



USER'S GUIDE

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1. Introduction

VERMEER Cosmolife is a software designed for cosmetic industries to facilitate and harmonize the safety assessment process of cosmetics.

The software allows an overall evaluation of cosmetic ingredients and provides detailed investigation of cosmetic risk scenarios.

The software performs a risk characterization of the given chemicals provided by the user, based on a battery of QSAR models (from the VEGA platform) and returning as output complete reports (in HTML format).

Moreover, the software checks if the ingredient is present in the Annexes of the *“Regulation (EC) No. 1223/2009 of the European parliament and of the Council of 30 November 2009 on cosmetic products”*.

VERMEER Cosmolife supports single or multiple user-defined molecular structures. They could be entered by SMILES, CAS or INCI.

VERMEER Cosmolife is a Java standalone application. It has been designed with flexible capabilities for future extensions in mind (e.g. other models for new toxicological endpoints, refined exposure scenarios or updated regulatory framework).

2. Installing and starting VERMEER Cosmolife

VERMEER Cosmolife is a JAVA application that works on every operating system (Windows/Linux/Mac) with JAVA Runtime Environment (JRE) version 7 installed. Before proceeding please check that the latest JRE (freely available at <http://www.java.com>) is installed on your computer.

Download and unpack the zipped file. To start the application, move to the application folder and run the file VC-launcher-WIN.bat (on Windows platforms), VC-launcher-LINUX.sh (on Linux platforms) or VermeerCosmolife.jar (on Mac platforms).

If you experience problems with the mentioned launchers, you can just run the file VermeerCosmolife.jar with the Java Runtime Environment (JRE). 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 on Windows systems or BASH shell on Linux), move to the application folder and type:

```
java -jar VermeerCosmolife.jar
```

3. How to use

3.1 User Requirements Input

VERMEER Cosmolife has a user-friendly graphical interface, in which the user adds the structures of interest and runs the calculations. The user can insert single or multiple structures. These structures can be entered by SMILES, CAS or INCI. The software searches the structure in a database implemented within the software.

Another basic input information to be included is the concentration of the ingredient. Lastly, in a drop-down menu, the user has to insert the specific product type (body lotion, face cream, hand cream, shampoo, shower gel, deodorant, etc.) according to the product type defined within the Table 2A, Table 2B and Table 3 of *“The SCCS Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation 11th revision”*, to define an exposure scenario. Moreover, the user has the possibility to decide the directory for output.

3.1.1 Select directory for output

The main VERMEER Cosmolife application window has a bar where the user can select the directory for output.

The user has to click on **‘Select directory’** button and decide where the output will be saved (see figure 3.1).

