VERSION 0.8.4

USER GUIDE

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1. Introduction

ToxEraser FCM is a software designed for the food contact materials (FCM) sector with the aim to identify risky substances and stimulate their replacement with safer alternatives. The approach applied for the substitution takes into account three main parameters: the level of safety, the similarity algorithm and the identification of hazardous structural groups/alerts. To determine the level of safety, ToxEraser automatically verifies whether the substance of interest is included in two existing lists with 'safe[1] chemicals', i.e. (i) Annex I of the EU Regulation 10/2011 containing the substances allowed for use as starting products in plastic FCM and (ii) the US-EPA Safer Chemical Ingredient List (SCIL). More details on these two lists are provided in Appendix I of this user guide. By including a read-across analysis, ToxEraser also identifies within each of these two lists substances that are structurally similar to the substance of interest. These substances may provide more insights in the safety of the substance of interest based on the structural similarity or could be interesting candidates for substitution. Finally, a series of structural alerts have been implemented in order to detect possible evidence of toxicity for different toxicological endpoints. The structural alerts implemented within the tools are: Benigni-Bossa ruleset for carcinogenicity and mutagenicity (from Toxtree) and endocrine disruptors alerts developed by IRFMN considering EU and WHO lists.

ToxEraser FCM works with a single substance, entered by the end user in the Graphical User Interface (GUI).

ToxEraser FCM is a Java standalone application. It has been designed with flexible capabilities for future extension in mind (possibility to add new lists of compounds or set new functionalities).

The tool is designed to be used in combination with VERMEER FCM in order to obtain a unique integrated powerful platform. Actually, when used as a standalone tool, ToxEraser allows to quickly assess whether a substance of interest is included in the list with authorised starting products for plastic FCM (with a specific migration limit and/or restricted use) and/or the SCIL. In case the substance is not included in either of these lists, there might be a toxicological concern and substitution might be needed. To further investigate the possible toxicological concerns, other tools than the ToxEraser platform should be used such as VERMEER FCM. The latter allows to obtain more insights in the potential migration of the substance from the FCM into the food as well as its toxicological properties. The scientific background of VERMEER FCM can be found on (https://www.vegahub.eu/portfolio-item/VERMEER FCM) and in the user guide VERMEER FCM-v3.4-User-guide.pdf (vegahub.eu).

Note: The ToxEraser FCM tool has been developed for 'organic single substances' and is thus not applicable to for example mixtures, salts or polymers.

[1] 'Safe' refers to the conditions of use in FCM.

2. Installing and starting ToxEraser FCM

ToxEraser FCM is a JAVA application that works on every operating system (Windows/Linux/Mac) supporting Java. Before proceeding, please check what version of Java is installed in your OS and if the JAVA_PATH environment variable is correctly set (for further details, please refer to Oracle documentation https://docs.oracle.com/cd/E19182-01/821-0917/inst_jdk_javahome_t/index.html).

ToxEraser FCM works with Java 8 or OpenJDK Java 11+: depending on what version is installed or set in your operative system please follow the instructions below:

WINDOWS:

- **JAVA 8:** Download and unpack the zipped file. To start the application, move to the application folder and run the file *starter.bat*
- **OPEN JDK JAVA 11 or greater**: Download and unpack the zipped file. To start the application, you can just run the file *ToxEraserGUI-0.8.4.jar*. On most systems, it is enough to double-click it. If you are not able to directly run it, open a command line window (like Command Prompt or PowerShell on Windows systems) move to the application folder and type:

java -jar ToxEraserGUI-0.8.4.jar

LINUX/MAC OS:

- Make sure to install the latest LTS version of Java. First, in a shell update the apt package index with *sudo apt update* command.
- Once the package index is updated install the default Java OpenJDK package with *sudo apt install default-jdk*
- When the installation is complete, move to the application folder and execute *sh starter.sh* or *bash starter.sh*, or double click on *starter.sh* file

3. How to use

3.1 User Requirements Input

ToxEraser FCM has a user-friendly graphical interface, in which the user adds the structure, selects the number of structurally related substances to be displayed in the output and runs the calculation.

