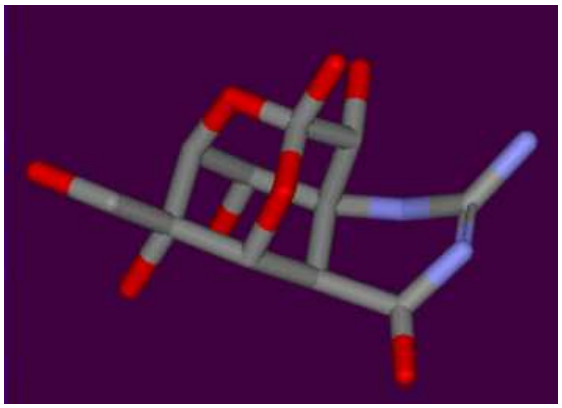


Fig. 10. Result of computation for the puffer fish toxin Tetrodotoxin, CAS 4368-28-9, (only part of the SMILES string is visible in the TerraQSAR SMILES window) with a computed *iv*. LD50 value for rat / mouse of 0.0073 mg/kg b.w.

Technical Requirements

Operating system: PC with Windows 95, 98, NT, 2000, ME, or 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 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, use the Windows – Control – Install/Remove Software command to run the "Setup.exe" in the Accelrys folder and follow the instructions.

Part 2. Installation of TerraQSAR

To install any **TerraQSAR** module, use the Windows – Control – Install Software command to run the "TerraQSAR-Setup.exe" in any TerraQSAR folder and follow the instructions.

Customer Support

TerraBase Inc. is committed to effective customer support. With the rapid change in PC technology, operating systems and other software and hardware changes, 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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