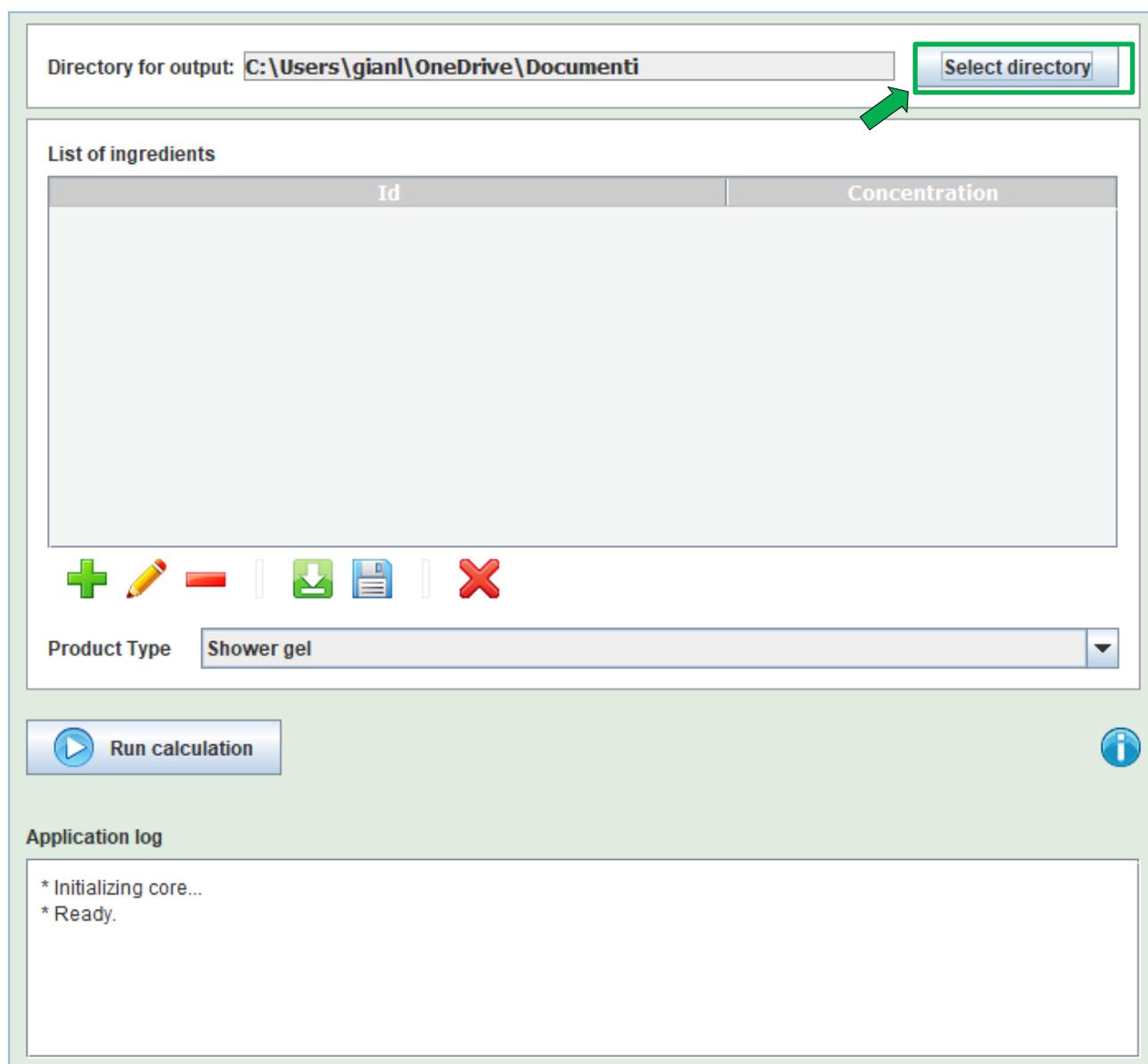


Figure 3.1: Selection of directory output

3.1.2 Insert single ingredient

In the main application window, the user can insert a single structure, clicking on 'plus green button'  (see figure 3.2). The structure could be entered by **SMILES**, **CAS** or **INCI** (see figure 3.3). The software searches this structure in the internal database implemented within the software.

Please note that molecules provided by their CAS or INCI identifiers can be processed only if the identifier is found in the internal database of the application, whereas compounds provided with their SMILES string will be always processed. Using the magnifier icons, it is possible to perform a look-up by CAS or by INCI in the internal database. If a match with the provided CAS/INCI is found, the data available for the compound will be loaded (SMILES and neutralized SMILES).

If the user provides the input structure via its SMILES representation, it has to be noticed that the system also requires a SMILES representation for the neutral form of the compound (in case the original compound is a salt). This is needed because most of the predictive models are not able to accept as input compounds with disconnected structures (e.g. salts).

Moreover, the user must insert the **CONCENTRATION** of the ingredient (see figure 3.3).