3.1.1 Insert the substance of interest

In the main application window, the user can insert a single structure by entering its SMILES (see Figure 1). The software searches this structure in the internal archive of substances implemented within the software.

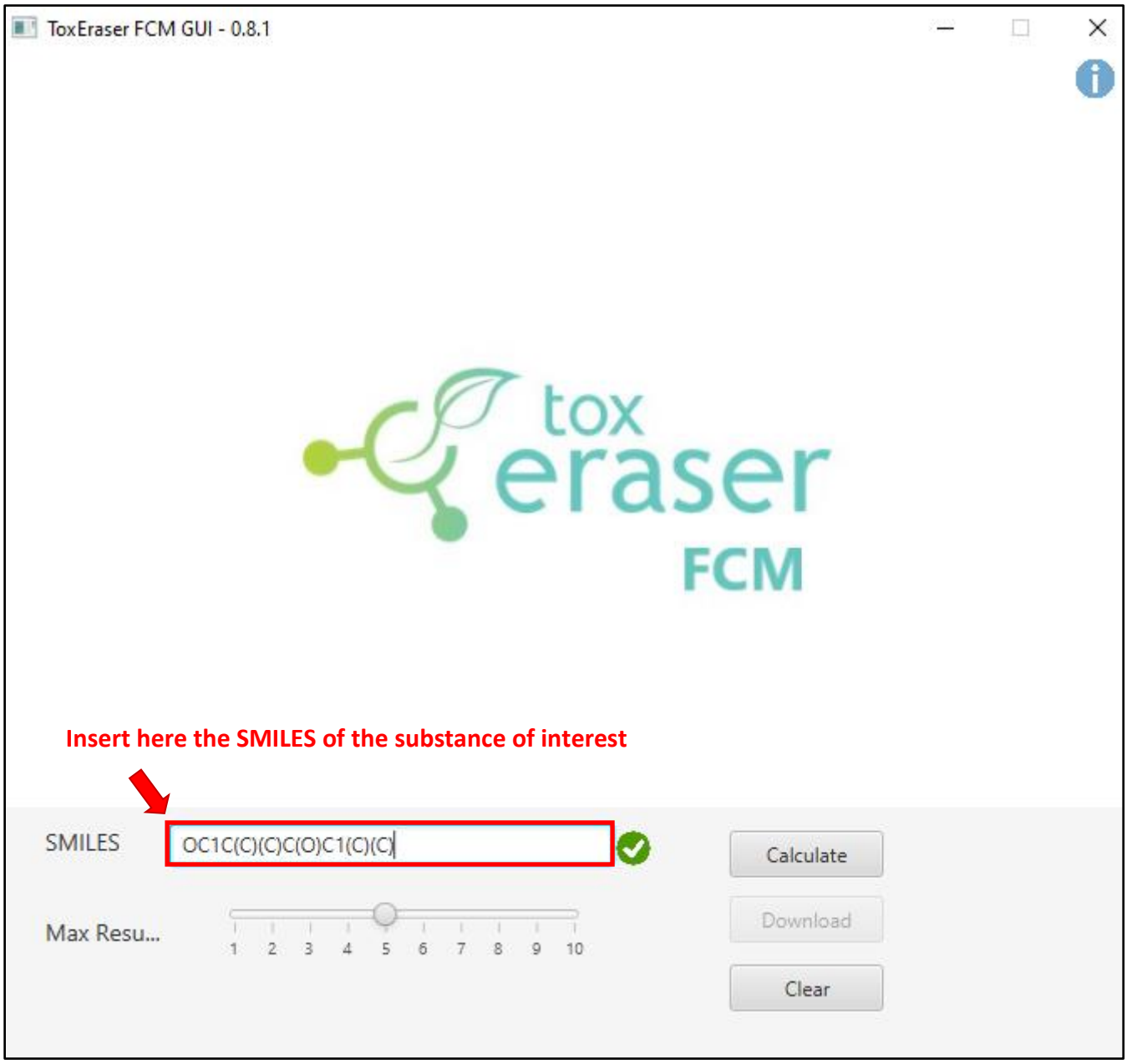

Figure 1: The figure shows how to insert a substance of interest.

