VERMEER Food Contact Materials
(VERMEER FCM v3.4)

User Manual

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1. Model purpose

1.1. Goal

The VERMEER Food Contact Materials (VERMEER FCM) tool is used to provide information with respect to exposure (i.e. migration) and hazard endpoints for chemicals (e.g. additives, etc) intended to be used in plastics food contact materials (FCM). Chemicals originally present in FCM and able to migrate to foods are called 'migrating chemicals' or 'chemical migrants'.

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

1.2. General information

Regulations related to FCMs (e.g. Regulation (EC) No. 1935/2004 and Regulation (EU) No. 10/2011) require the estimation of upper-bound (i.e. conservative) concentrations of the migrating chemicals. State-to-the-art migration models and the model implemented in MERLIN-Expo provide useful information for the evaluation of the chemical migrants.

The VERMEER FCM tool predicts:

1. the concentration of chemical migrants in food (expressed in $mg.kg^{-1}$ of e.g. drinking water, soda, solid foods) in contact with FCM. The predicted concentrations depend on:
    a. contact time between food and FCM;
    b. contact temperature;
    c. material type (e.g. type of plastic polymer);
    d. food (e.g. fatty vs non-fatty foods);
    e. physico-chemical properties of the chemical migrants (e.g. lipophilicity).
2. various hazard endpoints required for regulatory purposes:
    a. *in vitro* mutagenicity;
    b. *in vitro* micronucleus formation;
    c. sub-chronic oral toxicity;
    d. carcinogenicity;
    e. developmental toxicity.

The VERMEER FCM predictions can be used within the context of Regulation (EC) No 10/2011 on plastic materials and articles intended to come into contact with food.

Note: Before using the VERMEER FCM tool, it is important to install the VEGA software (https://www.vegahub.eu/download/) on your computer.

2. Model applicability

2.1. Spatial scale and resolution

The FCM model is a one-dimensional diffusion model consisting of two layers (compartments), corresponding to one FCM layer and one Food layer. It is thus not adapted for multi-layer FCM.

The FCM layer is described by the parameters corresponding to its specific material. Within each compartment, chemical migrants are assumed to be homogeneously and instantaneously distributed in the whole volume.

The model can be used for any geometry of the simulated layers (i.e. FCM and Food thickness and FCM-Food contact area).

2.2. Chemicals considered

The FCM model can be applied for a variety of chemicals present in FCMs (e.g. additives, monomers, catalyst residues, etc.[1]). Parameter values related to diffusion coefficients of plastic FCM and partition coefficient between FCMs and food were obtained from experimental data covering a given range of chemical properties. Parameter values are then generally applicable for a given range of molecular weights. Applicability domains related to molecular weights depend on the model parameters described in Section 3.

The FCM model is applicable for plastic FCM corresponding to the following categories: polyolefines, i.e. low density polyethylenes (LDPE), high density polyethylenes (HDPE), polypropylenes (PP-random, PP-homo, PP-blockcopolymer); polystyrenes, i.e. general-purpose polystyrene (PS), high impact polystyrene (HIPS) and styrene-butadiene-styrene block-copolymer (SBS); polyesters, i.e. polyethylene terephthalate (PET), and polyethylene naphthalate (PEN); polyamides (PA); polyvinylchloride (PVC). There is also an option to use 'other polymers' in case the end-user knows the different parameter values.

2.3. Steady-state vs dynamic processes

The FCM model is governed by time-dependent (dynamic) transfer diffusion processes between the layers (i.e. one layer for the FCM and one layer for food).

The transfer of chemical migrants at the interface between FCM and Food is also governed by their partition between the two media in contact (i.e. interface between one FCM and the food). Such partition is described by a Partition coefficient, which is assumed to be at equilibrium (i.e. the chemical migrant is instantaneously distributed between the two media of concern).

3. Scientific background

The scientific background of the migration model is presented in detail in the documentation of the MERLIN-Expo FCM model (available on https://merlin-expo.eu/). Only the main principles on the model are summarized here for a better understanding of the assessment process.

3.1. Process n°1: Diffusion between FCM and Food

The transfer of chemical migrants from FCM to Food is assumed to be mainly driven by diffusion from the FCM to food.

A one dimensional (1D) diffusion model between the FCM layer and Food was considered here. The governing partial differential equation describing diffusion is the second Fick's Law:

(1) $$\frac{\partial C_i}{\partial t} = D_i . \frac{\partial^2 C_i}{\partial x^2}$$

where: C_i is the concentration of the chemical in compartment i (in mg.g^{-1}); D_i is the diffusion coefficient in compartment i (in m.s^{-2}).

When only one FCM layer is considered, the mass-balance equation based on Fick's second law (Equation **Errore. L'origine riferimento non è stata trovata.**)) satisfies an analytical solution, as described in Crank (1975) and adapted in Piringer et al (2008)

[1] For predicting some physico-chemical and toxicological endpoints, a SMILES for the targeted chemical must be available and entered in the VERMEER FCM tool.

(2) $$m_{Food}(t) = m_{FCM,0}.\left(\frac{\rho_{FCM}.\alpha}{\rho_{Food}+\rho_{FCM}.\alpha}\right).\left[1-\sum_{n=1}^{\infty}\frac{2\alpha.(1+\alpha)}{1+\alpha+\alpha^2 q_n^2}exp\left(-D_{FCM}.t.\frac{q_n^2}{d_{FCM}^2}\right)\right]$$

where $m_{Food}(t)$ represents the amount of the migrating chemical after the contact time t in food (mg); $m_{FCM,0}$ is the initial amount of the chemical in FCM (mg); with the volumes V_{FCM} and V_{Food} of FCM and food (cm^3).

α (unitless) represents the ratio:

(3) $$\alpha = \frac{V_{Food}}{V_{FCM}.K_{FCM,Food}} = \frac{d_{Food}}{d_{FCM}.K_{FCM,Food}}$$

with $K_{FCM,Food}$ representing the partition coefficient of the chemical between FCM and Food; d_{Food} is the thickness of food layer (cm); d_{FCM} is the thickness of FCM layer (cm).

(4) $$K_{FCM,Food} = \left(\frac{\rho_{FCM}.C_{FCM}}{\rho_{Food}.C_{Food}}\right)_{equ}$$

where C_{FCM} is the concentration of the chemical in FCM ($mg.g^{-1}$); C_{Food} is the concentration of the chemical in Food ($mg.g^{-1}$); ρ_{FCM} is the FCM density ($g.cm^{-3}$); ρ_{Food} is the Food density ($g.cm^{-3}$).

The parameters q_n involved in Equation (2) are the positive roots of the transcendent equation: $\tan(q_n) = -\alpha q_n$. Solutions of this latter trigonometric identity are tabulated for some values of α. Approximated solutions can also be used, i.e. (Equation 5):

$$for\ \alpha \ll 1, \qquad q_n \approx \frac{n\pi}{1+\alpha}$$

$$else, \qquad q_n \approx \left[n - \frac{\alpha}{2(1+\alpha)}\right]\pi$$

The selected model works for one FCM layer and is not designed for predicting the migration of chemicals in multi-layers structures (i.e. a packaging composed of several successive layers).

3.2. Process n°2: Models for the calculation of the Diffusion coefficient

For running the diffusion transport equation (Equation (2)), diffusion coefficient in FCM D_{FCM} must be determined for the targeted chemical migrant and for each type of FCM. The diffusion coefficients are related to chemical properties (e.g. molecular size) and FCM properties, as well as temperature.

A simplified, empirical approach to obtain diffusion coefficients for the migration modelling was approved in EU (FACET, 2017; Simoneau, 2010), for the cases where only little or no data exist for the system of interest. The model that was approved for this use was the semi-empirical model proposed by Piringer (2008) for safe overestimation of diffusion coefficients. Safe overestimation means that the model is optimized to predict or overpredict at least 95% of the diffusion coefficient data that was used for the development of the model. The aim, when developing the specific model, has been to make a reliable model with as few as possible parameters, easy to use for industrial applications. The model correlates the diffusion coefficient with the relative molecular mass, *M*, of the chemical migrating in FCM, with a matrix-specific parameter, noted A_i, and with the absolute temperature, *T*. An equation for D_{FCM} in a reference amorphous polyolefin material was developed (Brandsch et al, 2000; Piringer 2000) and extended to other FCMs:

(6) $$D_{FCM} = D_{ref}.exp\left(A_{FCM} - 0.1351.M^{2/3} + 0.003.M - \frac{10454+\tau}{T}\right)$$

with the unit reference diffusion coefficient, $D_{ref} = 1\ m^2.s^{-1}$ (or $D_{ref} = 10000\ cm^2.s^{-1}$ or $D_{ref} = 8.64.10^8\ cm^2.d^{-1}$)

A_{FCM} is a standard polymer-specific diffusivity parameter (unitless); M is the relative molecular mass of the migrating chemical (Da); T is the temperature (in K); τ is the specific contribution of the polymer matrix to the diffusion activation energy (K).

The diffusion coefficient then results from three contributions: the term $exp(A'_{FCM})$ describes the contribution of the polymer matrix of the FCM; the term $exp\left(-0.1351.M^{2/3} + 0.003.M\right)$ describes the effect of the migrating chemical incorporated in the FCM; the term $exp\left(-\frac{10454+\tau}{T}\right)$ describes the effect of temperature.

The parameter A_{FCM} is specific to the FCM material. It may be assimilated to a `conductance' of the polymer matrix towards the diffusion of the migrating chemical. In soft/flexible polymers, such as low density polyethylene (LDPE), A'_{FCM} values are high reflecting high diffusion behavior and hence high migration through the polymer, while stiff chain polymers such as polyesters have lower A'_{FCM} values due to the lower diffusion behavior, and hence lower migration of the same chemical will occur.

The molecular mass is used as estimator for the molecular volume which represents the real parameter determining the diffusion. For deriving the influence of molecular mass on diffusion coefficient and then the term $exp\left(-0.1351.M^{2/3} + 0.003.M\right)$, the starting point was the development of an equation for n-alkanes with the elementary composition C_iH_{2i+2} (Piringer 2008). Piringer (2008) correlates the diffusion coefficient to the cross-sectional area of the diffusing molecule, representing the relative resistance of the polymer matrix against the movement of the diffusing molecule. In the special situation of n alkanes, this area can be represented by the term $0.1351.M^{2/3}$. However, a slower decrease of the diffusion coefficient D_{FCM} at high molecular masses was observed. The correction factor $0.003.M$ was then introduced.

The effect of temperature was simulated according to the Arrhenius relationship: $D = D_0.\exp\left(-\frac{E_a}{RT}\right)$, where D_0 is the hypothetical diffusion coefficient at very high temperature, E_a is the activation energy of diffusion (J/mol), R the gas constant (J/mol K) and T the temperature (K). A reference activation energy of $E_a = 86.9\ kJ.mol^{-1}$, corresponding to diffusion process in the reference amporphous polyolefin matrix, divided by R leads to the reference value 10454 K in Equation **Errore. L'origine riferimento non è stata trovata.**). The parameter τ with the dimension *Kelvin* accounts for a specific contribution of the polymer matrix to the diffusion activation energy. Depending on the nature of the polymer, this contribution may lead to higher or respectively lower E_a than the reference activation energy of 86.9 kJ.mol^{-1}.

3.3. Process n°3: Partition between FCM and Food

In a two-phase food/polymer system, transfer of the migrating chemical from one phase to the other occurs in order to reach thermodynamic equilibrium. This thermodynamic equilibrium is described by a partition coefficient $K_{FCM,Food}$.

A partition coefficient $K_{FCM,Food}$ is defined as the ratio at equilibrium of the migrating chemical concentration in FCM, C_{FCM}, to its equilibrium concentration, in the food phase, C_{Food}. $K_{FCM,Food}$ is defined as:

(7) $$K_{FCM,Food} = \left(\frac{\rho_{FCM}.C_{FCM}}{\rho_{Food}.C_{Food}}\right)_{equ}$$

$K_{FCM,Food}$ is higher than one when more chemical is absorbed into the polymer than in the food. For food safety, a large $K_{FCM,Food}$ limits migration from the FCM to food; conversely, a lower $K_{FCM,Food}$ indicates that more chemical is adsorbed into the food. Partition coefficients depend on the solubility coefficient of the chemical for both the FCM and Food.

Seiler et al. (2014) showed that certain characteristics of foodstuffs such as fat, water or carbohydrate content dominate their solubility for organic chemicals. Solubility of migrating chemicals for foods may be correlated with ethanol–water mixtures; foods can then be expressed in ethanol–equivalents. In the present model, the ethanol-equivalency EtOH-eq is then used as the food proxy.

In the VERMEER FCM tool, we considered the model developed by Huang et al. (2019), who built the following generic QPPR model for predicting $K_{FCM,Food}$:

(8) $$log(K_{FCM,Food}) = -1.96 + 1.16.log(K_{ow}) - 0.0059.EtOH_{equ} - 0.0079.log(K_{ow}).EtOH_{equ} + 805.\left(\frac{1}{T} - \frac{1}{298.15}\right)$$

(N=1847, R^2=0.894, R^2_{adj}=0.893, SE=0.95, RMSE=0.89)

This model was selected in the MERLIN-Expo FCM model because it is based on an important number of data and statistical analysis of the QPPR is explicitly given.

Taking into account the theory on regression, the uncertainty in the prediction can be estimated. Assuming identical, independent and normally distributed errors, the uncertainty in the prediction of the variable $log(K_{FCM,Food})$ can be defined from the predictive mean $\overline{log(K_{FCM,Food})}$ and standard error of predictions $SE\left[\overline{log(K_{FCM,Food})}\right]$, i.e.

(9) $$log(K_{FCM,Food}) = \overline{log(K_{FCM,Food})} + t_{n-k-1}.SE\left[\overline{log(K_{FCM,Food})}\right]$$

where t_{n-k-1} is the student t-distribution with n-k-1 degrees of freedom, *n* is the number of data in the training set, *k* is the number of descriptors in the model (and *k+1* is the intercept plus the number of descriptors). Here *n*=1847; *k*=3.

An uncertainty variable noted $\varepsilon_{log(K_{FCM,Food})}$ is then defined as:

(10) $$\varepsilon_{log(K_{FCM,Food})} = SE.t_{1843} = 0.95.t_{1843}$$

And then:

(11) $$log(K_{FCM,Food}) = -1.96 + 1.16.log(K_{ow}) - 0.0059.EtOH_{equ} - 0.0079.log(K_{ow}).EtOH_{equ} + 805.\left(\frac{1}{T} - \frac{1}{298.15}\right) + \varepsilon_{log(K_{FCM,Food})}$$

3.4. Hazard models

3.4.1 Hazard models predicted by VEGA

Several hazard models from VEGA can be imported in VERMEER FCM for predicting hazards of the targeted chemical(s). All the details regarding each of the models can be found in the *ad hoc* VEGA reports. Hazard endpoints are subdivided in three successive levels:

- Level 1: according to the EFSA Note for Guidance, data from a bacterial reverse gene mutation test and an *in vitro* mammalian cell micronucleus test need to be provided when the concentration

of the chemical in food is below 0.05 mg.kg^{-1}. In case a positive result is obtained, further *in vivo* genotoxicity tests may be required. Block "Hazard data level 1" provides predictions on: (i) bacterial (Ames) mutagenicity; and (ii) *in vitro* micronucleus formation. For this purpose, the following models can be imported from VEGA:

  - the consensus VEGA model providing a qualitative prediction of mutagenicity;
  - the IRFMN model providing a qualitative prediction of *in vitro* micronucleus activity.

- Level 2: according to the EFSA Note for Guidance, data of a 90-day oral toxicity study as well as data to demonstrate the absence of an accumulation potential in humans need to be provided in addition to the hazard data for level 1 when the migration of the chemical is between 0.05 and 5 mg.kg^{-1}. Block "Hazard data level 2" provides the prediction of the NOAEL value for sub-chronic oral toxicity and needs to be combined with the hazard data of Block "Hazard data level 1". Although no direct predictions are made for the accumulation potential of the chemical migrant, the predicted logP value can be used as a first indication. For this purpose, the following models can be imported from VEGA:
  - the IRFMN model providing a quantitative prediction of log(NOAEL);
  - the MlogP model providing a quantitative prediction of logP.
- Level 3: according to the EFSA Note for Guidance, data on (i) adsorption, distribution, metabolism and excretion (ADME), (ii) reproductive and developmental toxicity and (iii) chronic toxicity/carcinogenicity need to be provided in addition to the hazard data for level 1 and 2 when the migration of the chemical is above 5 mg.kg^{-1}. Block "Hazard data level 3" provides predictions for carcinogenicity and developmental toxicity and needs to be combined with the hazard data of Block "Hazard data level 1" and "Hazard data level 2". For this purpose, the following models can be imported from VEGA:
  - a model predicting developmental reproductive toxicity;
  - the CAESAR model providing a qualitative prediction of development toxicity;
  - the ANTARES model providing a qualitative prediction of carcinogenicity;
  - the CAESAR model providing a qualitative prediction of carcinogenicity;
  - the ISSCAN model providing a qualitative prediction of carcinogenicity;
  - the ISS model providing a qualitative prediction of carcinogenicity;
  - the IRFMN model providing a qualitative prediction of oral classification;
  - the IRFMN model providing a quantitative prediction of oral slope factor.

3.4.2 Translation of Boolean VEGA predictions into a numerical scale

Some VEGA models predicting hazard data provide qualitative predictions, like Non-carcinogen vs Possible carcinogen vs Carcinogen, Non-carcinogen vs Carcinogen vs Not predicted, Non-Mutagen vs Mutagen, etc. In order to compare such variables with quantitative variables (i.e. with the chemical concentration in food/Specific Migration Limit ratio) and integrate them in global assessments, the VERMEER FCM tool translates such Boolean predictions into a numerical scale from 0 to 1, according to the following process.