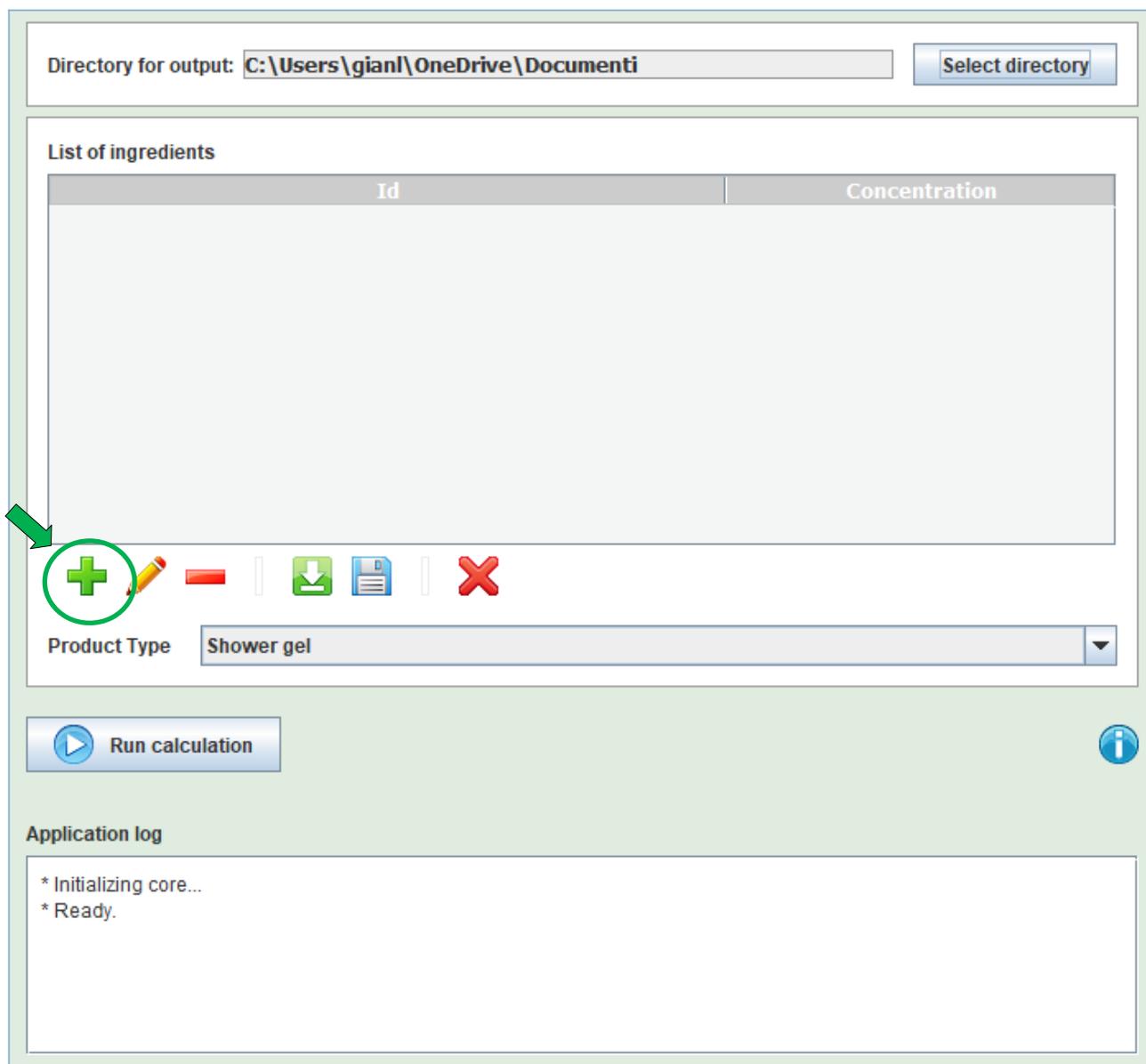


Figure 3.2: The figure shows how to add a single ingredients

The image shows a software dialog box titled "New ingredient". It features several input fields: "Ingredient Id", "SMILES", "SMILES (Neutral form)", "CAS", "INCI", and "Concentration (%)". The "SMILES" and "SMILES (Neutral form)" fields are highlighted with a green border. The "CAS" field is highlighted with an orange border. The "INCI" field is highlighted with a yellow border. The "Concentration (%)" field is highlighted with a purple border. There are search icons next to the "CAS" and "INCI" fields. At the bottom, there are "Cancel" and "Add ingredient" buttons.

Figure 3.3: The figure shows how to insert a structure by **SMILES**, **CAS** or **INCI** and the **CONCENTRATION**.

3.1.3 Insert multiple ingredients

The user has the possibility to insert multiple ingredients. In this case the user can generate a list of ingredients as .txt file, clicking on 'save button'  (1)

Subsequently, the user can upload this file clicking the 'upload button'  (2)

The list of the ingredients will appear on the screen (3) (see figure 3.4)

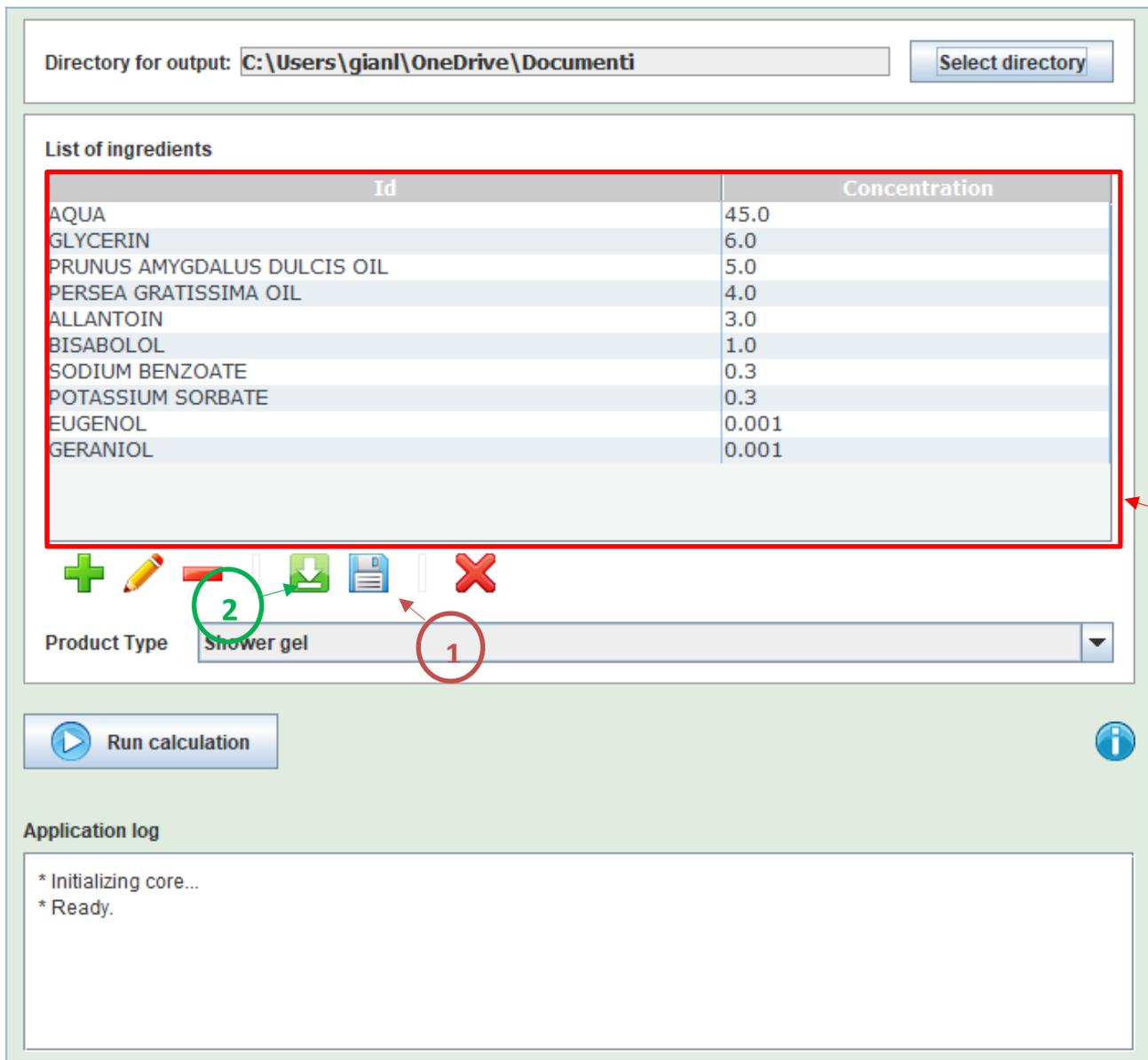


Figure 3.4: Procedure to add multiple ingredients.