3.1.2 Define the number of structurally related substances for output

In the 'Max Results' tab of the GUI, the user has to indicate the desired maximum number of structurally related substances to be displayed in the output of ToxEraser FCM (see Figure 2).

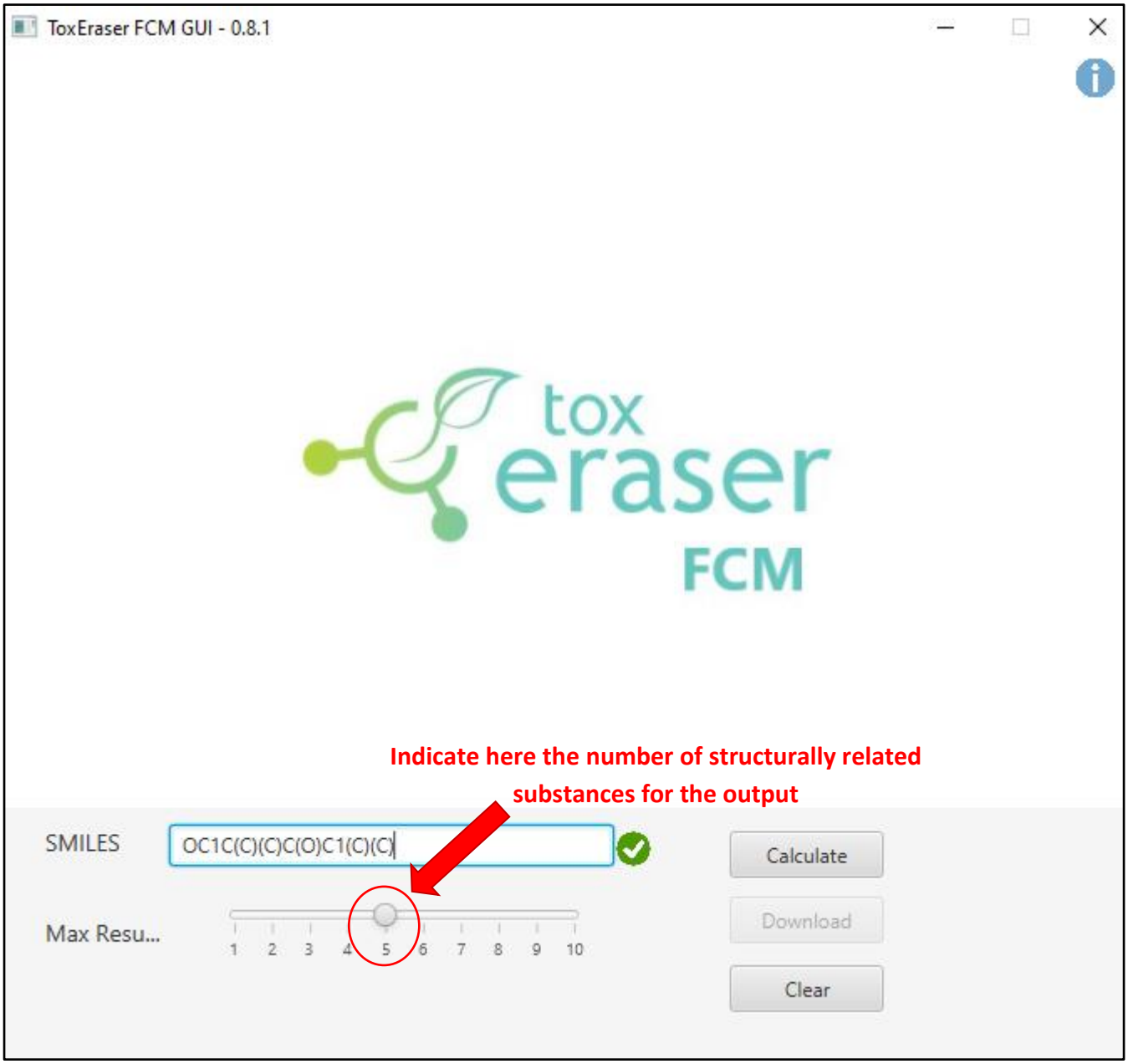

Figure 2: The figure shows how to select the number of structurally related substances to be displayed in the output.

3.1.3 Run calculation

Once each parameter has been correctly set, the user has to click on the button **'Calculate'** in order to start the calculation (see Figure 3).