Let's consider the endpoint called 'Tox' (e.g. 'Tox' ='Carcinogenic' or 'Mutagenic', etc), qualitative information is translated into quantitative information according to the function:

  - If 'VEGA result=NON-Tox, then 'Tox' =0;

- If 'VEGA result=Possible NON-Tox, then 'Tox' =0.25;
- If 'VEGA result=Not Predicted, then 'Tox' =0.5;
- If 'VEGA result=Possible Tox, then 'Tox' =0.75;
- If 'VEGA result= Tox, then 'Tox' =1.

3.4.3 Combining hazard predictions with ADI

For a given chemical and a given model, VEGA also provides an Applicability Domain Index (ADI). '*ADI=1*' means that the prediction is within the applicability domain of the model; '*ADI=0*' means that the prediction is outside of the applicability domain of the model. Intermediate values (from 0 to 1) measure membership to the applicability domain. VERMEER FCM integrates this kind of information in the assessment according to the methodology described below.

For integrating ADI in the assessment, a 'degree of belief' approach (based on fuzzy logics) was adopted, according to the following principles:

- '*ADI=0*' means that we have no confidence in the prediction. As a consequence, the 'Tox' endpoint should be 0.5 (i.e an intermediate between NON-Tox and Tox, which can be translated into '*I don't know*');
- '*ADI=1*' means that we are confident in the prediction. As a consequence, the prediction is confirmed;
- '*0<ADI<1*' means that we are in a 'grey' zone, where we are partially confident in the prediction.

Mathematically, the degree of belief approach gives:

- If 'VEGA result=NON-Tox', then $Tox = 0.5.(1 - ADI)$. For extreme ADI values, the formula gives:
  - If 'VEGA result=NON-Tox' with ADI=0 (i.e. non confidence in the prediction), then $Tox = 0.5$ (i.e. '*I don't know*');
  - If 'VEGA result=NON-Tox' with ADI=0.5 (i.e. partial confidence in the prediction), then $Tox = 0.25$ (i.e. '*Rather NON-Tox*');
  - If 'VEGA result=NON-Tox' with ADI=1 (i.e. total confidence in the prediction), then $Tox = 0$ (i.e. '*NON-Tox*');
- If 'VEGA result=Tox', then $Tox = 0.5.(1 + ADI)$. For extreme ADI values, the formula gives:
  - If 'VEGA result=Tox' with ADI=0 (i.e. non confidence in the prediction), then $Tox = 0.5$ (i.e. '*I don't know*');
  - If 'VEGA result= Tox' with ADI=0.5 (i.e. partial confidence in the prediction), then $Tox = 0.75$ (i.e. '*Rather Tox*');
  - If 'VEGA result= Tox' with ADI=1 (i.e. total confidence in the prediction), then $Tox = 1$ (i.e. '*Tox*').

3.4.4 Construction of a weighted model (for carcinogenicity)

For carcinogenicity, four qualitative models are available in VEGA (i.e. ANTARES, CAESAR, ISSCAN, ISS). A weighted prediction is proposed through the integration of these four predictions.

For this purpose, all the models weighted by their respective ADI. Mathematically:

$$Tox = \frac{\sum ADI_i . Tox_i}{nb\ of\ models}$$

Where Tox_i is the prediction provided by the i[th] model ($i=1$ *to* 4); ADI_i is the applicability domain index of the prediction provided by the i[th] model ($i=1$ *to* 4); $nb\ of\ models$ is the number of models (here 4); Tox is the weighted toxicity prediction.

4. How to build an assessment with the VERMEER FCM tool

The VERMEER FCM tool is based on the MERLIN-Expo platform. All the potential features of the MERLIN-Expo platform are described in detail on https://wiki.merlin-expo.eu/doku.php.

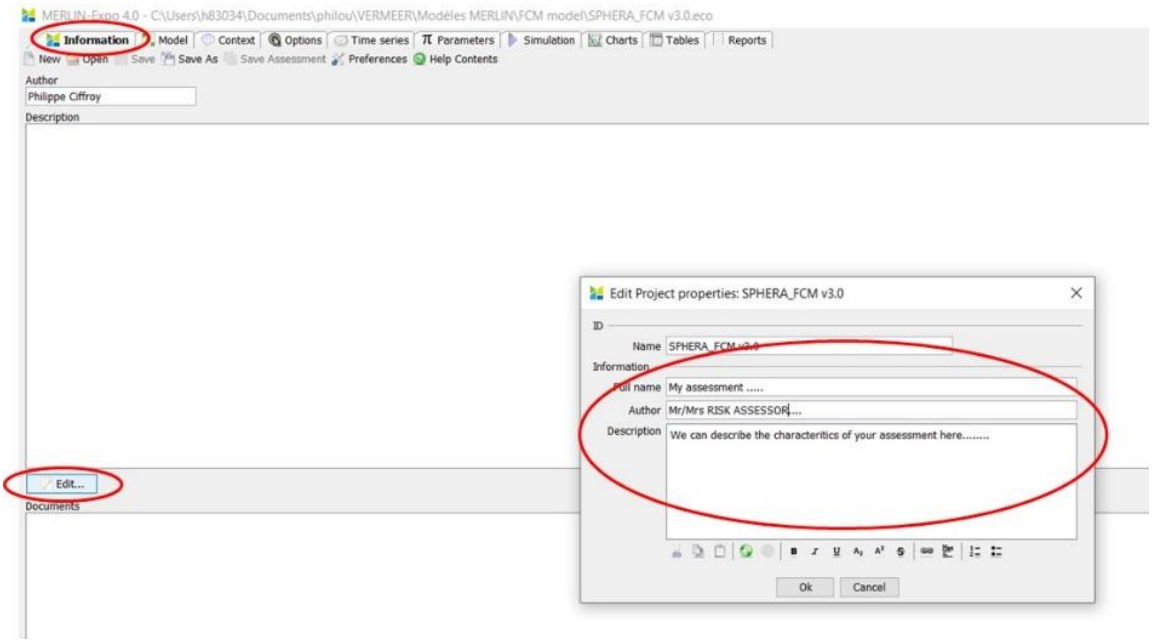
Only the main features are described in this chapter to facilitate the use of the VERMEER FCM tool, but issues that are not covered in the present chapter can be found in more detail on https://wiki.merlin-expo.eu/doku.php.

4.1. Describing your assessment: the Information tab

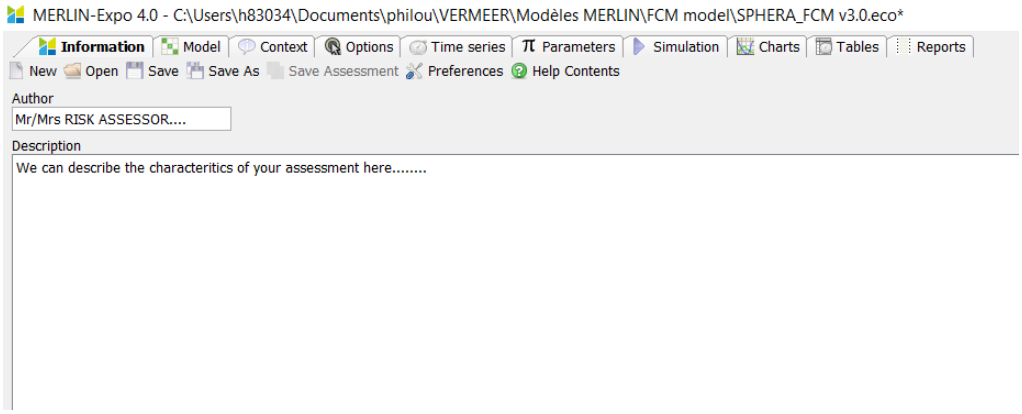
Let's start building an assessment!

You can first provide some information about your assessment:

- Go to the 'Information' tab;
- Click on 'Edit' to open the Description window;
- Additional information can be written in the Description window: e.g. Title of the assessment; Name of the assessor; Characteristics of the assessment, etc…

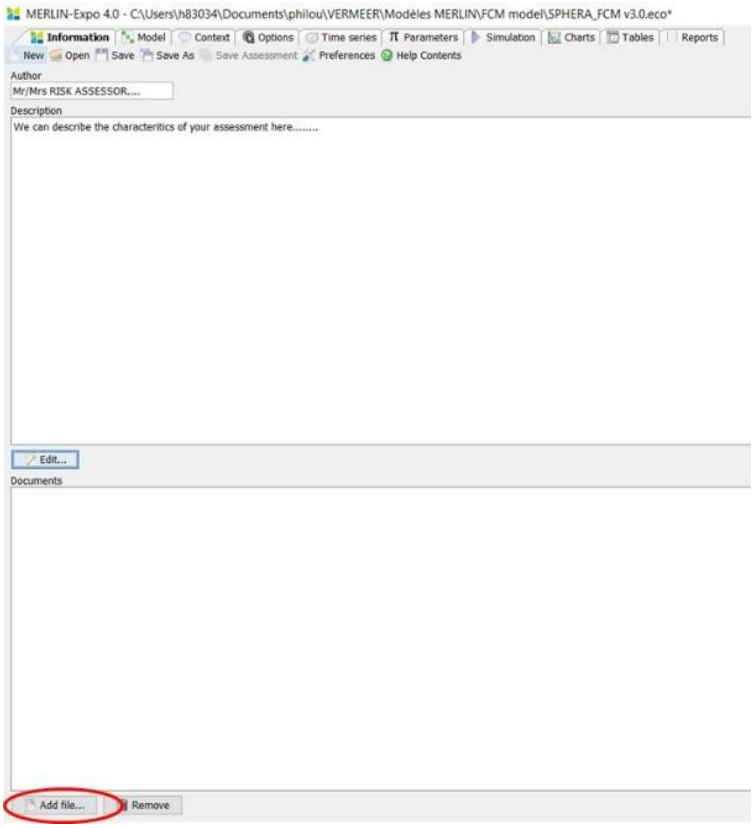


The information you have written will be visible in the 'Description' window:

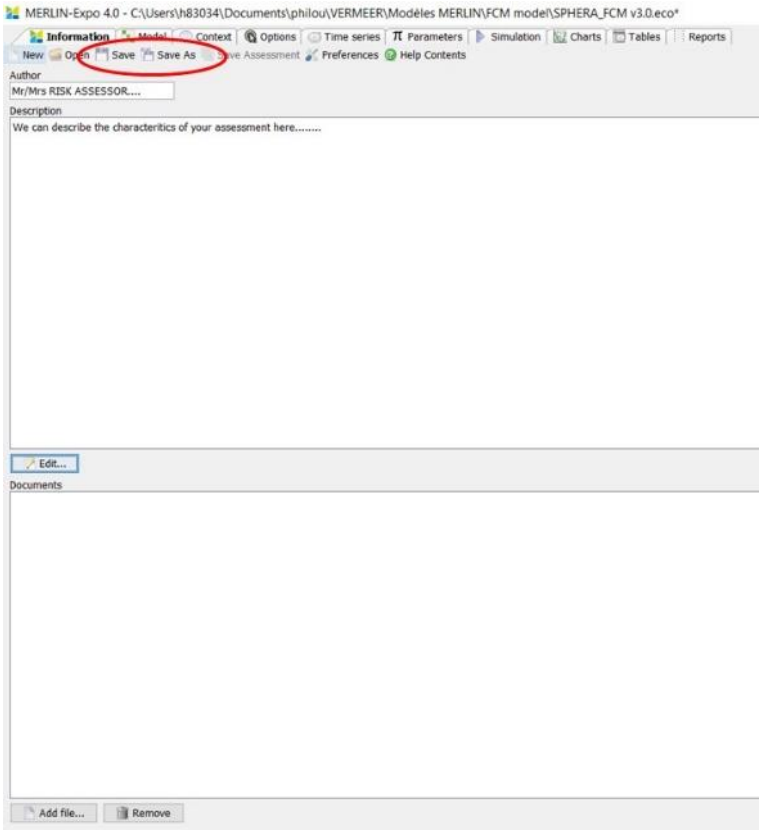


You can also attach any file that is associated to your assessment (e.g. database, report, etc):

- Go to ‘Add file’;
- Attach your file



Don’t forget to save (‘Save as’ the first time, and then ‘Save’) your assessment regularly when building it:

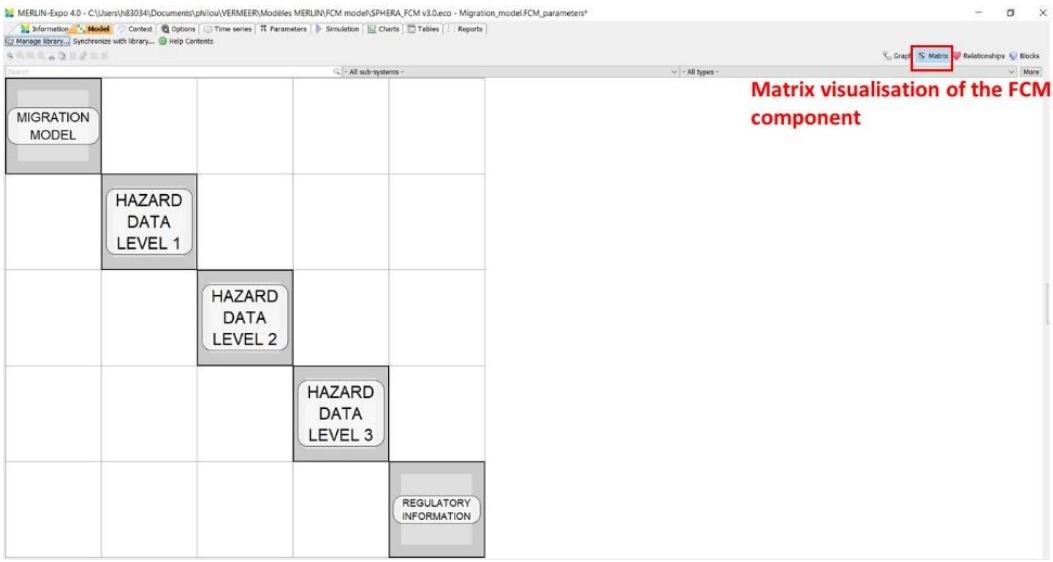


4.2. Selecting the MERLIN-Expo models: the Model tab

Depending on the type and amount of information needed, you can decide whether you run the entire FCM model or only one or more specific blocks of the model.

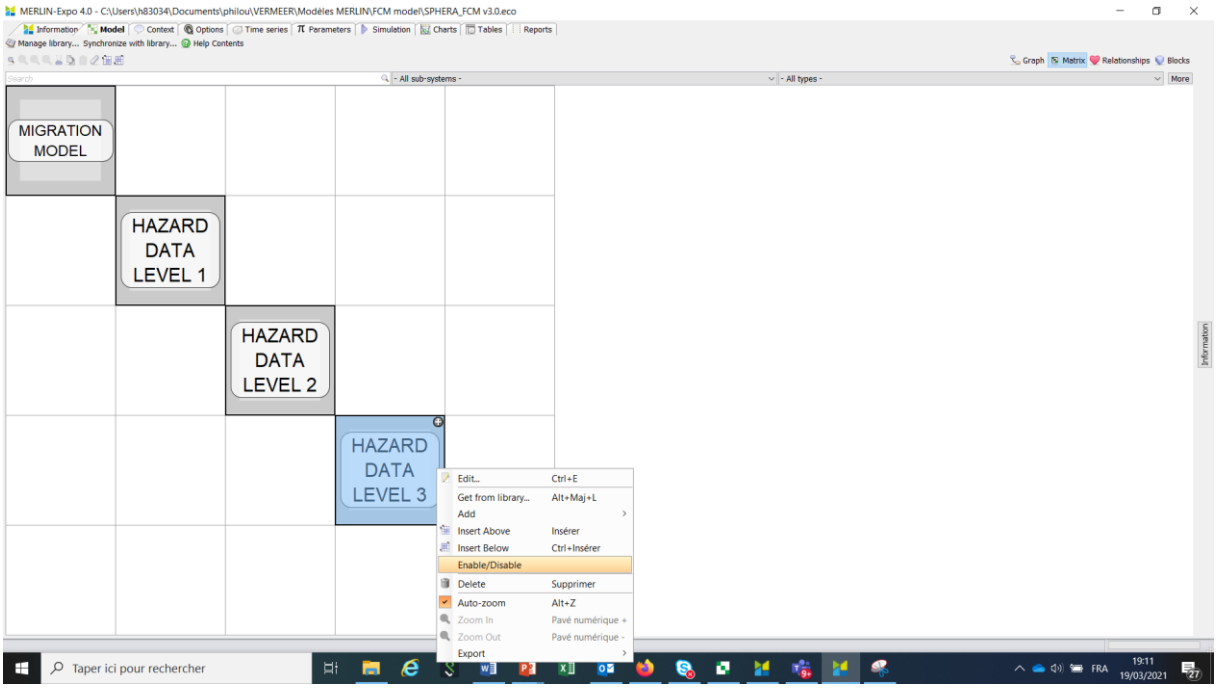
The comprehensive FCM model is subdivided in five main blocks:

- Block 1: the 'Migration model' block, which simulates the migration of chemicals between FCM and food. The main output of this block is the predicted 'Concentration of the migrant in food' (in $mg.kg^{-1}$);
- Block 2-4: the three 'hazard' blocks, each providing information corresponding to one of the three levels of the tiered approach described in the EFSA Note for Guidance. The hazard data predicted in each of the blocks is discussed in more detail in Section 3.4.1.
- Block 5: the 'Regulatory information' block, which indicates whether the chemical is included in Annex I of Regulation 10/2011 and if available, the value of the Specific Migration Limit (SML - if no SML is available for the substance of concern, -999 is indicated by default) or if the use of the substance is restricted to specific applications.