3.1.4 Select the product type

Lastly, in a drop-down menu, the user has to insert the specific product type (body lotion, face cream, hand cream, shampoo, shower gel, deodorant, etc) according to the product type defined within the Table 2A, Table 2B and Table 3 of *“The SCCS Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation 10th revision”* (SCCS – Scientific Committee on Consumer Safety; SCCS/1602/18), to define an exposure scenario (see figure 3.5).

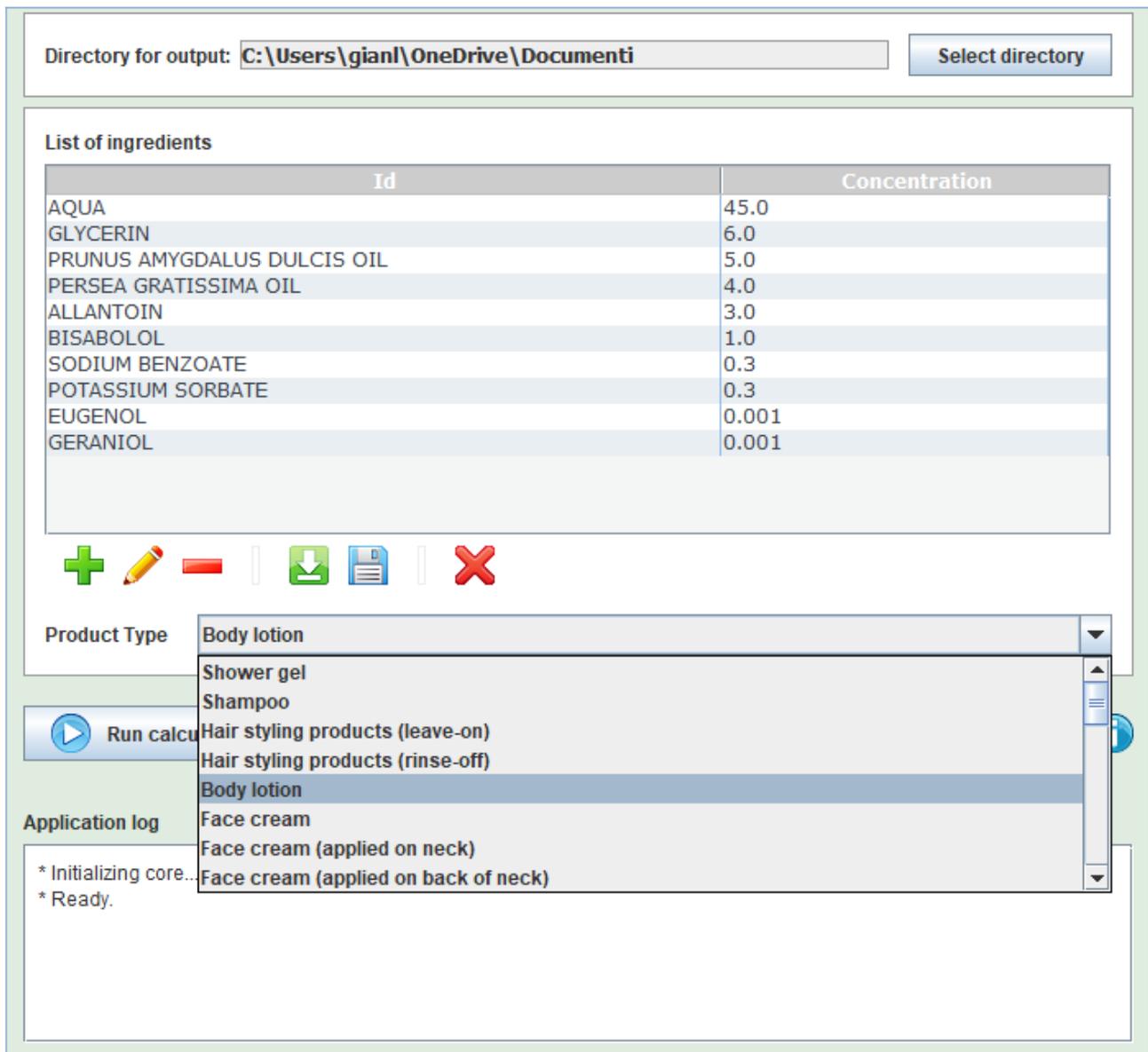


Figure 3.5: Selection of the product type in a drop-down menu

3.1.5 Run calculation

Once every parameter has been correctly set, the user has to click on the button **'Run calculation'** in order to start the evaluation (see figure 3.6).