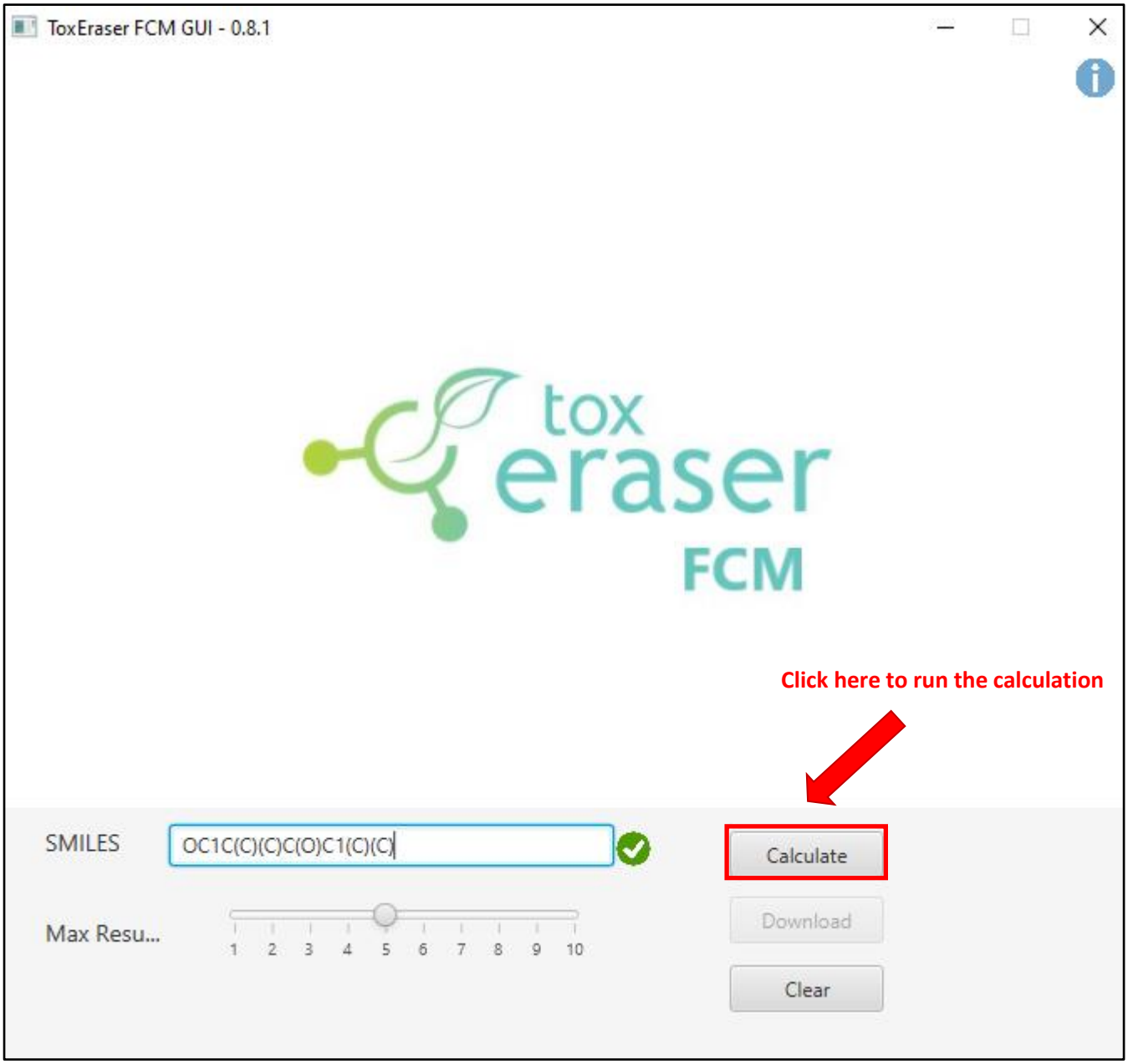

Figure 3: The figure shows how to start the calculation.

3.1.4 Download the output and select the directory

Once the calculation is concluded, the software indicates that the output is ready to download (see Figure 4). The user has to click the **'Download'** button to download the results (see Figure 5). Then the user has to select the directory of the output; he/she has to select the folder, indicate a name and save the file (see Figure 6). The output file is a PDF file.