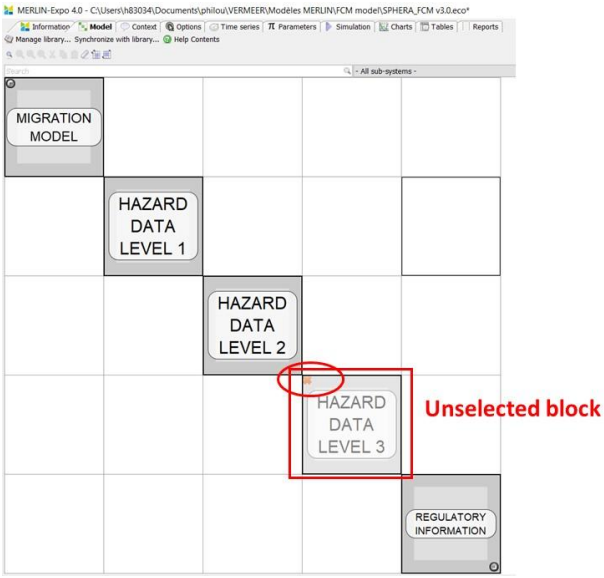


You can select one or more blocks or sub-blocks for the simulation. To this extent,

- right click on the block you want to deselect (in the picture below, the 'Hazard data level 3' block);
- click on Enable/Disable (which means Select/Unselect);
- the block you haven't chosen for this operation will be removed from the simulation (and therefore, you don't have to inform parameter values required for this block).



Unselected blocks are then indicated by a red cross:

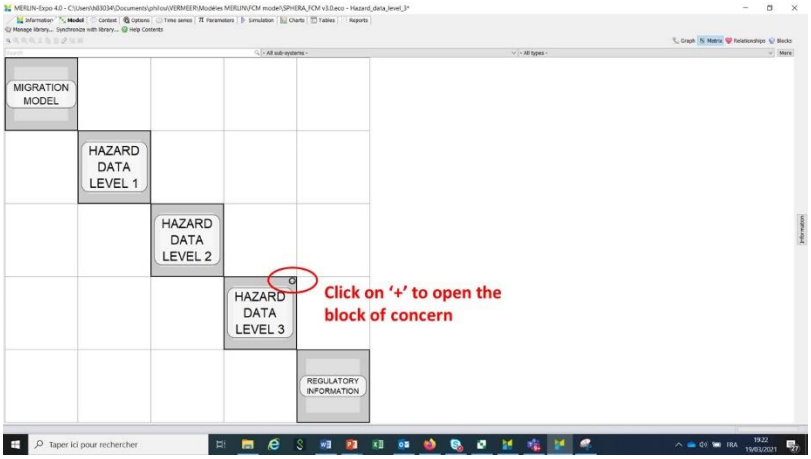


For selecting a block which had been previously unselected, do the same operation:

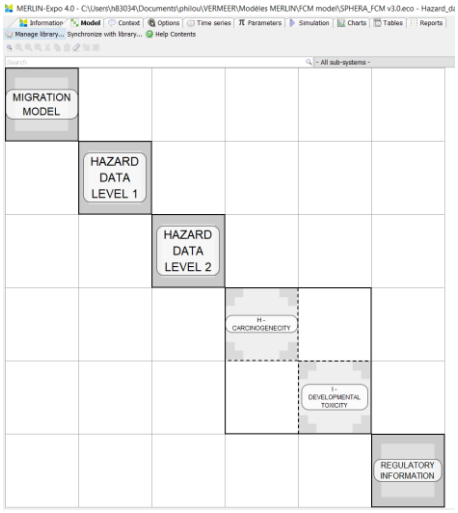
- right click on the block you want to deselect (in the picture below, the 'Hazard data level 3' block;
- click on Enable/Disable;
- the block you have chosen for this operation will be selected again for the simulation.

You can do the same operation for sub-blocks, for example the 'Carcinogenicity' sub-block within Block 4. To this extent:

- open the 'Hazard data level 3' with the '+' indicated at the top right;



- the sub-blocks included in the block of concern are now visible:



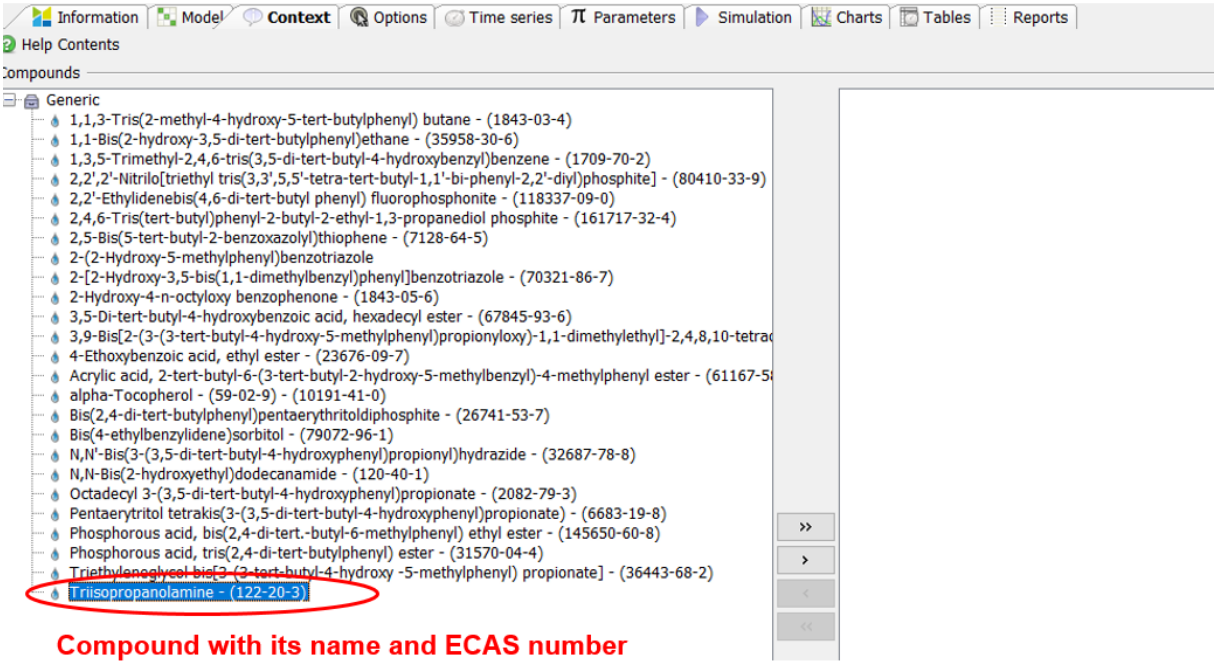
- You can proceed as indicated above for deselecting/reselecting, e.g. the 'Carcinogenicity' sub-block.

4.3. Selecting the compounds and the foods of concern: the Context tab

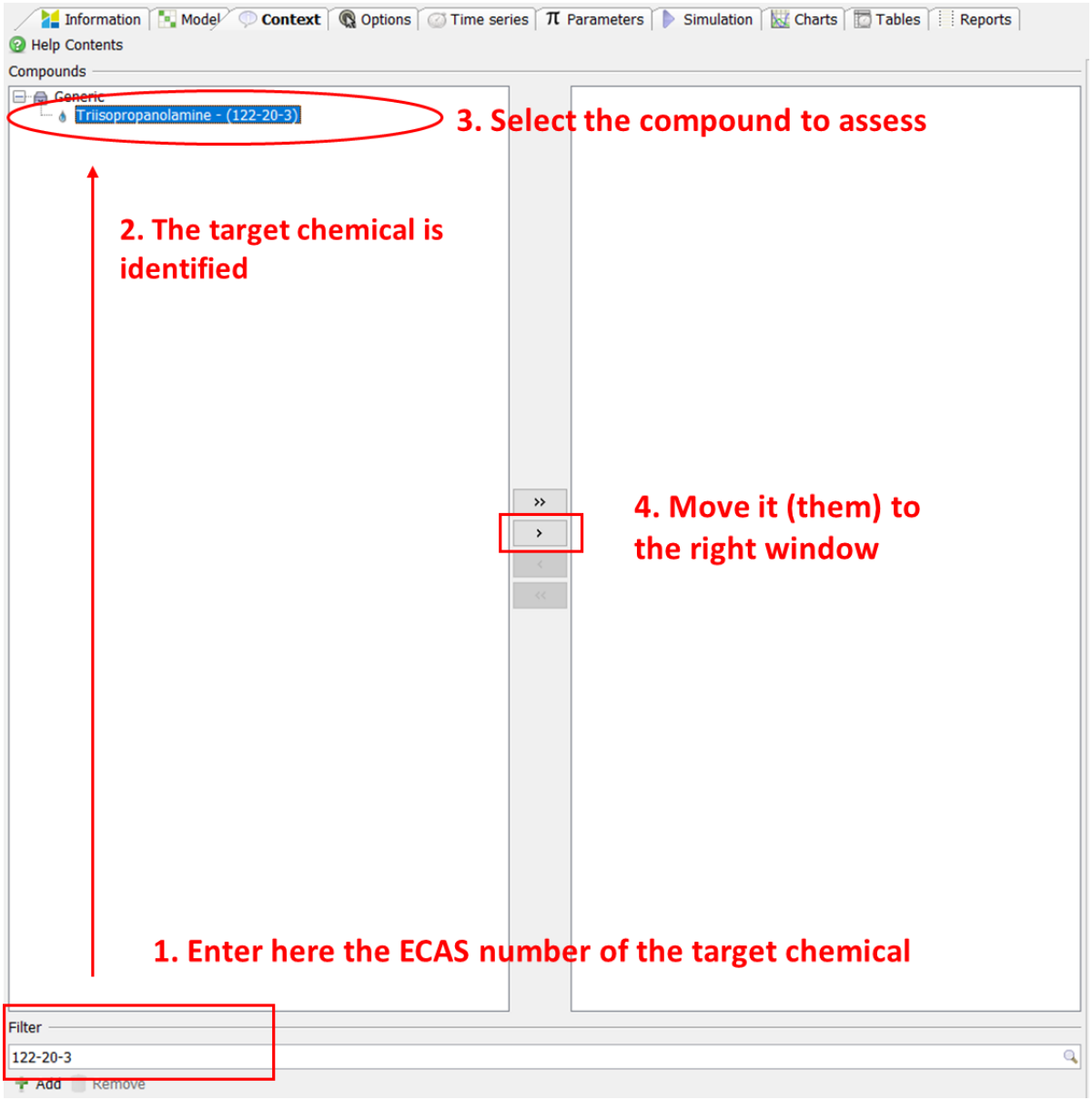
In the Context tab, you can select the chemical(s) of interest (in VERMEER FCM tool referred to as 'compounds') and the foods you want to assess.

4.3.1 Selecting the compound(s)

A comprehensive list of possible migrating chemicals is proposed in the VERMEER FCM tool under the 'context' tab. Each compound is described by its name and ECAS number:



You can search a specific compound with the Filter option, specifying e.g. an ECAS number. To select the compound you want to assess, choose it/them in the left window and move them to the right window (or inversely from the right to the left to unselect):

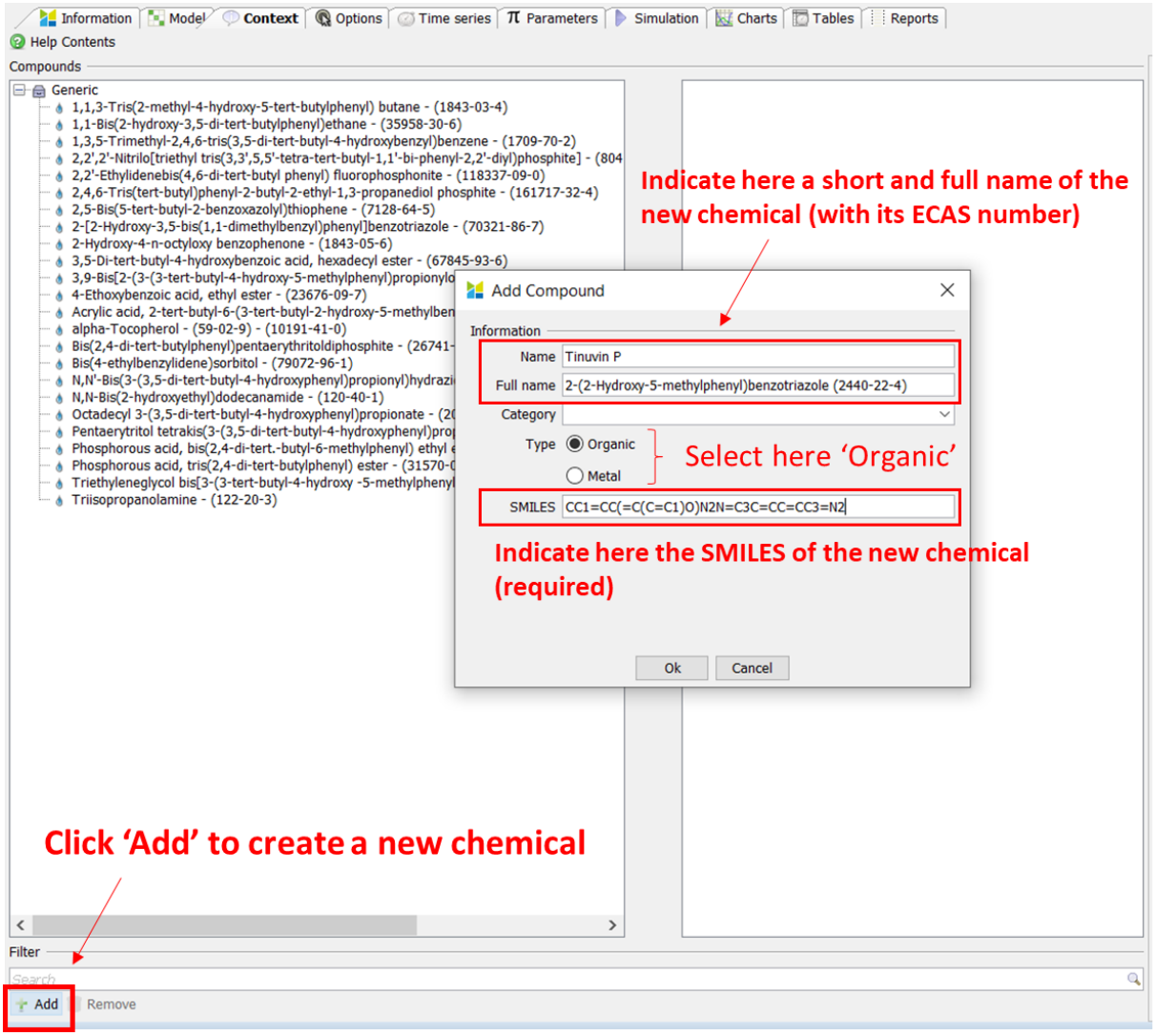


4.3.2 Creating a new compound

If the compound you want to assess is not in the list proposed by the VERMEER FCM tool, you can create it yourself:

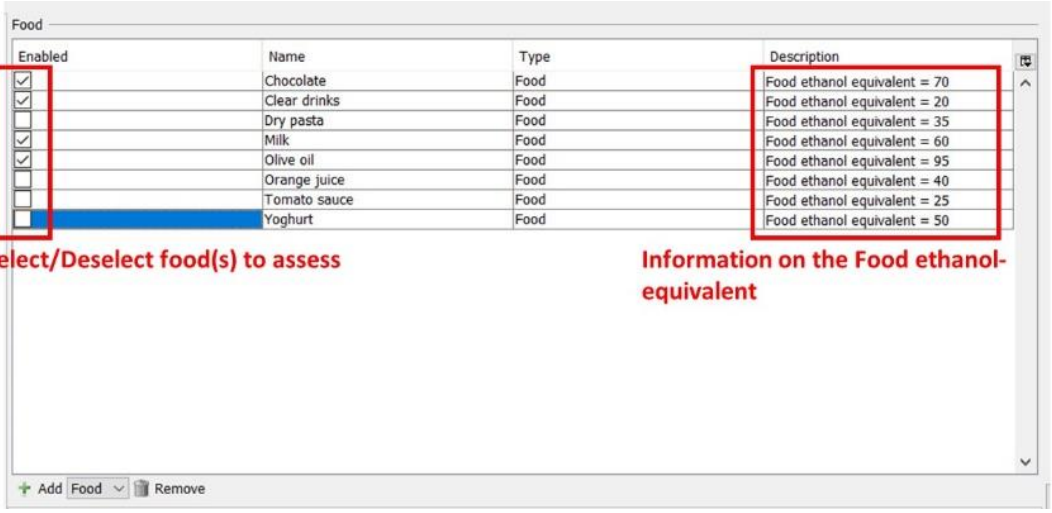
- Click on ‘Add’ for creating a new compound:
- In the Add Compound window, indicate a short name, a full name (eventually the same), and the compound SMILES; Choose ‘Organic’.
- Click OK.

The new compound is created and added to the list of possible migrating chemicals.



4.3.3 Selecting the food(s) to assess

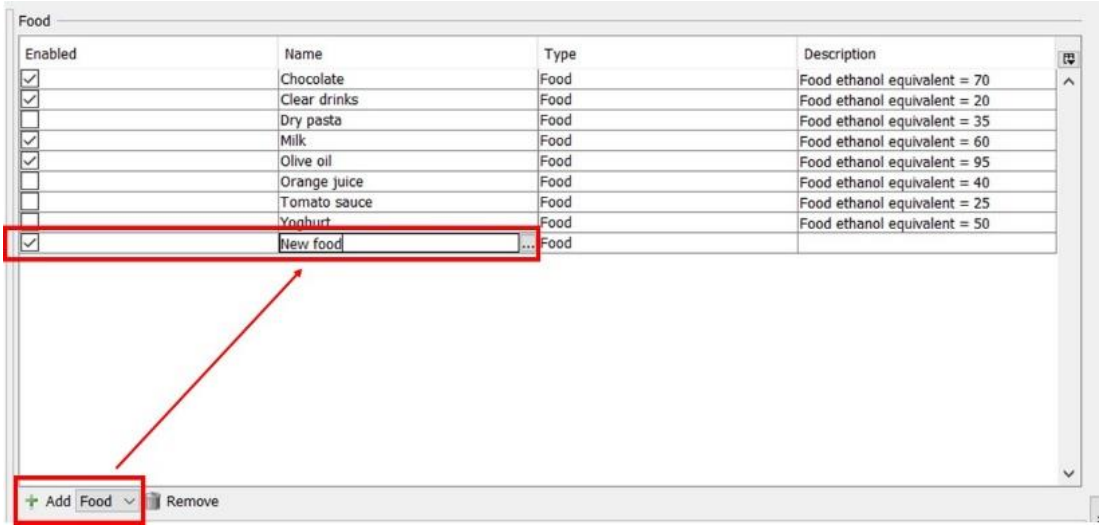
Several foods are proposed and parameterized in the VERMEER FCM tool. You can select one or several foods to be assessed.