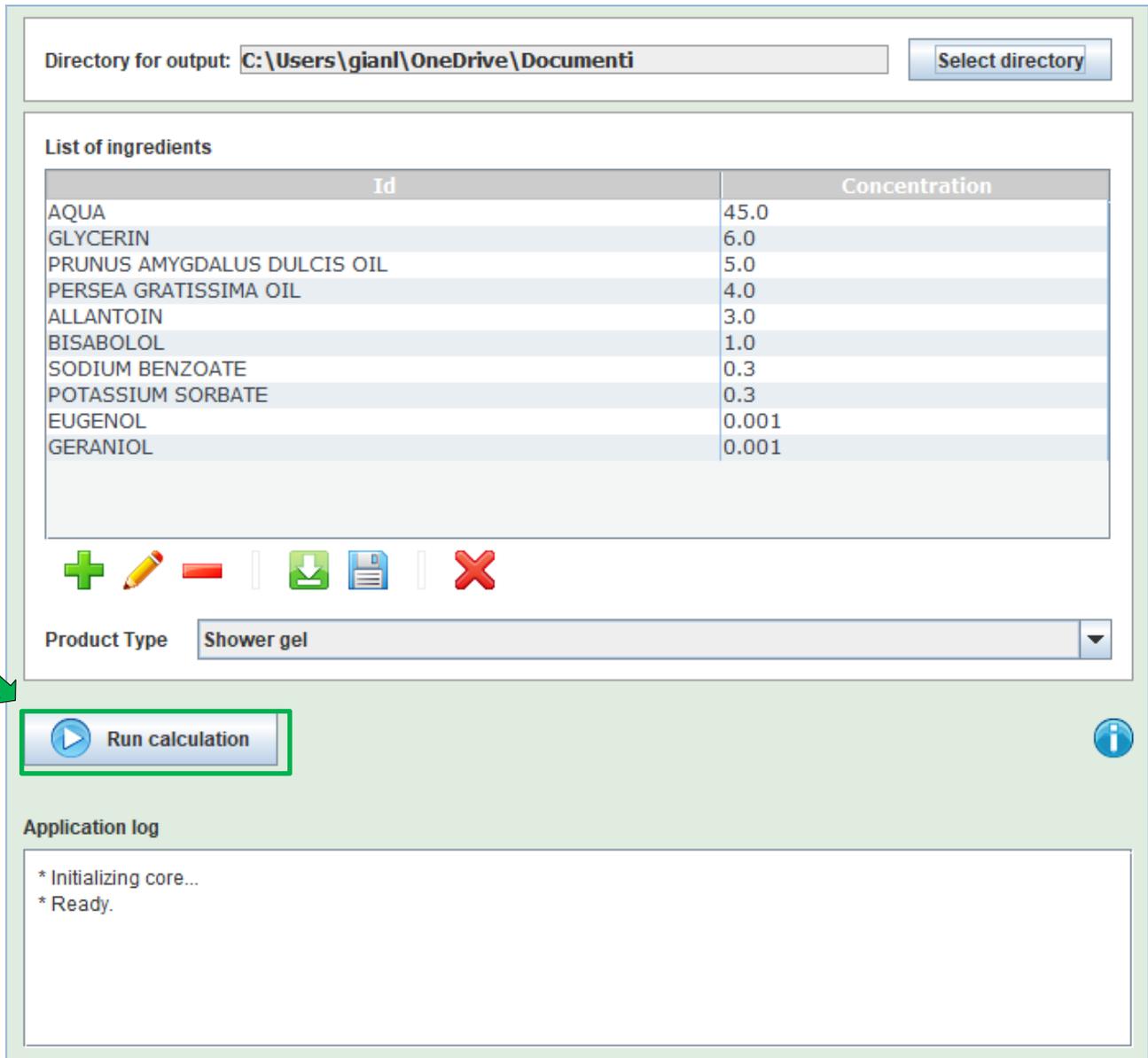


Figure 3.6: The figure shows how to start the software elaboration clicking on 'Run calculation' button

3.2 Software elaboration

VERMEER Cosmolife provides a local HTML output file (that can be viewed with any internet browser) with a summary table containing the hazard and exposure features related to every ingredients.

Moreover, the software provides specific reports for every ingredient with detailed information about the safety assessment of them. This report is divided in 7 sections.

3.2.1. Summary output table

The software provides a preliminary output table with a summary of the hazard and exposure features of the ingredients, previously selected in the input file (see figure 3.7).

| | Ingredient Id | CAS | INCI | Conc. % | Annex | Mutagenicity | Skin Sensitization | Dermal abs. | MoS | TTC |
|-------------------------|-----------------------------|------------|-----------------------------|---------|-------|------------------------------------|-------------------------------------|-------------|-----------|---------------------|
| Details | AQUA | 7732-18-5 | AQUA | 45.0 | - | - | - | - | - | |
| Details | GLYCERIN | 56-81-5 | GLYCERIN | 6.0 | - | NON-Mutagen (EXPERIMENTAL value) | NON-Sensitizer (EXPERIMENTAL value) | 80% | 582.05 | 0.03 mg/kg bw/day |
| Details | PRUNUS AMYGDALUS DULCIS OIL | | PRUNUS AMYGDALUS DULCIS OIL | 5.0 | - | - | - | - | - | |
| Details | PERSEA GRATISSIMA OIL | | PERSEA GRATISSIMA OIL | 4.0 | - | - | - | - | - | |
| Details | ALLANTOIN | 97-59-6 | ALLANTOIN | 3.0 | - | NON-Mutagen (moderate reliability) | Sensitizer (low reliability) | 40% | 268.64 | 0.0015 mg/kg bw/day |
| Details | BISABOLOL | 23089-26-1 | BISABOLOL | 1.0 | - | NON-Mutagen (good reliability) | Sensitizer (moderate reliability) | 40% | 133.5 | 0.0015 mg/kg bw/day |
| Details | SODIUM BENZOATE | 532-32-1 | SODIUM BENZOATE | 0.3 | V | NON-Mutagen (EXPERIMENTAL value) | NON-Sensitizer (EXPERIMENTAL value) | 80% | 93.55 | 0.03 mg/kg bw/day |
| Details | POTASSIUM SORBATE | 24634-61-5 | POTASSIUM SORBATE | 0.3 | V | NON-Mutagen (EXPERIMENTAL value) | Sensitizer (good reliability) | 40% | 3382.03 | 0.03 mg/kg bw/day |
| Details | EUGENOL | 97-53-0 | EUGENOL | 0.001 | III | NON-Mutagen (EXPERIMENTAL value) | Sensitizer (EXPERIMENTAL value) | 80% | 233360.39 | 0.03 mg/kg bw/day |
| Details | GERANIOL | 106-24-1 | GERANIOL | 0.001 | III | NON-Mutagen (EXPERIMENTAL value) | Sensitizer (EXPERIMENTAL value) | 40% | 158441.56 | 0.03 mg/kg bw/day |