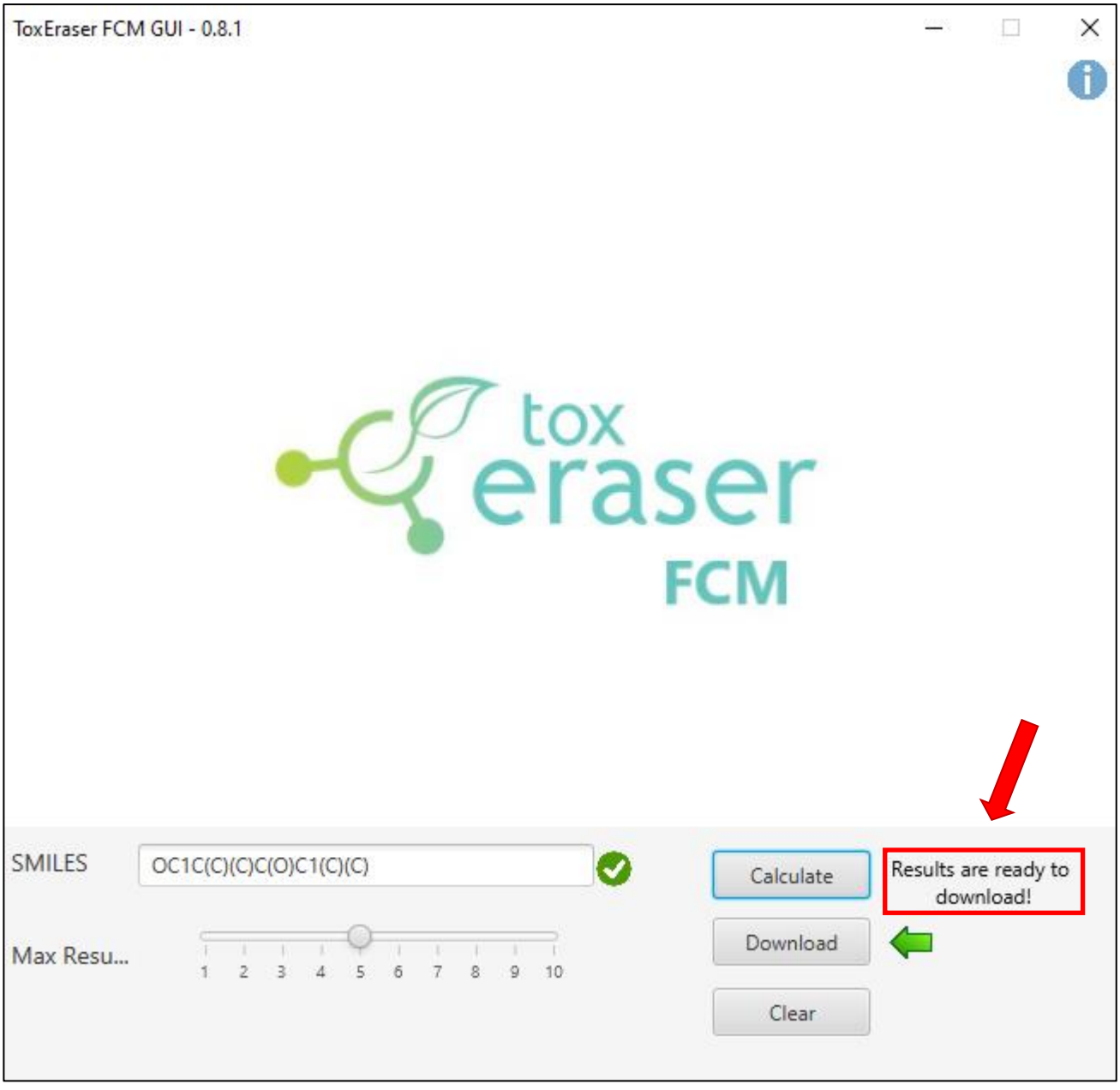

Figure 4: The figure shows the message that is displayed by the software when the results are ready to download.