4.3.4 Creating a new food

If the food you want to assess is not in the list proposed by the VERMEER FCM tool, you can create it yourself:

- Click on 'Add' + 'Food' for creating a new food;
- A new food is created in the list of foods;
- Write the name of the new food (since it is a new food, you will have to inform the value of the food ethanol-equivalent in the Parameter tab – see below)



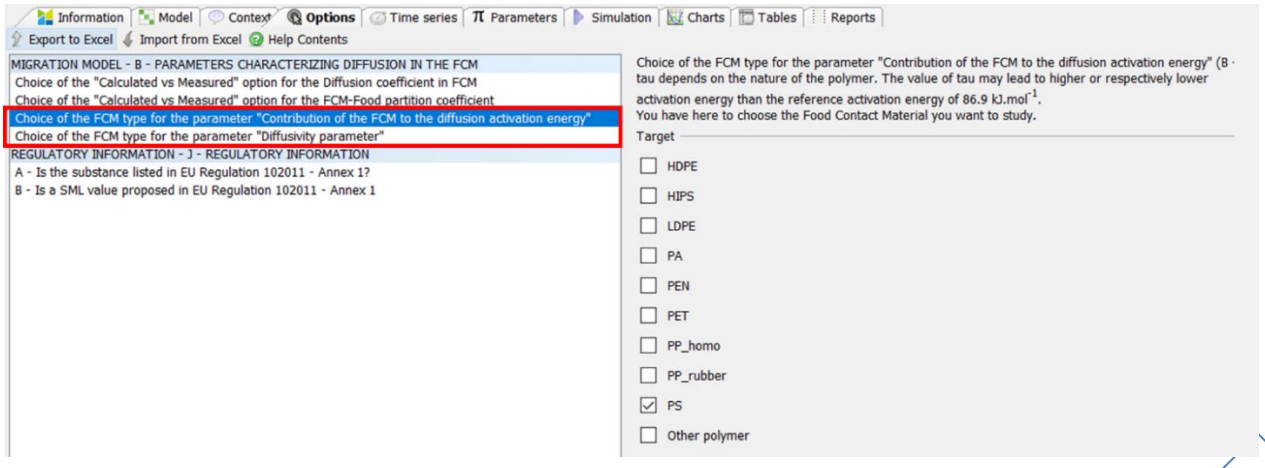
4.4. Selecting the FCM of concern and other options: the Option tab

In the Context tab, you can select the FCM you want to assess.

4.4.1 Selecting the FCM of concern

You must select the FCM of concern for two parameters of the model ('Contribution of the FCM to the diffusion activation energy' - τ in Equation (6) ; 'Diffusivity parameter' - A_{FCM} in Equation (6)). For this purpose:

- Select the parameter of concern;
- Select the FCM of concern (you can also choose 'Other polymer'. In this case, no default values are proposed for the two abovementioned parameters. You will have to provide a value in the Parameter tab – see 4.6)



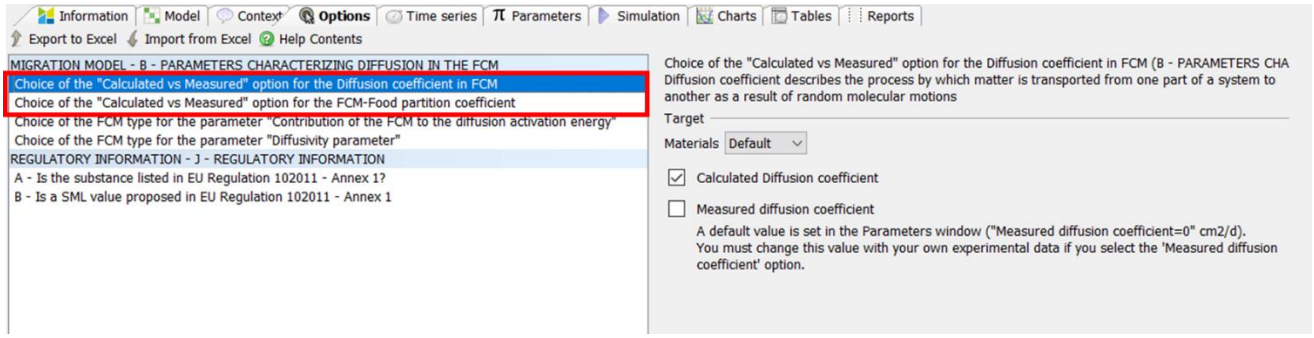
4.4.2 Measured vs Calculated parameters

The VERMEER FCM tool can calculate the two following parameters:

- the Diffusion coefficient in FCM (Equation 6);
- the FCM-Food partition coefficient (Equation 11).

If you have measured values for one of these parameters, or for both, you can use these measured experimental values instead of calculated values. For this purpose:

- Select the *Choice of the "Calculated vs Measured"* option for the parameter of concern;
- Select 'Calculated' or 'Measured' (If you choose 'Measured', default values are proposed for the selected parameter, but they obviously do not correspond to your own measured value. Therefore, you will have to provide a value in the Parameter tab – see 4.6).



4.4.3 Regulatory information

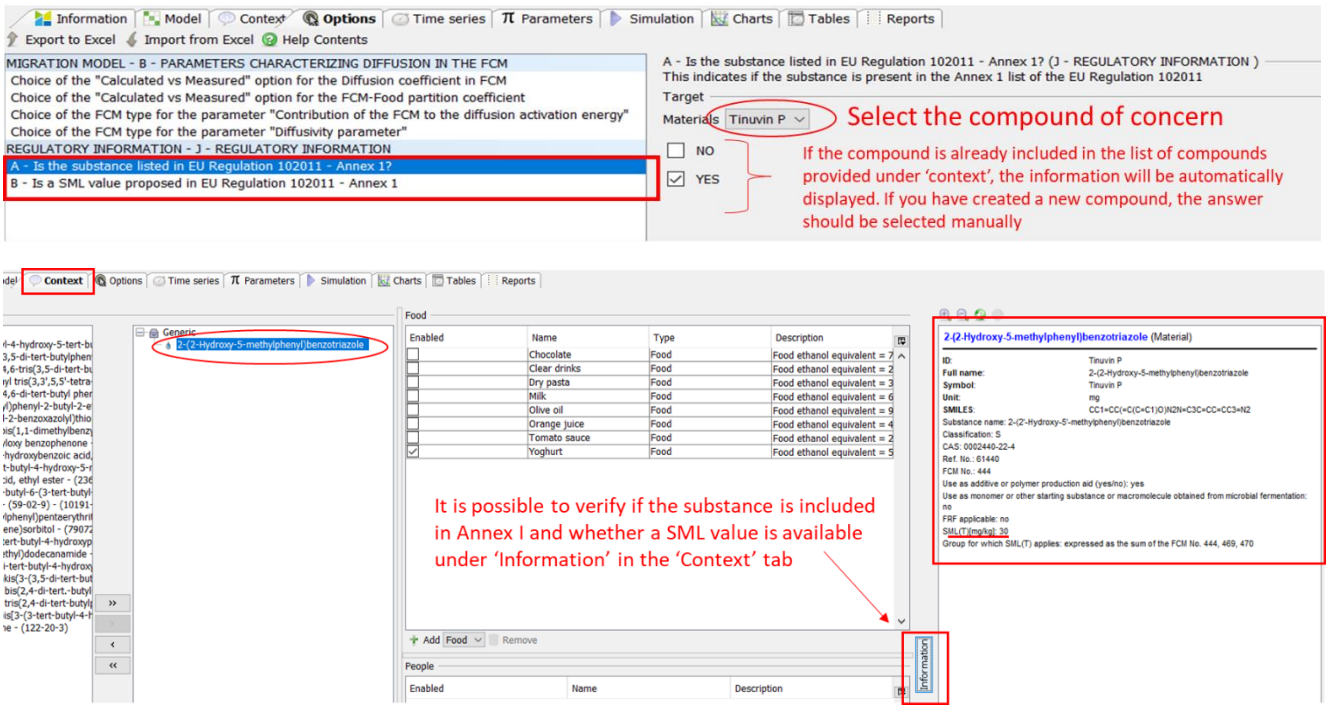
The VERMEER FCM tool provides some regulatory information about the compound(s) that have been selected for the assessment:

- Is the Substance listed in EU Regulation 102011 – Annex 1?
- If yes, is a Specific Migration Limit (SML) proposed in EU Regulation 102011 – Annex 1?

When the compound of interest was already included in the list of compounds provided under the 'Context' tab of the VERMEER FCM tool, the answers to these two questions will be correctly displayed. However, if you have created a new compound (or several compounds) (cfr. 4.3.2), the correct answers will not be automatically displayed. By default, the VERMEER FCM tool indicates that the new compound(s) is(are) not listed in the EU Regulation 102011-Annex 1 and that no SML(s) is(are) available.

The user should check therefore select the correct answers to these questions manually. This can be done as follows:

- Select the question of concern;
- Select the compound of concern;
- Select the correct answer i.e. YES vs NO. Importantly, the information on whether a compound is included in Annex I and whether an SML value is available can be found under the 'Information' section of the 'Context' tab of the VERMEER FCM tool.



Note: The regulatory information is not used for the simulation.

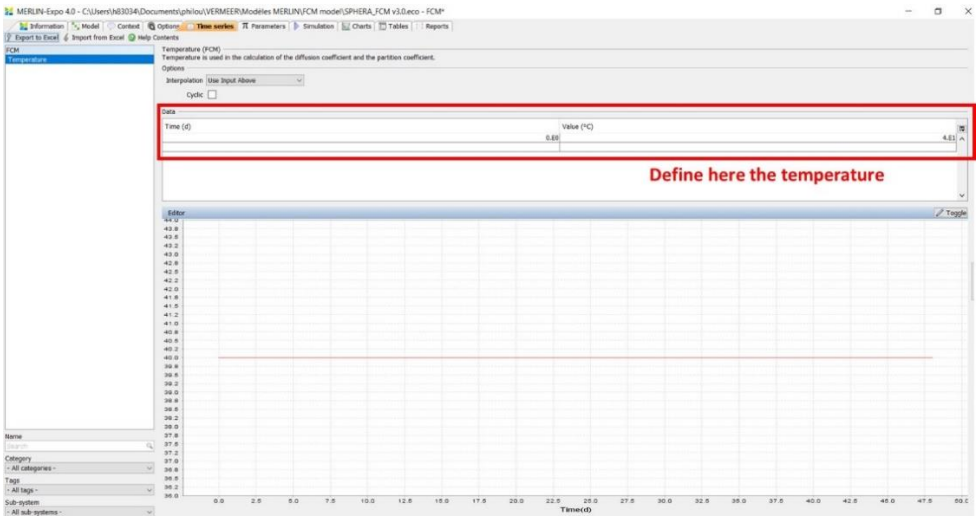
4.5. Selecting the temperature: the Time series tab

In the Time series tab, you can select the temperature at which the migration modelling should be performed. Temperature can be constant over time, or show temporal variations.

4.5.1 Defining a constant temperature

For defining a constant temperature:

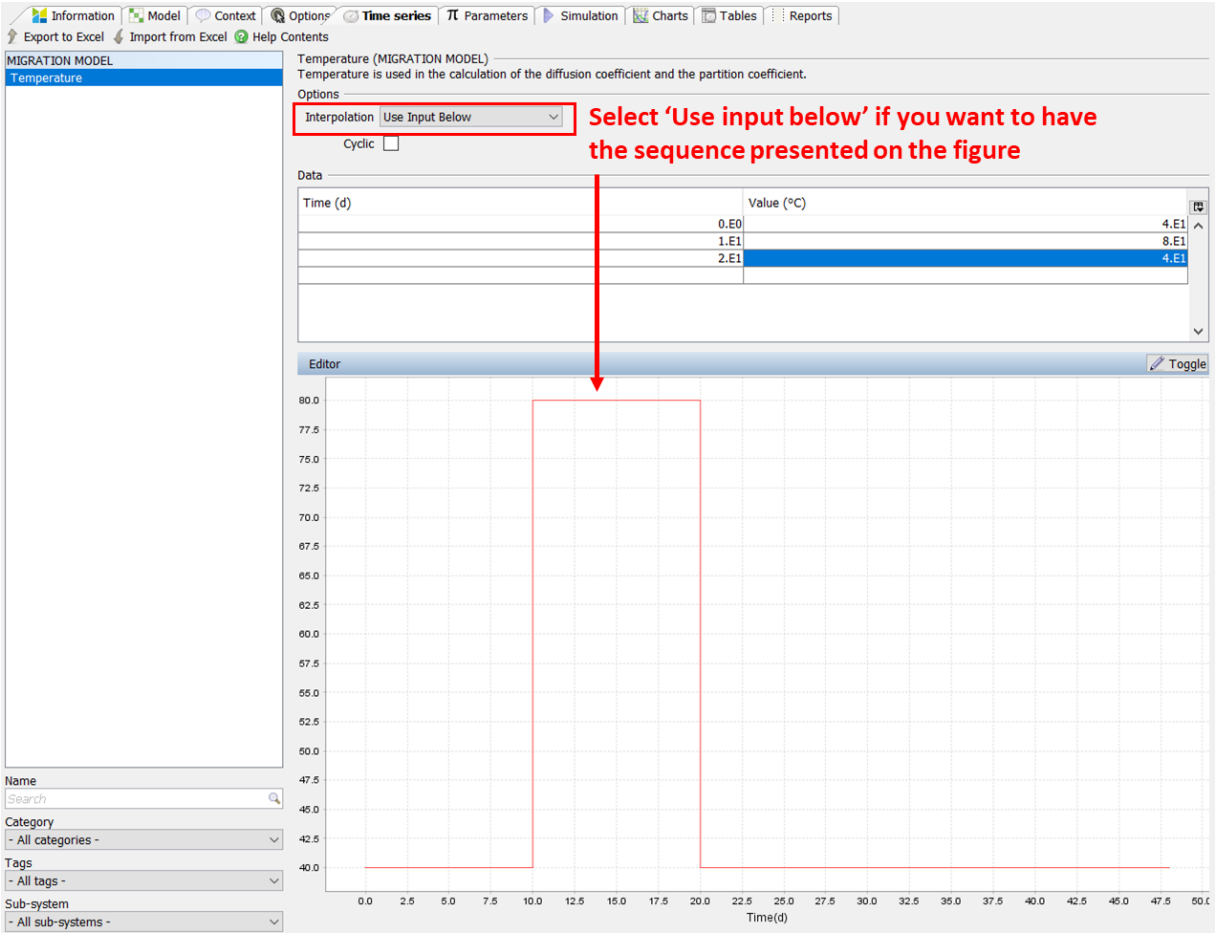
- Go to 'Data'
- Define for Time=0, the chosen temperature (in °C).
- Insert for the end time the same temperature (in °C).



4.5.2 Defining a variable temperature

For defining a variable temperature:

- Go to 'Data'10
- Define the sequence of the chosen temperatures (in °C) (e.g. in the figure below: 40°C from 0 to 10 days; 80°C from 10 to 20 days; 40°C from 20 days to infinity)
- Define the 'Option' for the interpolation between dates (e.g. in the figure below: constant temperature from 0 to 10 days; constant temperature from 10 to 20 days; constant temperature from 20 days to infinity). You can test other 'Options'; the corresponding sequence will appear on the figure.
- The 'Cyclic' option can be selected if you want to repeat the same sequence several times.



4.6. Selecting the parameter values: the Parameters tab

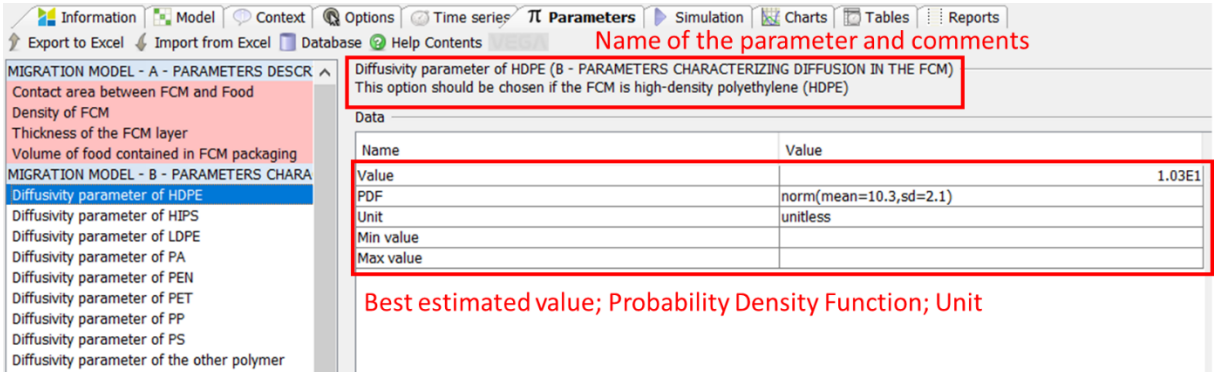
For running the model, values have to be set for each of the parameters. Parameters were subdivided in several categories.