Figure 3.7: Summary output table

No assessment is provided for the substances for which the SMILES is not retrieved, for inorganic compounds and for mixtures. Only a matching with the internal database is possible.

Moreover salts are neutralized. Therefore the assessment is done for the neutralized structure.

Clicking on 'Details', the user accesses to the specific report for the selected ingredient.

3.2.2. Report for specific ingredient

The report for the specific ingredient contains details and calculations based on the information retrieved in the database (if a match for the input compound is found) and on a battery of QSAR models from VEGA.

Values from VEGA models are always reported along with additional information about their reliability. VEGA models perform a look-up research in their training set (set of compounds with known experimental value, used to develop the model itself) and they provide an experimental value (instead of a prediction) if the input compound is found in their training set. In this case the label “EXPERIMENTAL value” is found in the report. Otherwise, the prediction is provided and it will be followed by an evaluation of its reliability (good, moderate or low).

3.2.2.1 Information about the input molecule

A summary of the input parameters is given.

Moreover, the software shows the structural formula of the ingredient (see figure 3.8).

Input Molecule

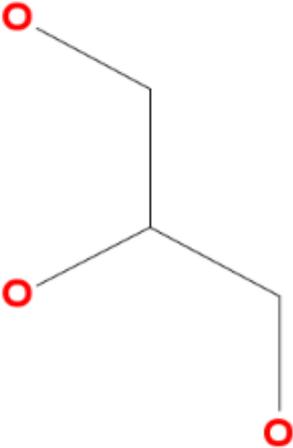
| | |
|--|-------------|
| SMILES | OCC(O)CO |
| SMILES (neutralized) | OCC(O)CO |
| CAS no. | 56-81-5 |
| INCI | GLYCERIN |
| Product Type | Body lotion |
| C (Product concentration) as percentage | 6 % |
| C _x (Product concentration) | 60 mg/g |
|  | |

Figure 3.8: Input parameters

3.2.2.2 Retrieved parameters for the product type

In this section the software shows the parameters related to the selected product type, retrieved from the SCCS Notes of Guidance.

These parameters are the “Calculated Relative Daily Exposure” (in mg/kg bw/day), the surface area involved (cm²), the time of exposure (h) and the kind of exposure (Leave-on or Rinse-off).

In the figure 3.9 below, an example of the output table is shown.

Retrieved parameters for the product type

Values retrieved from: *The SCCS notes of guidance for the testing of cosmetic ingredients and their safety evaluation - 10th revision*

| | |
|--|-----------------------|
| E _{product-rel} (Relative daily exposure) | 123.2 mg/kg bw/day |
| A (Surface area involved) | 15670 cm ² |
| Type of exposure | Leave-on |
| T _{exp} (Time of exposure) | 24 h |

Figure 3.9: Table with the retrieved parameters for the product type

3.2.2.3 Matching with the Annexes, CLP Regulation and SCIL (Section 1)

The software provides the check with the Annexes of the Regulation (EC) n°1223/2209.

Cosmetics Regulation has six Annexes. Five of them (Annex II, III, IV, V and VI) contain lists of ingredients prohibited in cosmetic products or which use is allowed following established threshold and conditions.

These annexes are:

- ANNEX II: LIST OF SUBSTANCES PROHIBITED IN COSMETIC PRODUCTS
- ANNEX III: LIST OF SUBSTANCES WHICH COSMETIC PRODUCTS MUST NOT CONTAIN EXCEPT SUBJECT TO THE RESTRICTIONS LAID DOWN
- ANNEX IV: LIST OF COLORANTS ALLOWED IN COSMETIC PRODUCTS
- ANNEX V: LIST OF PRESERVATIVES ALLOWED IN COSMETIC PRODUCTS
- ANNEX VI: LIST OF UV FILTERS ALLOWED IN COSMETIC PRODUCTS

The database implemented within the software contains these lists, with all the information reported in the Regulation, which are the maximum concentration, the product type in which the ingredient is allowed or the wording of conditions of use and warning.

Moreover, in this section the software provides a check with the Classification, Labelling and Packaging (CLP) Regulation and a check with the Safer Chemical Ingredients List (SCIL), that is a list of chemical ingredients, arranged by functional-use class, that the Safer Choice Program has evaluated and determined to be safer than traditional chemical ingredients (<https://www.epa.gov/saferchoice/safer-ingredients>).

Also in this case, the internal database contains the information of classification and labelling according to CLP Regulation and verifies if the ingredient is part of the SCIL.

Figure 3.10 gives an example of section 1.

1. Annex lists

Data are based on the annexes list updated on November, 27th 2019.