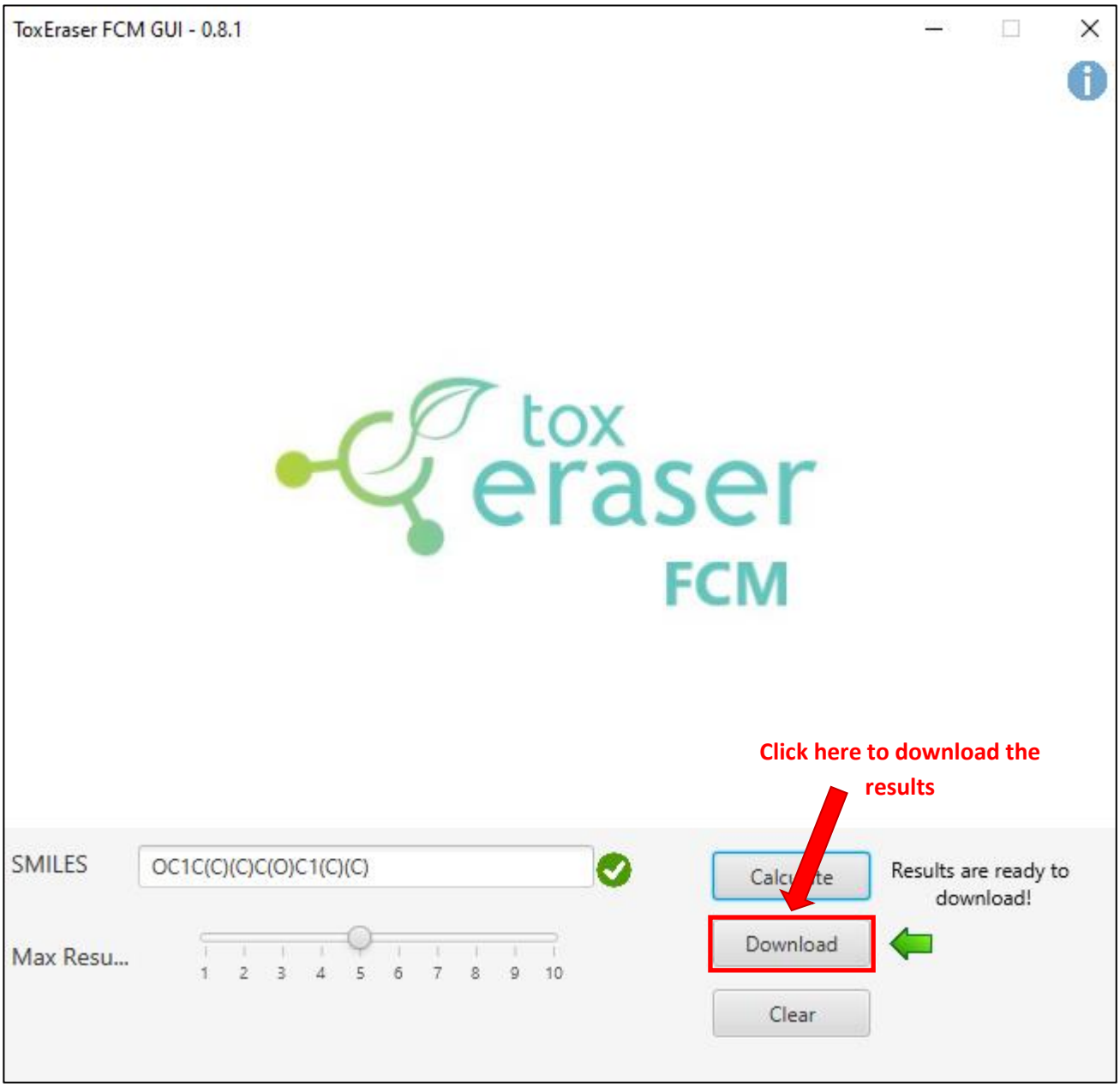

Figure 5: The figure shows how to download the results.