4.6.1 Generic presentation of parameters

When you select a parameter, you automatically open a window which contains the following information:

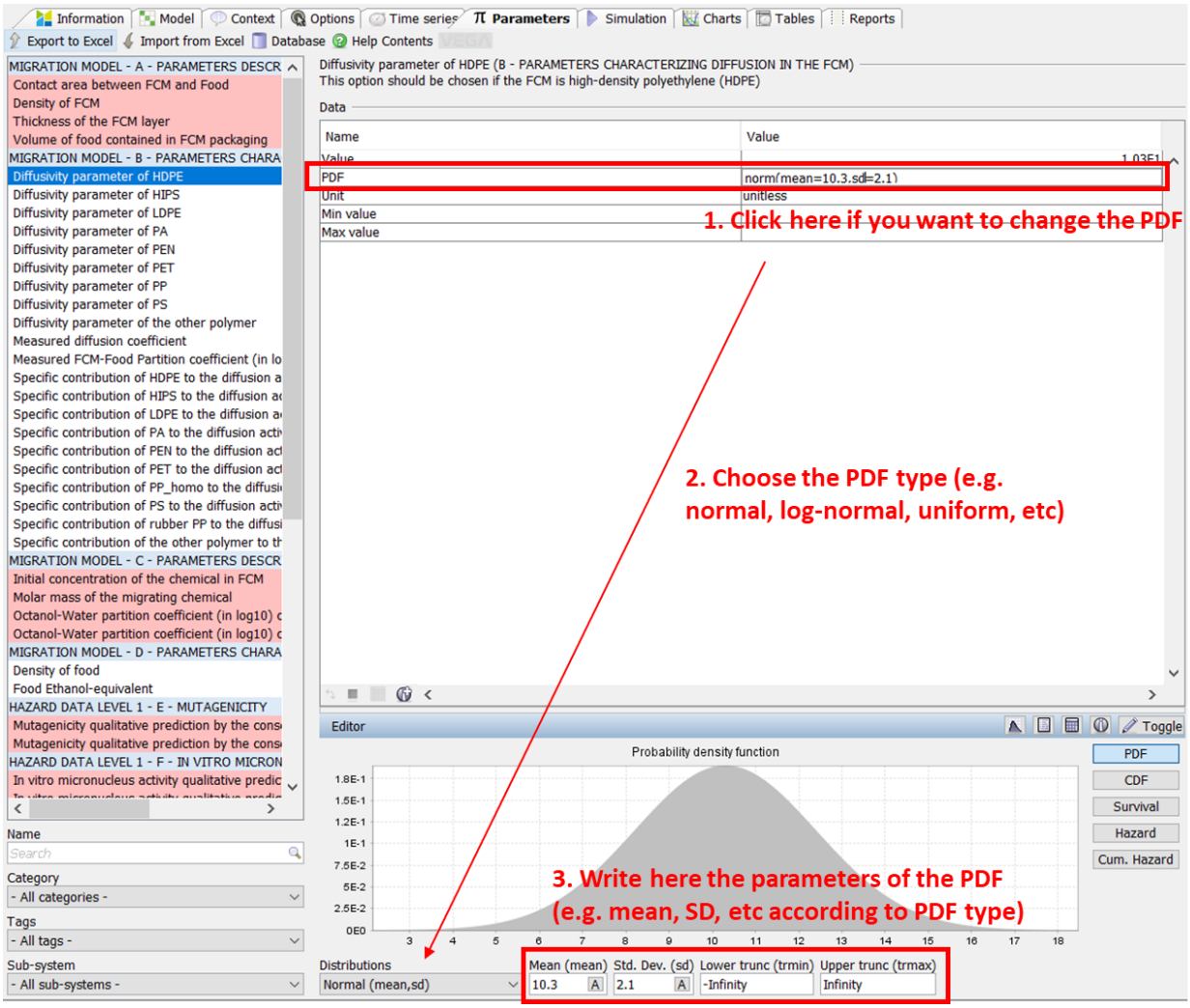
- Name of the parameter, and eventually, comments about the parameter;
- Unit;

- Best estimate (or default) value. For most of the parameters, best estimates are proposed by the VERMEER FCM tool. You can change the proposed value with your own value if available and relevant;
- Probability Density Function (PDF). PDF is optional and is used when parameter values are uncertain. Uncertainty is described by a PDF (e.g. normal PDF, log-normal PDF, uniform PDF, etc). PDFs are used for probabilistic simulations (see 4.7).



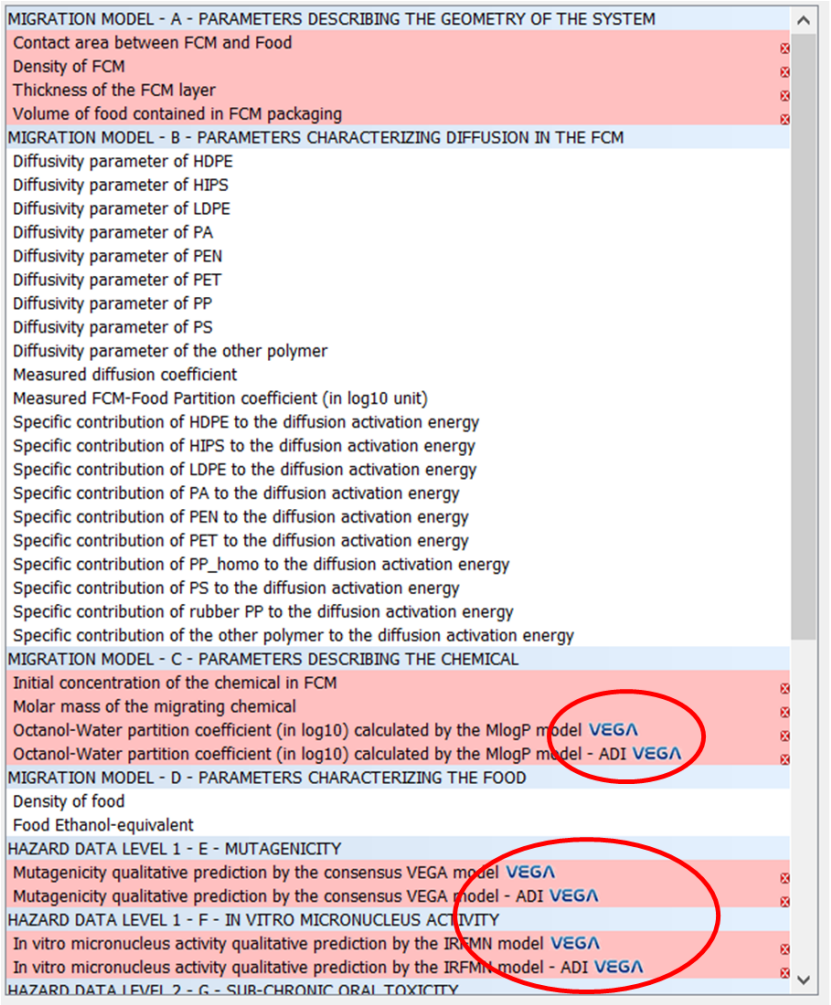
If you want to change the PDF:

- Click on the PDF box;
- Select the PDF type you want to use (a large list of potential PDF types is available);
- Indicate the parameters of the chosen PDF (e.g. arithmetic mean and standard deviation for normal PDF; geometric mean and geometric standard deviation for log-normal PDF; minimum and maximum values for uniform PDF; mean and degrees of freedom for Student PDF, etc).



4.6.2 Parameter values predicted by a VEGA model

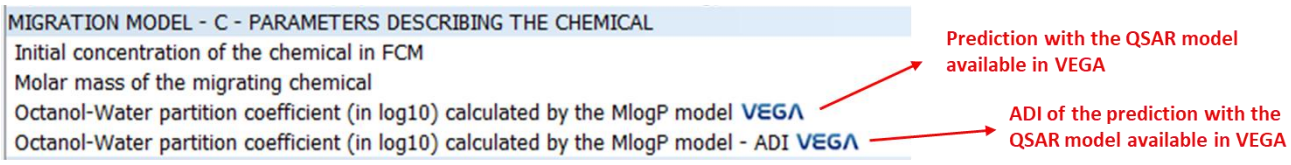
Some parameters are chemical-specific, i.e. their value depends on the compound that is targeted by the assessment. For such parameters, specifying the parameter value can be done through a direct access to the VEGA tool, which is a library of QSAR models for the prediction of values for an extended list of endpoints. All the parameters that are linked to a relevant QSAR model available in VEGA are indicated by the VEGA tag:



All the parameters with a 'VEGA' tag are linked to a QSAR model available in the VEGA tool

Each model available in the VEGA platform provides two kinds of information for a given parameter: 1) the quantitative or qualitative value of the prediction; 2) the Applicability Domain Index (ADI) of the prediction for the chemical of concern, on a [0;1] scale. ADI is a summary index indicating the confidence related to the prediction: 0 means that the chemical is outside of the applicability domain; 1 means that the chemical is integrally within the applicability domain. For this reason, each parameter associated to a VEGA model is described by two lines in the VERMEER FCM interface:

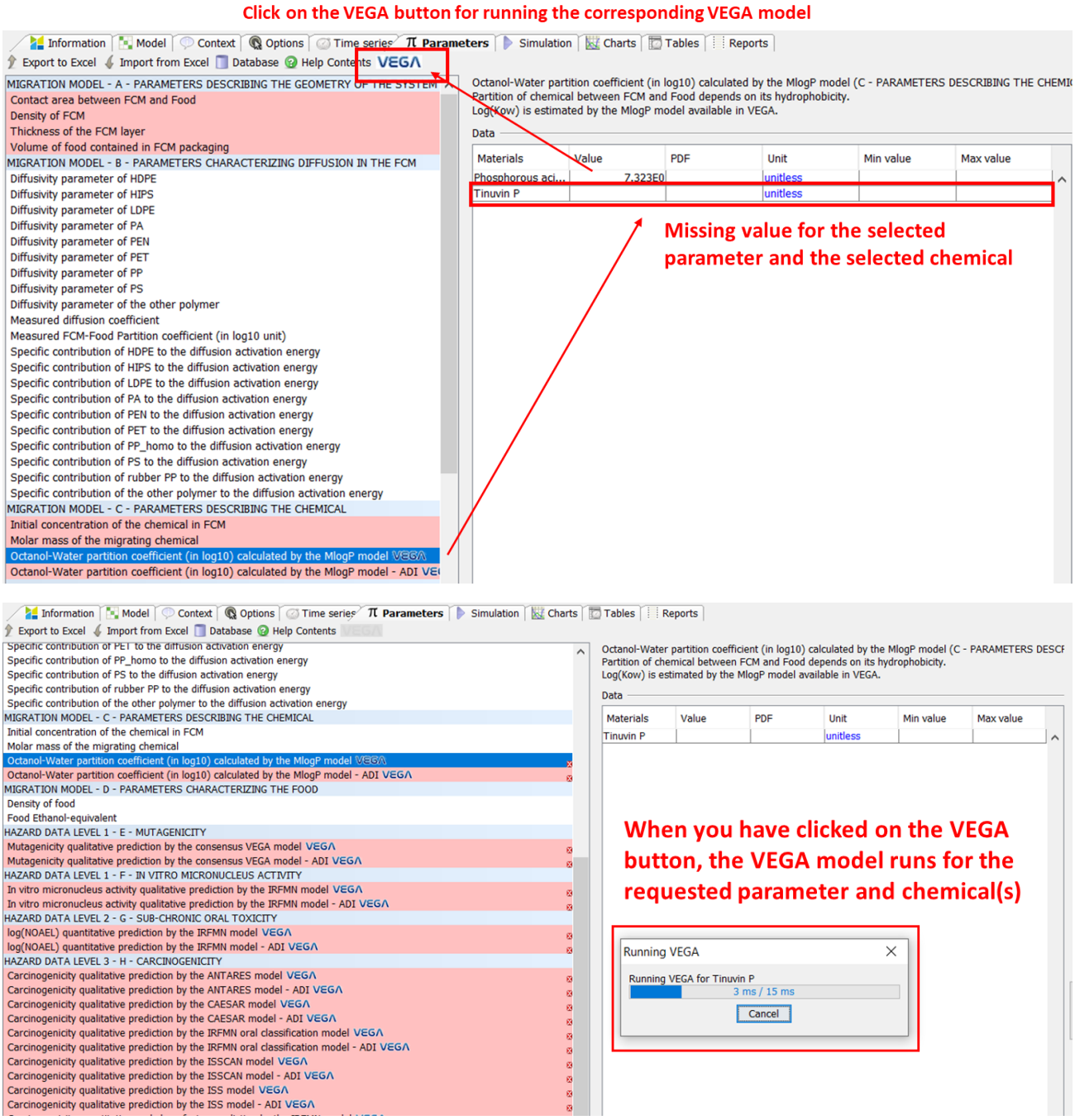
- 'Name of the parameter'. This line refers to the parameter (quantitative or qualitative) prediction from the VEGA model;
- 'Name of the parameter – ADI'. This line refers to the ADI of the prediction for the chemical of concern. ADI is taken into account for probabilistic simulations aimed at uncertainty/sensitivity analysis.

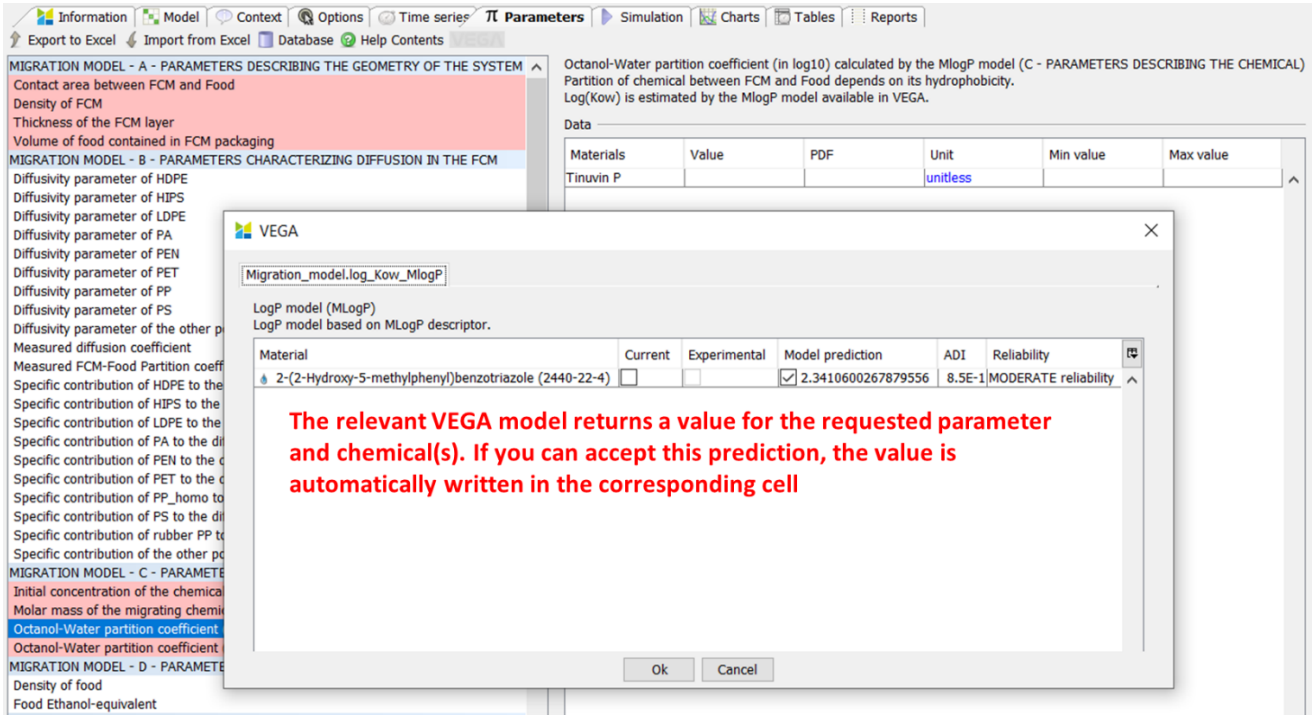


When data are missing for a given compound, you can generate a relevant value calling the corresponding VEGA model as follows:

- Click on the VEGA button at the top of the window to run the corresponding VEGA model;

- The corresponding VEGA model returns the prediction for the requested parameter and chemical(s). By accepting the prediction, the outcome is automatically displayed in the corresponding cell.





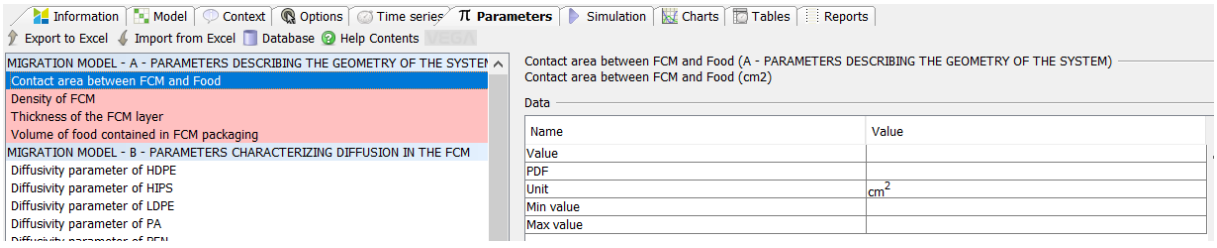
You have to follow the same process for the ADI of the targeted parameter (line just below)[2].

Note: Multiple VEGA models can be run simultaneously.

4.6.3 Parameters describing the geometry of the system

Four parameters describing the geometry of the system are required for running a simulation. These four parameters appear in red since no default values are proposed in the VERMEER FCM tool for them. By definition, indeed, the geometry of the system is specific to each assessment and the assessor has to define them. These four parameters are:

- the contact area between FCM and food (in cm^2);
- the volume of food contained in FCM packaging (in cm^2);
- the density of FCM (in $g.cm^{-3}$);
- the thickness of the FCM layer (in cm);

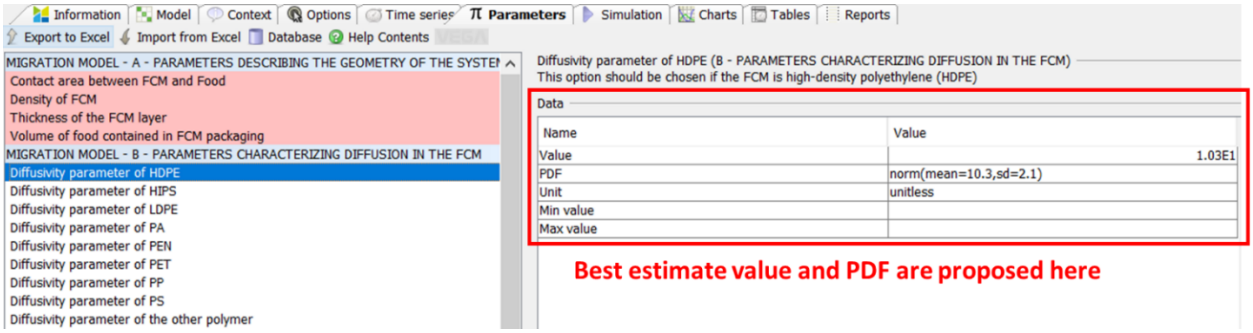


[2] Note that for Mutagenicity ("Mutagenicity qualitative prediction by the consensus VEGA model'), a 'consensus score' is generated by VEGA, and not a stricto sensu ADI. For this reason, the 'consensus score' generated through the activation of the VEGA button must be then manually copied in the corresponding cell by the end-user.