Molecules found in the annex lists: 2

| | |
|--------------------------------------|---|
| Found molecule no. 1 | |
| CAS | 24634-61-5 |
| INCI | POTASSIUM SORBATE |
| Found in annex | ANNEX V: LIST OF PRESERVATIVES ALLOWED IN COSMETIC PRODUCTS |
| Annex details | ANNEX V: Reference Number: 4 ANNEX V: MAX Concentration in ready for use preparation: 0.6% (as acid) |
| Found Safer Chemicals classification | Green |
| Safer Chemicals details | Safer functional use: Preservatives-antioxidants |
| Found in CLP list | Yes |
| CLP details | CLP HARMONIZED CLASSIFICATION (Link): https://echa.europa.eu/it/information-on-chemicals/cl-inventory-database/-/discli/details/22644 HAZARD CLASS AND CATEGORY CODE (CLASSIFICATION): Eye Irrit. 2 HAZARD STATEMENT CODE (CLASSIFICATION): H319 PICTOGRAM, SIGNAL WORD CODE (LABELLING): GHS07 Wng HAZARD STATEMENT CODE (LABELLING): H319 |

Figure 3.10: Annexes, CLP and SCIL check.

3.2.2.4 External Exposure (Section 2)

The software calculates the External Dermal Exposure. This calculation is done using the formulas proposed within the SCCS Notes of Guidance. We refined these formulas for a convenient adaptation to the software concept. Finally, we proposed and used the following formula:

$$\text{External Dermal Exposure} = \frac{E_{\text{product}} * C}{100}$$

Eproduct: Calculated Relative Daily exposure (mg/kg bw/day). It is a value tabulated within the tables of the SCCS Notes of Guidance.

C: Concentration of the ingredient (%)

3.2.2.5 Internal Exposure (Section 3)

The output of this step is the Systemic Exposure Dose (SED), that is the amount expected to enter the blood stream (and therefore be systemically available) per kg body weight and per day. It is expressed in mg/kg bw/day.

For this purpose, we take into consideration the formula proposed within the SCCS Notes of Guidance. This formula takes into account the amount of the finished cosmetic product applied per day (Eproduct), the concentration of the substance under study in the cosmetic product and the dermal absorption expressed as a percentage.

$$SED = \frac{\frac{E_{\text{product}} * C}{100} * DA}{100}$$

A tiered approach is followed for the calculation of the systemic exposure dose. The first-tier assessment is based on 100% of absorption that represents the oral/inhalation exposure. In the second-tier assessment, 50% of absorption is considered. This 50% bioavailability is used according to the SCCS Notes of Guidance 10th edition.

Two values for **Kp** (skin permeability coefficient) are provided by VEGA models, implementing the equations of Potts and Guy and Ten Berge (*Skin Permeation (logKp) model (Potts and Guy) – v.1.0.0* and *Skin Permeation (logKp) model (Ten Berge) – v.1.0.0*).

The two equations used are:

$$\text{Potts and Guy: } \log Kp = 0,71 \log(K_{O/W}) - 0.0061 MW - 2.7$$

$$\text{Ten Berge: } \log[K_{p\text{sk-water}}] = \log \left[\frac{1}{\frac{1}{klip+kpol} + \frac{1}{kaq}} \right]$$

Where:

- $K_{pol} = \frac{b_4}{MW^{b_5}}$
- $K_{aq} = \frac{b_6}{MW^{b_7}}$
- $K_{lip} = 10^{[b_1 + b_2 \log(K_{ow}) + b_3 * Mw]}$
- K_{lip} = permeation coefficient lipid medium
- K_{pol} = permeation coefficient corneocytes [proteins]
- K_{aq} = permeation coefficient epidermis [aqueous]
- K_{ow} = octanol/water partition coefficient.
- M_w = molecular weight.
- $b_1, b_2, b_3, b_4, b_5, b_6, b_7$ = regression coefficients:
 - $b_1 = -2,694$
 - $b_2 = 0,9809$
 - $b_3 = -7,868 * 10^{-3}$
 - $b_4 = 0,05523$
 - $b_5 = 1,383$
 - $b_6 = 1,121 * 10^3$
 - $b_7 = 1,957$

The software shows the results of both models and then selects the worst case scenario.

Once K_p is predicted, the software calculates the maximum flux of the substance, **Jmax**, expressed in $mg/cm^2/h$, according to the following equation:

$$J_{max} = K_p * C_{water, sat}$$

$C_{water, sat}$ is the water solubility parameter, obtained from the VEGA model *Water Solubility model – v.1.0.0*. $C_{water, sat}$ is expressed in mg/cm^3 .

Once J_{max} is obtained, the software applies the Kroes approach (Kroes et al., 2007). Based on J_{max} , Kroes proposed three default absorption values:

$$\%A = \begin{cases} 10\% & \text{if } J_{max} \leq 0.1 \mu g/cm^2/h \\ 40\% & \text{if } 0.1 < J_{max} \leq 10 \mu g/cm^2/h \\ 80\% & \text{if } J_{max} > 10 \mu g/cm^2/h \end{cases}$$

The three default skin absorption percentage are proposed to represent low, medium and high level of absorption. The software used these values in the unit of mg/cm²/h.

Figure 3.11 shows an example of section 3.