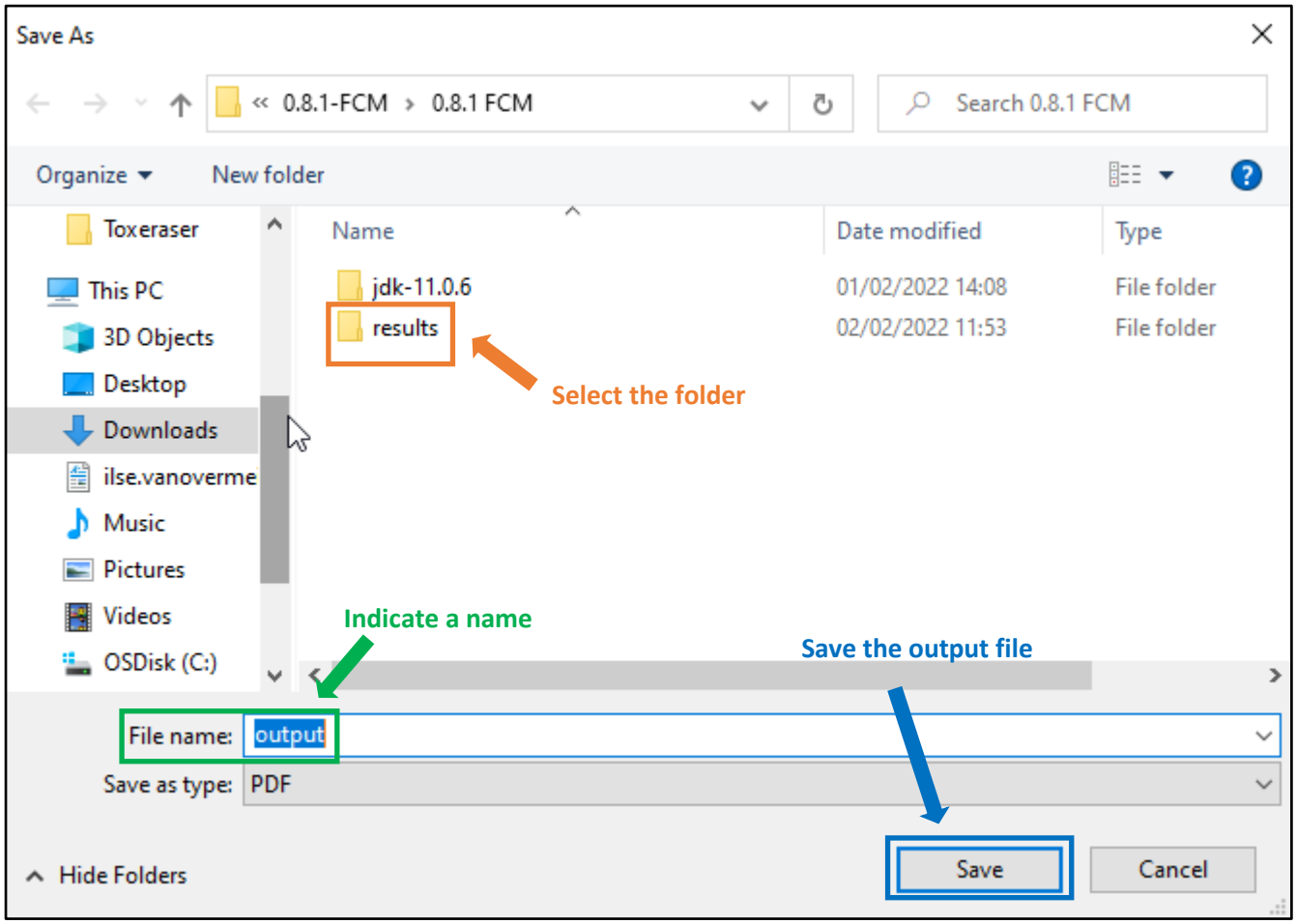

Figure 6: The figure shows how to select the output directory.

3.2 Software elaboration

ToxEraser FCM provides a PDF output file. An example of a PDF output file generated by the software is shown in the Appendix II of this user guide.

The first part of the report relates to the Annex I list. If the substance of interest is found in the database with Annex I compounds, the software will display first a 'match'. In this case, the similarity index is 1 and detailed information included in Annex I such as the specific migration limit and the restrictions of use, if applicable, is displayed. If the molecule is not present in the Annex I database, no match will be possible. Next, an overview of structurally related substances found in the Annex I database is provided in a decreasing order of similarity (from the most similar to the least similar).

In the second part of the report, similar information is displayed but now with respect to the SCIL list.

4. Acknowledgements and contacts

ToxEraser FCM was developed within the LIFE project VERMEER [LIFE16 ENV/IT/000167] (https://www.life-vermeer.eu/). The project is coordinated by Istituto di Ricerche Farmacologiche Mario Negri IRCCS.

The partners of the project are: Electricitè de France (EDF), SCIENSANO, SC Sviluppo Chimica s.p.a., German Federal Institute for Risk Assessment (BfR), Angel Consulting SAS, Institute National de l'Environnement Industriel et des Risques (INERIS), AFRY.

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5. References