4.6.4 Parameters characterizing diffusion in FCM

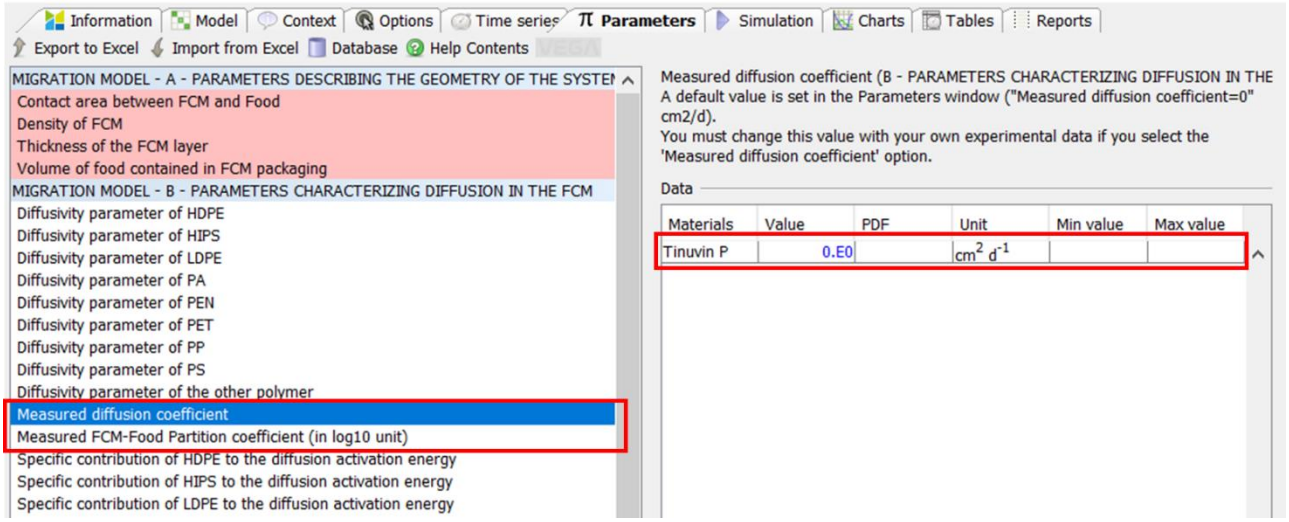
Two parameters are required for calculating the diffusion coefficient in FCM (Equation 6):

- the 'Diffusivity parameter' (A_{FCM} in Equation 6). Best estimates and PDFs are proposed by the VERMEER FCM tool for the 'Diffusivity parameter' for each of the FCM included in the tool. ⚠ *A default value is proposed for the 'Diffusivity parameter of the other polymer' (0), but you have to change it according to the polymer (not included in the predefined VERMEER list) you want to assess;*
- the 'Specific contribution of the FCM to the diffusion activation energy' (τ in Equation 6). Best estimates and PDFs are proposed by the VERMEER FCM tool for the 'Specific contribution of the FCM to the diffusion activation energy' for each of the FCM included in the tool. ⚠ *A default value is proposed for the 'Specific contribution of the other polymer to the diffusion activation energy' (i.e. 0 K), but you have to change it according to the polymer (not included in the predefined VERMEER list) you want to assess.*



⚠ *If you have chosen the 'Measured' option in 4.4.2, you have to specify the measured values for the selected parameters, i.e. for:*

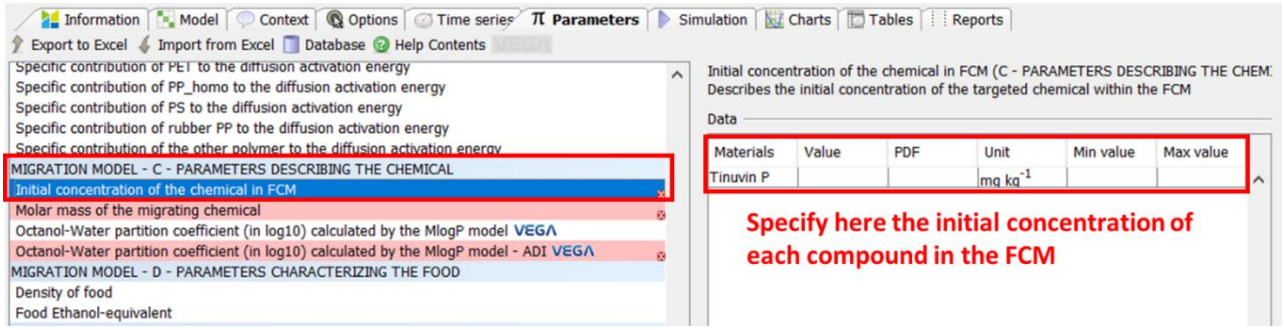
- *the measured 'Diffusion coefficient' (in $cm^2.d^{-1}$): Diffusion coefficient is specific to each compound. You have therefore to specify the measured 'Diffusion coefficient' for each of the compounds you have selected in 4.3.1.*
- *the measured 'FCM-Food partition coefficient' (in log unit): FCM-Food partition coefficient is specific to each couple compound/Food. You have therefore to specify the measured 'FCM-Food partition coefficient' for each of the compound/Foods couples you have selected in 4.3.1.*



4.6.5 Parameters describing the compound

The compound is characterized by:

- the 'initial concentration of the compound in FCM' (in $mg.kg^{-1}$). The VERMEER FCM tool proposes zero as default value, but you have to change this value according to the chemical content of the FCM you want to assess;



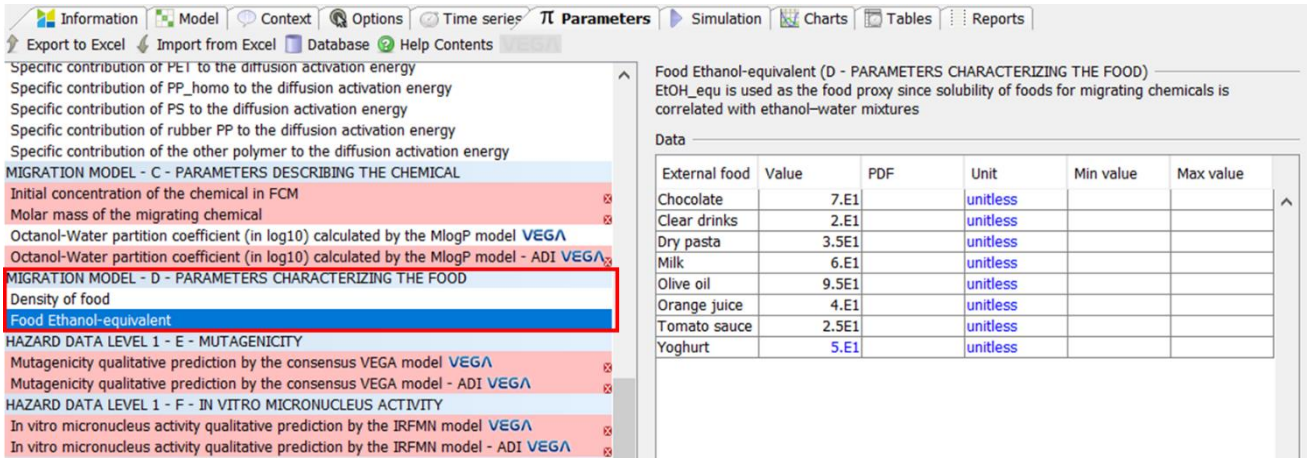
- the molar mass of the compound(s). Values are set in the VERMEER FCM tool for all the pre-defined compounds available in the 'Context' tab. ⚠ *If you have created a new compound in 4.3.2, you have to define here its molar mass;*
- the Octanol-Water partition coefficient (in log10 unit). This parameter can be calculated with a corresponding VEGA model, together with its ADI, according to the process described in 4.6.2.

4.6.6 Parameters characterizing the food

The food is characterized by:

- the density of food;
- the food-ethanol equivalent.

For each of these parameters and for each pre-defined food, the VERMEER FCM tool proposes default values.



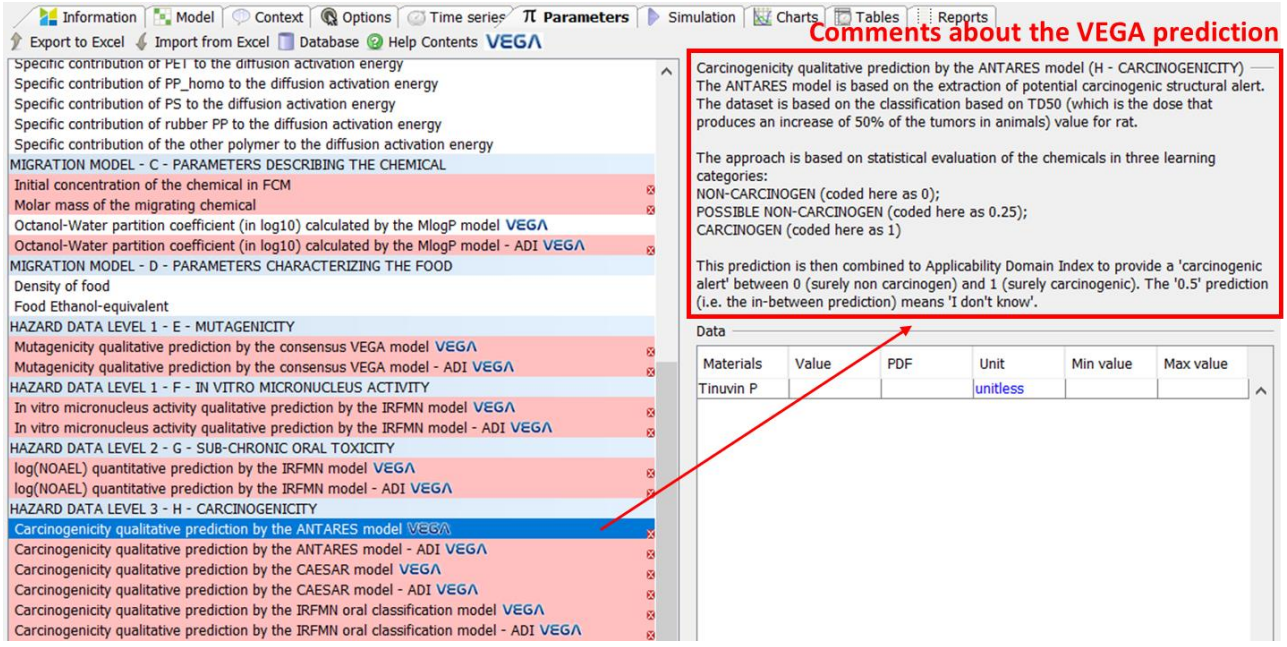
4.6.7 Hazard data

The VERMEER FCM tool is connected to several VEGA models for predicting hazard data related to each of the compounds selected for the assessment. Most of the endpoints predicted by VEGA are Boolean and then translated into the [0;1] numerical scale according to the process described in 3.4.2.

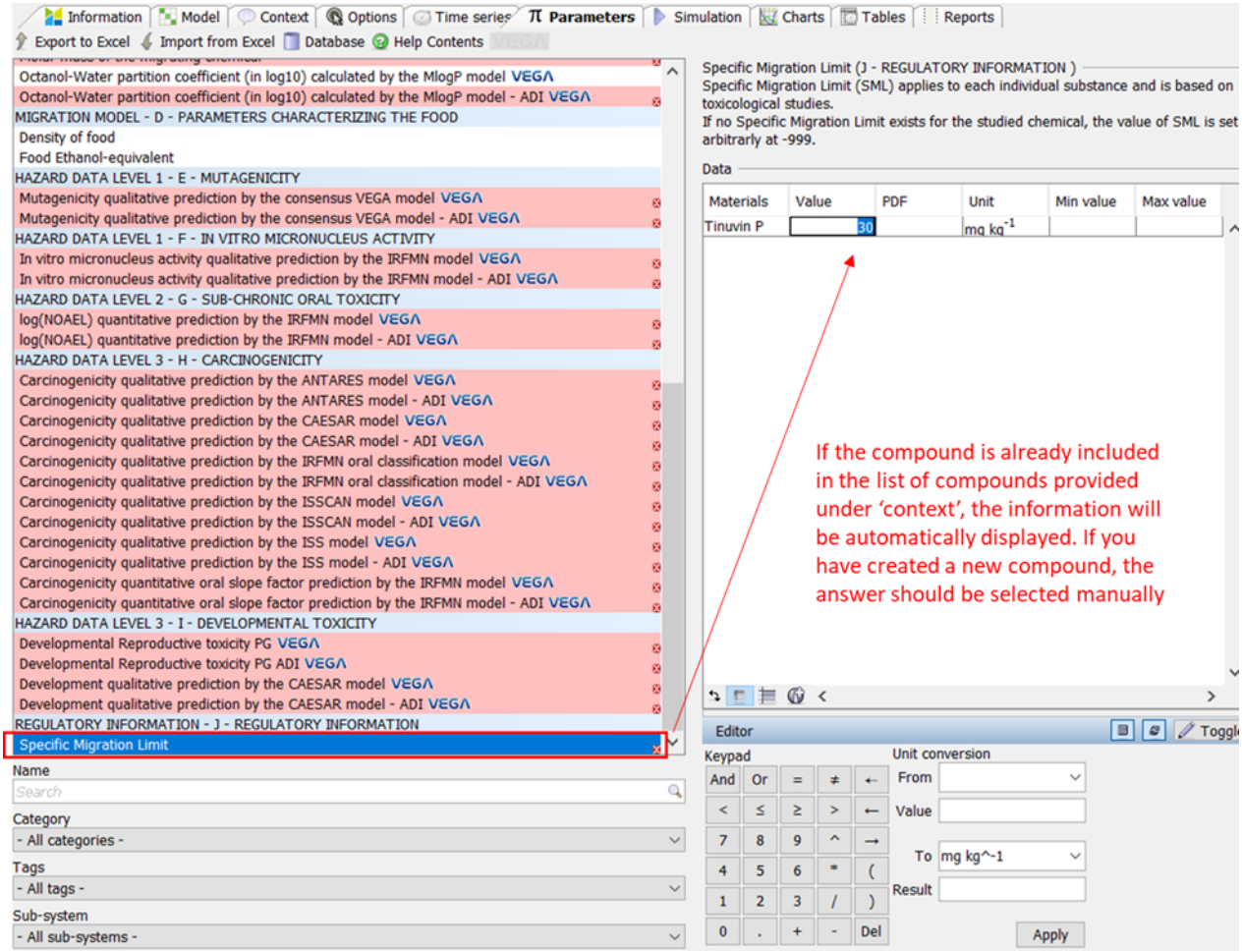
The hazard data available in the VERMEER FCM tool are presented below:

HAZARD DATA LEVEL 1 - E - MUTAGENICITY
Mutagenicity qualitative prediction by the consensus VEGA model VEGA
Mutagenicity qualitative prediction by the consensus VEGA model - ADI VEGA
HAZARD DATA LEVEL 1 - F - IN VITRO MICRONUCLEUS ACTIVITY
In vitro micronucleus activity qualitative prediction by the IRFMN model VEGA
In vitro micronucleus activity qualitative prediction by the IRFMN model - ADI VEGA
HAZARD DATA LEVEL 2 - G - SUB-CHRONIC ORAL TOXICITY
log(NOAEL) quantitative prediction by the IRFMN model VEGA
log(NOAEL) quantitative prediction by the IRFMN model - ADI VEGA
HAZARD DATA LEVEL 3 - H - CARCINOGENICITY
Carcinogenicity qualitative prediction by the ANTARES model VEGA
Carcinogenicity qualitative prediction by the ANTARES model - ADI VEGA
Carcinogenicity qualitative prediction by the CAESAR model VEGA
Carcinogenicity qualitative prediction by the CAESAR model - ADI VEGA
Carcinogenicity qualitative prediction by the IRFMN oral classification model VEGA
Carcinogenicity qualitative prediction by the IRFMN oral classification model - ADI VEGA
Carcinogenicity qualitative prediction by the ISSCAN model VEGA
Carcinogenicity qualitative prediction by the ISSCAN model - ADI VEGA
Carcinogenicity qualitative prediction by the ISS model VEGA
Carcinogenicity qualitative prediction by the ISS model - ADI VEGA
Carcinogenicity quantitative oral slope factor prediction by the IRFMN model VEGA
Carcinogenicity quantitative oral slope factor prediction by the IRFMN model - ADI VEGA
HAZARD DATA LEVEL 3 - I - DEVELOPMENTAL TOXICITY
Developmental Reproductive toxicity PG VEGA
Developmental Reproductive toxicity PG ADI VEGA
Development qualitative prediction by the CAESAR model VEGA
Development qualitative prediction by the CAESAR model - ADI VEGA

For each of these endpoints, a short comment summarizes the main features of the prediction provided by VEGA and its translation into the numerical scale.



In this section, the SML value can also be inserted as this will allow you to simulate the ratio between the concentration in food and the SML (cfr. 4.7.2). When the compound of interest was already included in the list of compounds provided under the 'Context' tab of the VERMEER FCM tool, the SML value will be automatically displayed. However, if you have created a new compound (or several compounds) (cfr. 4.3.2), the SML value needs to be entered manually. If available, the SML value is provided under the 'Information' section of the 'Context' tab of the VERMEER FCM tool. For compounds that are not yet included in the tool, the value -999 needs to be inserted manually in case there is no SML.