3. Internal exposure assessment

| | | | |
|---|-----------------------------|----------------------|---|
| Kp (Skin permeation, VEGA prediction - Ten and Berge formula) | 0.0052 cm/h | moderate reliability |  |
| Kp (Skin permeation, VEGA prediction - Potts and Guy formula) | 0.0036 cm/h | moderate reliability |  |
| Kp (Skin permeation, worst case used for calculations) | 0.0052 cm/h | | |
| Water solubility (VEGA prediction) | 1.9 mg/cm ³ | EXPERIMENTAL value |  |
| J _{max} (Maximum flux) | 0.0098 mg/cm ² h | | |

Systemic Exposure Dose calculated with three different absorption scenarios:

100% (oral absorption)

50% (dermal absorption)

40% (estimated absorption with the Kroes approach)

| | |
|--|-----------------|
| SED - Systemic Exposure Dose with 100% absorption | 0.37 mg/kg bw/d |
| SED - Systemic Exposure Dose with 50% absorption | 0.18 mg/kg bw/d |
| SED - Systemic Exposure Dose with 40% absorption (from Kroes thresholds) | 0.15 mg/kg bw/d |

Figure 3.11: Internal exposure assessment

3.2.2.6 Hazard identification (Section 4)

The software reports values (experimental if available or predicted) related to some toxicological endpoints.

At the moment the software provides an evaluation of mutagenicity/genotoxicity and skin sensitization. Other toxicological endpoints will be added in future versions.

For mutagenicity, the JANUS workflow based on Ames models is adopted (a consensus workflow, originally available in the JANUS application, where all the available VEGA models for Ames test are combined).

For genotoxicity, the new 'in vitro micronucleus' and 'Chromosomal aberration' models are selected for the evaluation.

Skin sensitization is evaluated using two models implemented in VEGA (*Skin Sensitization model (CAESAR) v.2.1.6* and *Skin Sensitization model (IRFMN/JRC) – v.1.0.0*). An integrated model based on the results of the two models is used for the final assessment of skin sensitization.

All the provided values are highlighted with a color to facilitate the user. The cell with the prediction will be red if the compound is predicted as mutagenic/genotoxic/sensitizer or green if it is safe, in case the prediction has a good reliability or if an experimental value is directly provided. These colors will be set respectively to orange and yellow if the reliability of the predictions is only moderate or low.

An output example is presented in figure 3.12.

4. Hazard identification

| | |
|---|-------------------------------------|
| Mutagenicity - Ames test (Janus workflow prediction) | NON-Mutagen (EXPERIMENTAL value) |
| In vitro micronucleus assay (IRFMN model prediction) | Inactive (EXPERIMENTAL value) |
| Chromosomal aberration test (Coral model prediction) | Inactive (good reliability) |
| Skin sensitization (Consensus of Caesar and JRC models) | NON-Sensitizer (EXPERIMENTAL value) |
| Skin sensitization (Caesar model prediction) | NON-Sensitizer (good reliability) |
| Skin sensitization (IRFMN/JRC model prediction) | NON-Sensitizer (EXPERIMENTAL value) |

Figure 3.12: Hazard identification (Mutagenicity/genotoxicity and skin sensitization)

3.2.2.7 Systemic Toxicity (NOAEL) (Section 5)

VERMEER Cosmolife provides the fundamental value of the No Observed Adverse Effect Level (NOAEL). The software searches in the internal database experimental values for NOAEL or predict this value using the CORAL NOAEL model implemented in VEGA (*NOAEL (IRFMN-CORAL) v.1.0.0*). If present, the experimental value will be used for risk characterization. Otherwise, the most conservative value will be selected.

3.2.2.8 Risk Characterization (Section 6)

The software carries out a risk characterization, considering the process proposed within the SCCS Notes of Guidance. For cosmetics, the focus is on systemic toxicity and the Margin of Safety (MoS) is calculated according to the formula:

$$MoS = \frac{POD(\text{Point Of Departure})}{SED(\text{Systemic Exposure Dose})}$$

Within VERMEER Cosmolife the POD can be an experimental, if available, or a predicted NOAEL.

To consider a substance not risky, MoS has to be higher than 100. Cells with values higher than 100 have green highlight color, while for values lower than 100 the color is red.

3.2.2.9 TTC assessment (Section 7)

The software includes the assessment considering the TTC approach. Moreover, the software compares the external and internal exposure values, previously obtained, with the TTC threshold related to the specific ingredient. The output is in a red or green cell, depending on whether external and internal exposure values are above or below the TTC threshold. For this purpose, the software will use the original Cramer decision tree, implemented in VEGA (*CRAMER CLASSIFICATION-TOXTREE V.1.0.0*)

This workflow allows an incorporation of dermal absorption into the use of TTC, according to the workflow proposed by Williams (Williams et al., 2016).

The threshold values used in the application are:

| Chemical class | TTC values ($\mu\text{g}/\text{person}/\text{day}$) | TTC values ($\mu\text{g}/\text{kg bw}/\text{day}$) |
|-------------------------|---|--|
| Cramer Class I | 2760 | 46 |
| Cramer Class III | 138 | 2.3 |

3.2.2.10 Additional information

In the final part of the report, additional information retrieved from the internal database is provided to give a complete overview of the substances.

4. Acknowledgements and contacts

VERMEER *Cosmolife* has been developed within the LIFE Project VERMEER (LIFE16 ENV/IT/000167).

The project is coordinated by: Istituto di Ricerche Farmacologiche Mario Negri IRCCS.

The partners of the projects are: Electricité de France SA, Kode s.r.l., SCIENSANO, SC Sviluppo Chimica S.p.A., Federal Institute for Risk Assessment, Angel Consulting SAS, Institut National de l'Environnement industriel et des Risques, AFRY.

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