EU Regulation 10/2011. European Union, 2011. Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. Off J Eur Union L12, 1-89. EUR-Lex - 32011R0010 - EN - EUR-Lex (europa.eu)

The Safer Chemical Ingredients List (SCIL). https://www.epa.gov/saferchoice/safer-ingredients#searchList

APPENDIX I: lists used to generate the level of safety

ToxEraser FCM uses the European list of compounds authorised to be used in plastic FCM and a list of safe compounds compiled by US EPA. Each list contains substances thoughtfully evaluated by panel of experts considering several toxicological endpoints.

The lists used are:

- Annex 1 of EU regulation 10/2011: is the European list of compounds authorised to be used in plastic FCM and it is freely accessible on EUR-Lex - 32011R0010 - EN - EUR-Lex (europa.eu). Please note that only single substances included in Annex I have been considered, and consequently, ToxEraser FCM is not applicable to mixtures, polymers or inorganic substances.

- Safer Chemical Ingredient List (SCIL): This list is designed to help manufacturers in finding safer alternatives that meet the criteria of the Safer Choice Program, concerning the evaluation of both experimental and modelled data. This program, sponsored by the United States Environmental Protection Agency (US EPA) was conceived to help stakeholders to find safer solutions for human health and the environment.

APPENDIX II: example of a complete output file

A complete output has been added as a PDF file to this user guide to better demonstrate the structure of the file.

In this example the target compound is 2,2,4,4-tetramethylcyclobutane-1,3-diol (TMCD) which is found in the Annex I list.