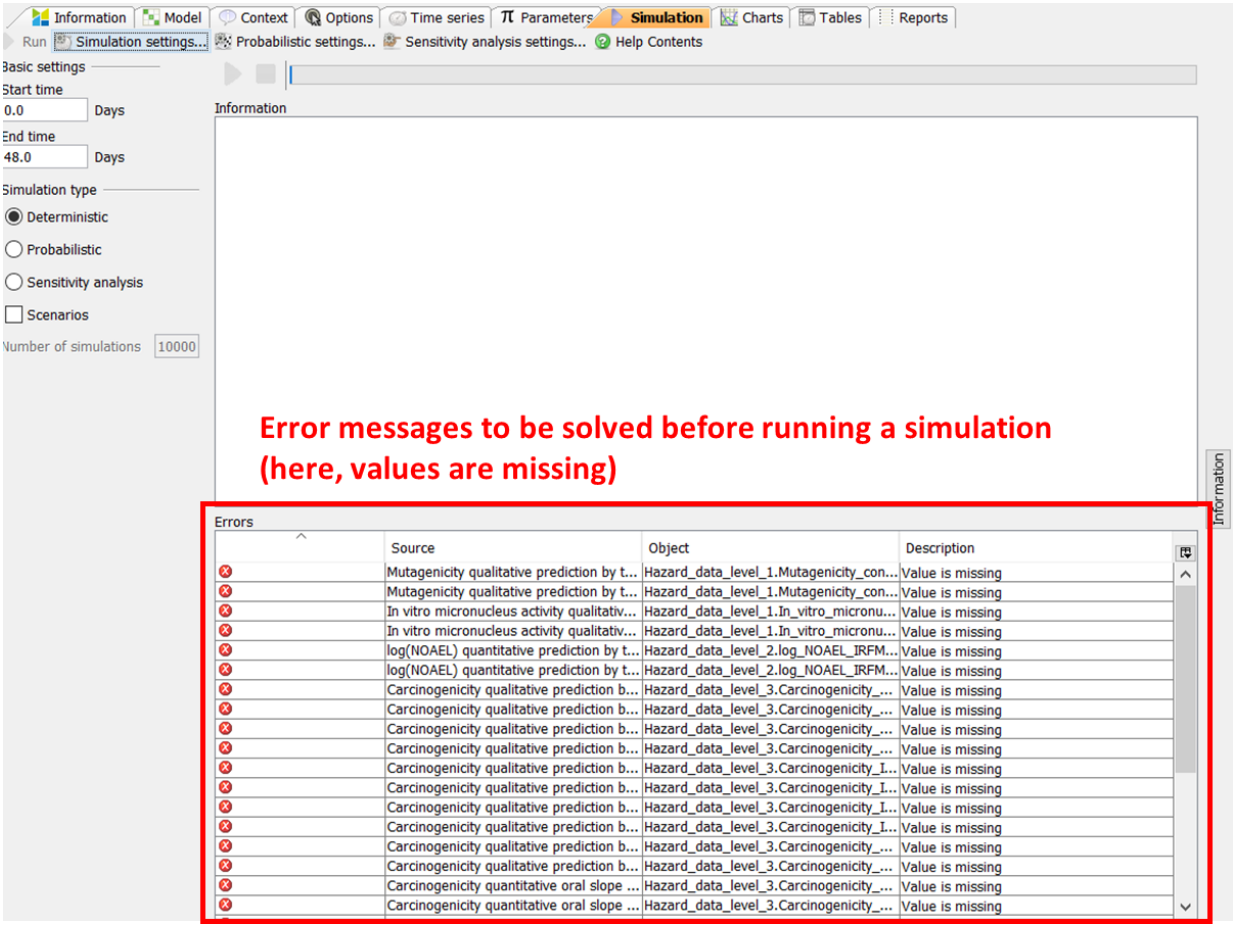


4.7. Running a simulation: the Simulation tab

The simulation page lets you run deterministic, probabilistic (Monte Carlo) or sensitivity analysis simulations. The error section lists problems that must be solved before a simulation can be performed.

4.7.1 Visualizing errors before running a simulation

For running a simulation, all the parameters must be informed, i.e. a quantitative value must be affected to each of them. If values are missing, the VERMEER FCM tool indicates them in the Simulation tab:

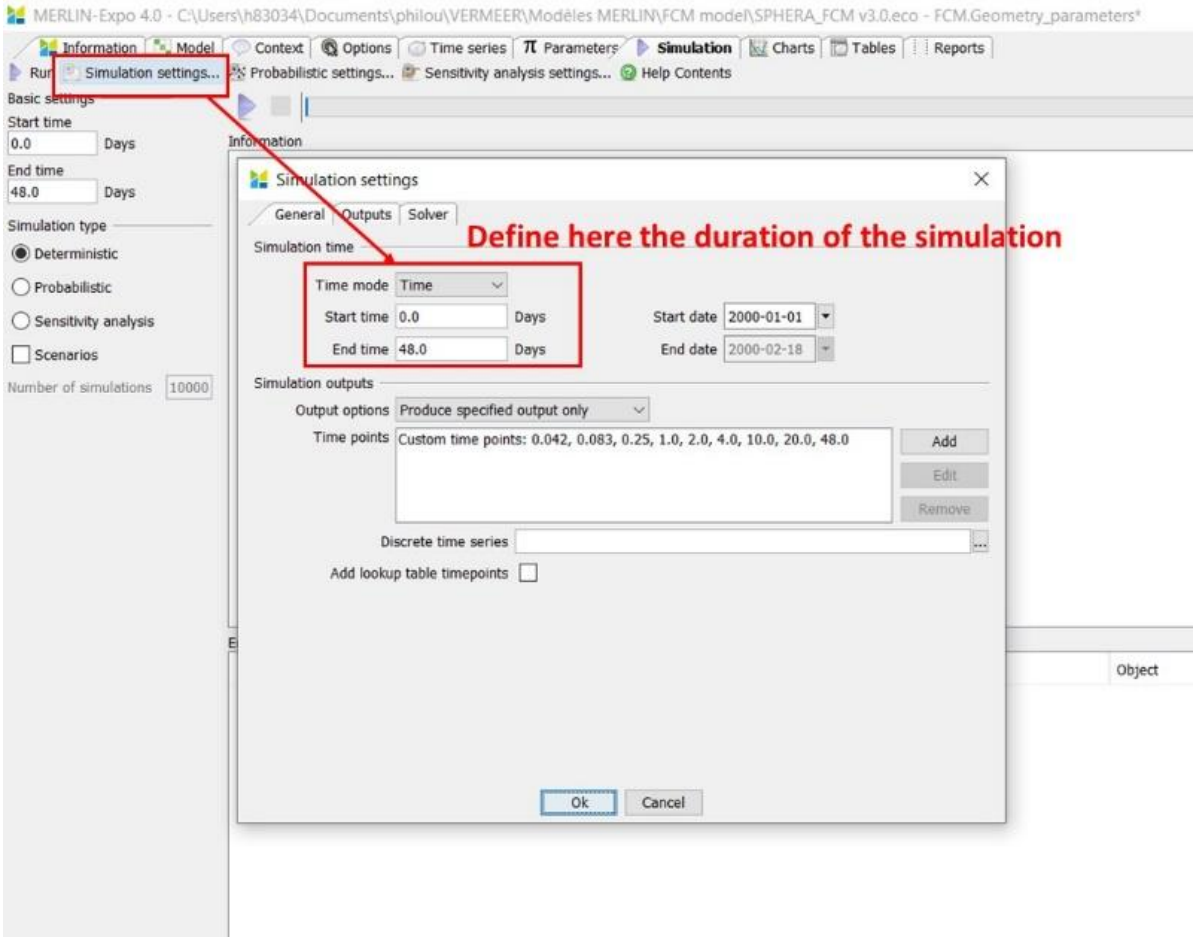


If such information appears, you have to complete the missing data.

4.7.2 Defining the simulation settings

Before running a simulation, you have to define some simulation settings in the 'Simulation settings' window:

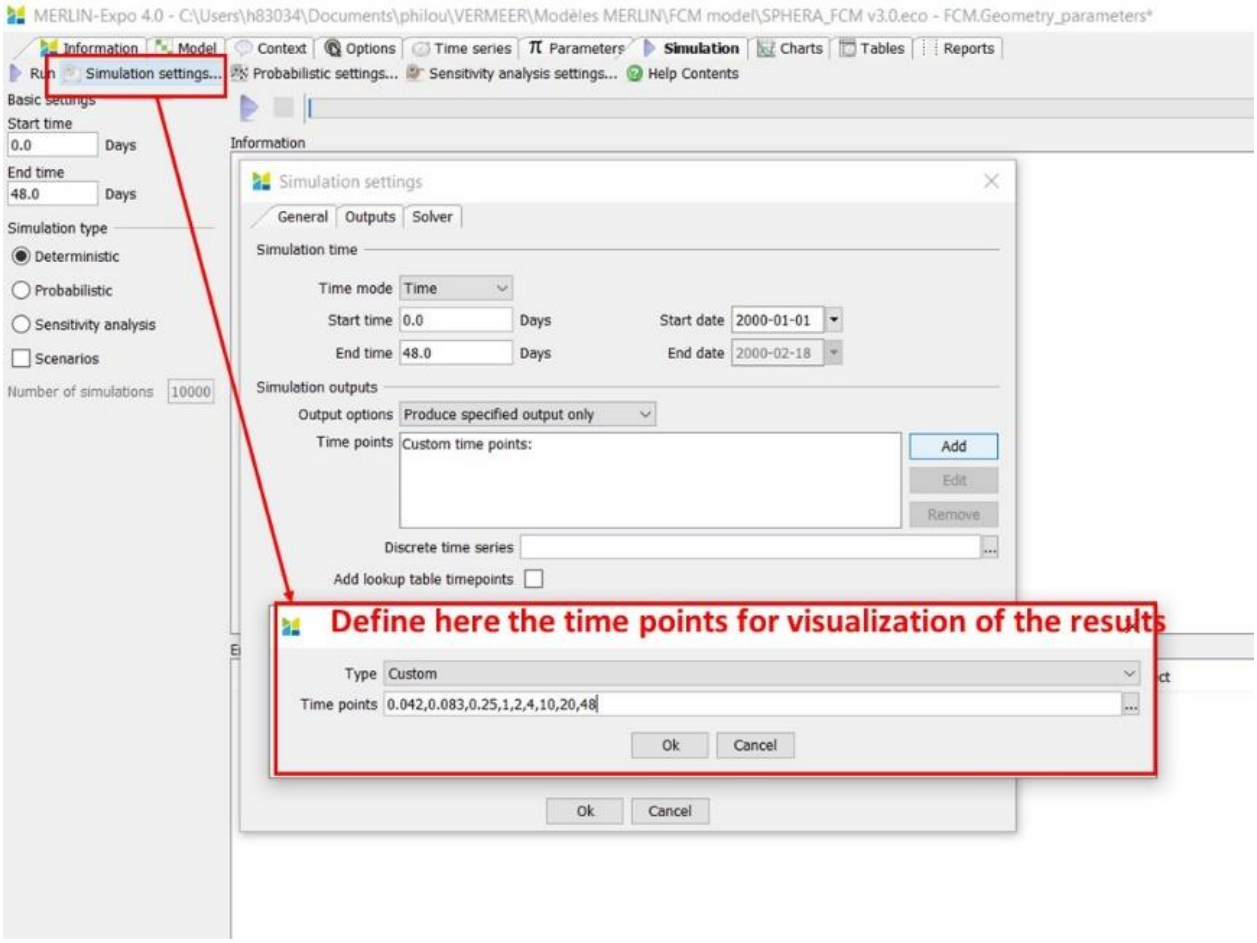
- **Maximum contact time between FCM and food**. For this purpose:
  - Define 'Start time' at 0;
  - Define 'End time' at the maximum contact time you have chosen;



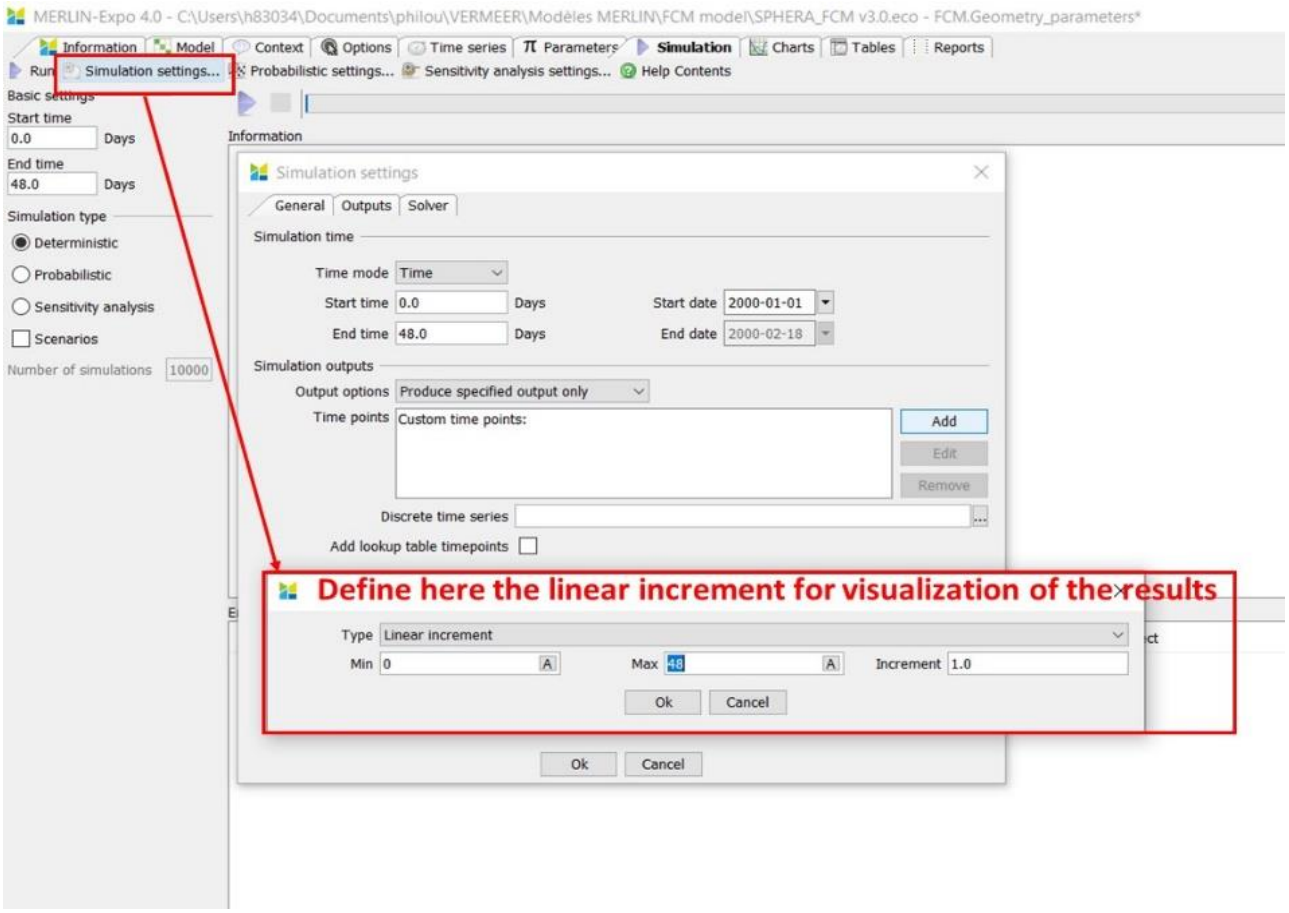
- **The time points for which you want to see the simulation results**. For this purpose, go to 'Simulation outputs' and:

o If you want to see the results only for some specific pre-defined time points,

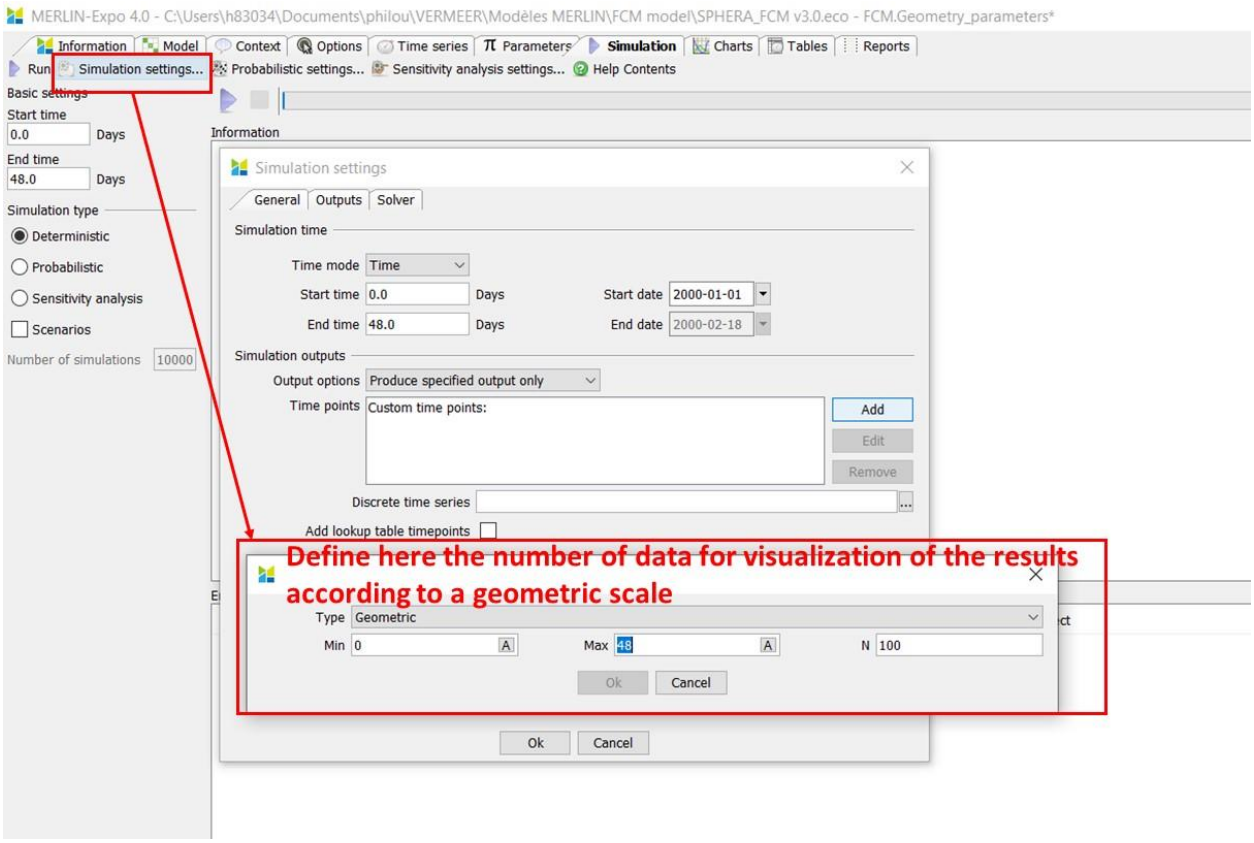
- select 'Produce specified output only',
- select 'Add',
- select 'Custom',
- define the chosen 'Time points' (for example, in the simulation shown below, results will be shown at nine time points: 0.042 d (=1 h), 0.083 d (=2 h); 0.25 d (6 h); 1d; 2 d; 4 d; 10 d; 20 d; 48 d);
- click on 'OK';



- If you want to see the results at a regular linear time increment,
  - select ‘Produce specified output only’,
  - select ‘Add’,
  - select ‘Linear increment’,
  - define the chosen Start time, End time and ‘Increment’ (for example, in the simulation shown below, results will be shown every day from 0 to 48 d);
  - click on ‘OK’;



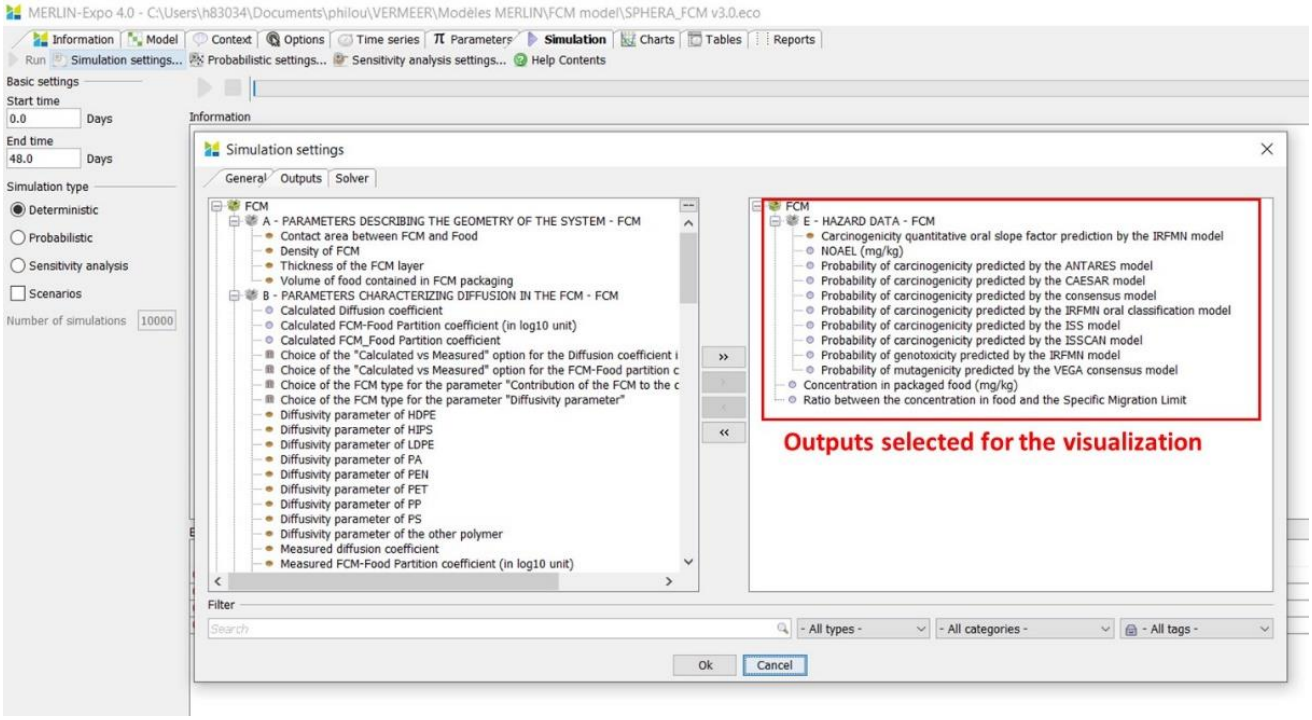
- If you want to see the results at a geometric time increment (i.e. more results at short times and less results at longer times),
  - select ‘Produce specified output only’,
  - select ‘Add’,
  - select ‘Geometric’,
  - define the chosen Start time, End time and ‘N’, number of data points to be visualized (for example, in the simulation shown below, results will be shown every from 0 to 48 d according to a geometric scale);
  - click on ‘OK’.



- **Outputs to be visualized**. All the state variables (i.e. variables calculated by the model) can be visualized by end-users. Some of them are however of poor interest for regulatory purposes since they are intermediate variables in the simulation process. For regulatory purpose, the most important variables are:

- the concentration of compound(s) in food (in $mg.kg^{-1}$);
- the ratio between the concentration in food and the Specific Migration Limit (SML), when the SML is available for the targeted compound(s);
- the probability of *in vitro* micronucleus formation predicted by the *ad hoc* VEGA model;
- the probability of mutagenicity predicted by the *ad hoc* VEGA model;
- the predicted NOAEL value for subchronic toxicity;
- the probability of carcinogenicity predicted by the different *ad hoc* VEGA models and the probability of carcinogenicity predicted by the consensus model;
- the carcinogenicity quantitative oral slope factor predicted by the *ad hoc* VEGA model;

All these outputs are selected by default for results visualization. But, you can add or remove endpoints by moving the corresponding endpoints from the left to the right bow (and inversely).

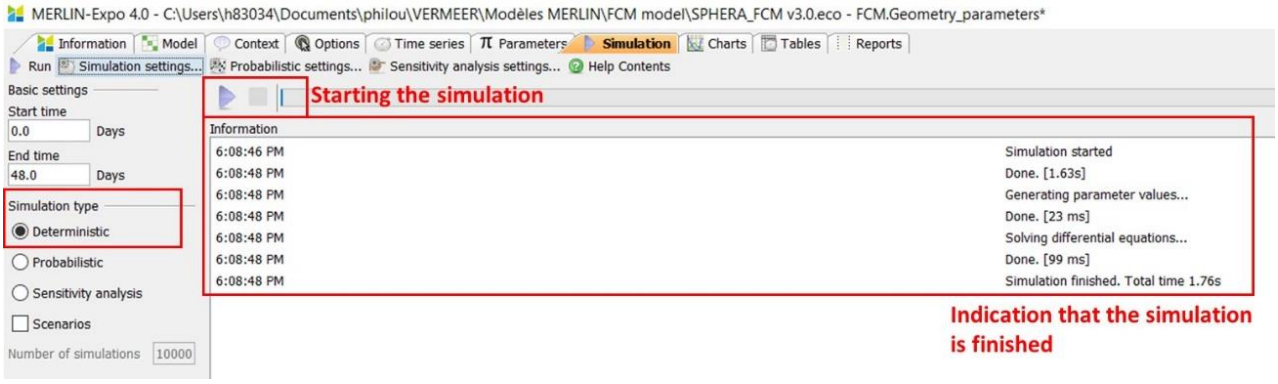


4.7.3 Running a deterministic simulation

Running a 'deterministic simulation' means that each parameter (defined at the previous step in the 'Parameters' tab – see 4.6) is described by its best estimated value. Eventual PDFs are therefore ignored.

For running a deterministic simulation:

- Select 'Deterministic' in the 'Simulation type';
- Click on the arrow for starting the simulation;
- When the simulation is finished, it is indicated in the 'Information' window. You can see the results (see 4.8).



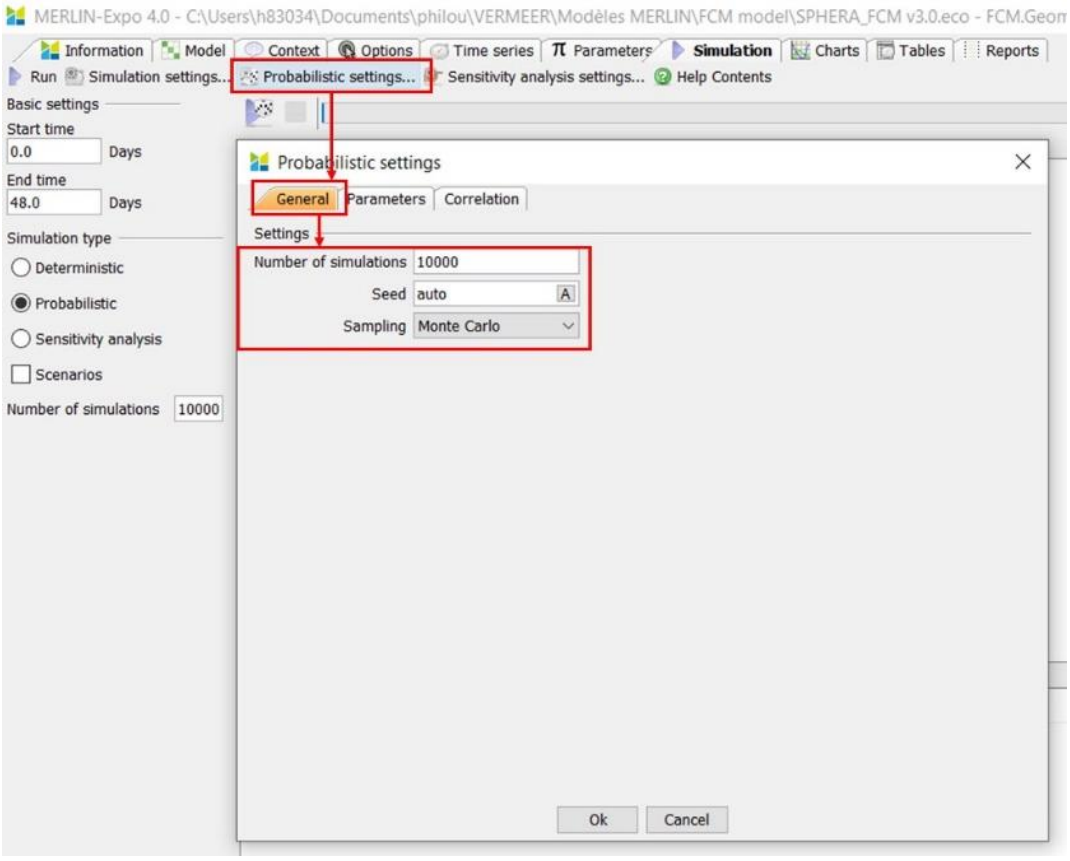
4.7.4 Running a probabilistic simulation

Running a 'probabilistic simulation' means that each parameter (defined at the previous step in the 'Parameters' tab – see 4.6) is described by its PDF. A Monte Carlo generator randomly samples a given number of parameter combinations according to the respective PDFs and the model runs for each of these combinations. This allows to generate a great number of simulations and associated results, and

summary statistics describing the parametric uncertainty can be calculated (e.g. mean, standard deviation, percentiles, etc).

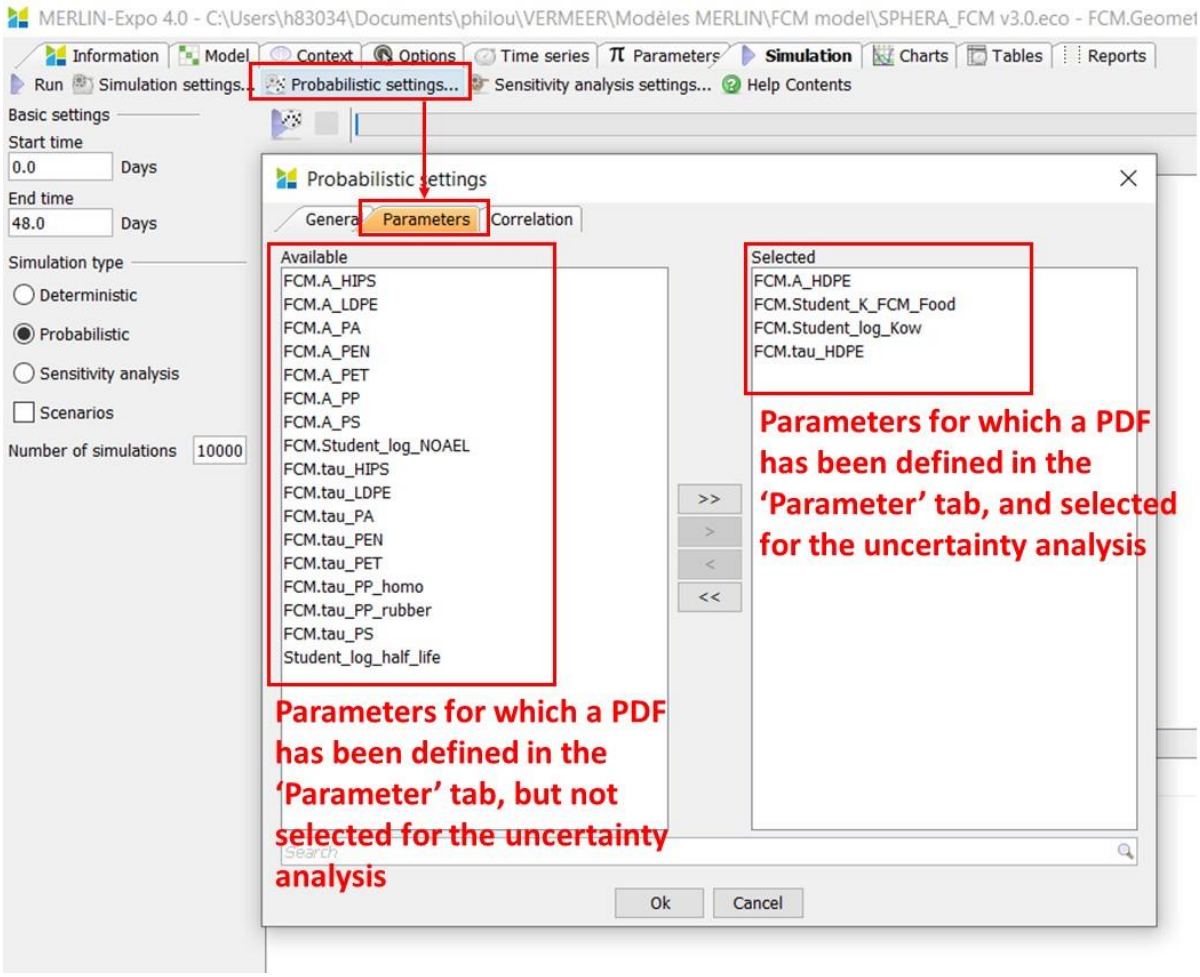
To run a probabilistic simulation, it is first necessary to define the 'Probabilistic settings' in the ad hoc window. For this purpose:

- Open the 'Probabilistic settings' window;
- In the 'General' window, you have to define:
  - the **'**Number of simulations'**.** This setting specifies how many simulations will be performed during a probabilistic simulation.
  - the 'Seed'[3]. The seed initializes the seed value for the random number generator. If you set the same seed, then the sequence will be the same each run. If you don't need this option, you can use the default selection 'auto';
  - the 'Sampling' scheme, either Monte Carlo (pseudo random numbers) or Latin hypercube sampling. For the applications of the VERMEER FCM tool, the Monte Carlo scheme is sufficient.



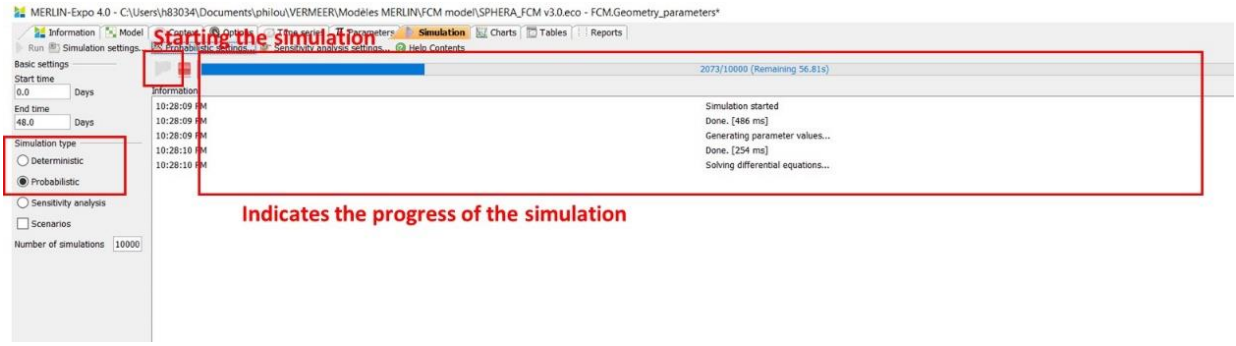
- The 'Parameters' window allows you to select the parameters that will be included in the uncertainty analysis. Only parameters that have been assigned PDFs can be selected. Note that you must select at least one parameter to run a probabilistic simulation.

[3] The seed is an initial number of the random number generator which returns a sequence of numbers that always generates the same sequence for given value.



- In the 'Correlations' window, correlations between parameters can be assigned in order to reduce noise and to avoid impossible parameter combinations. A priori, this option is not necessary for the VERMEER FCM tool.

When the 'Probabilistic settings' have been defined, you can start the probabilistic simulation:



4.8. Analysing results: the Charts and Tables tabs

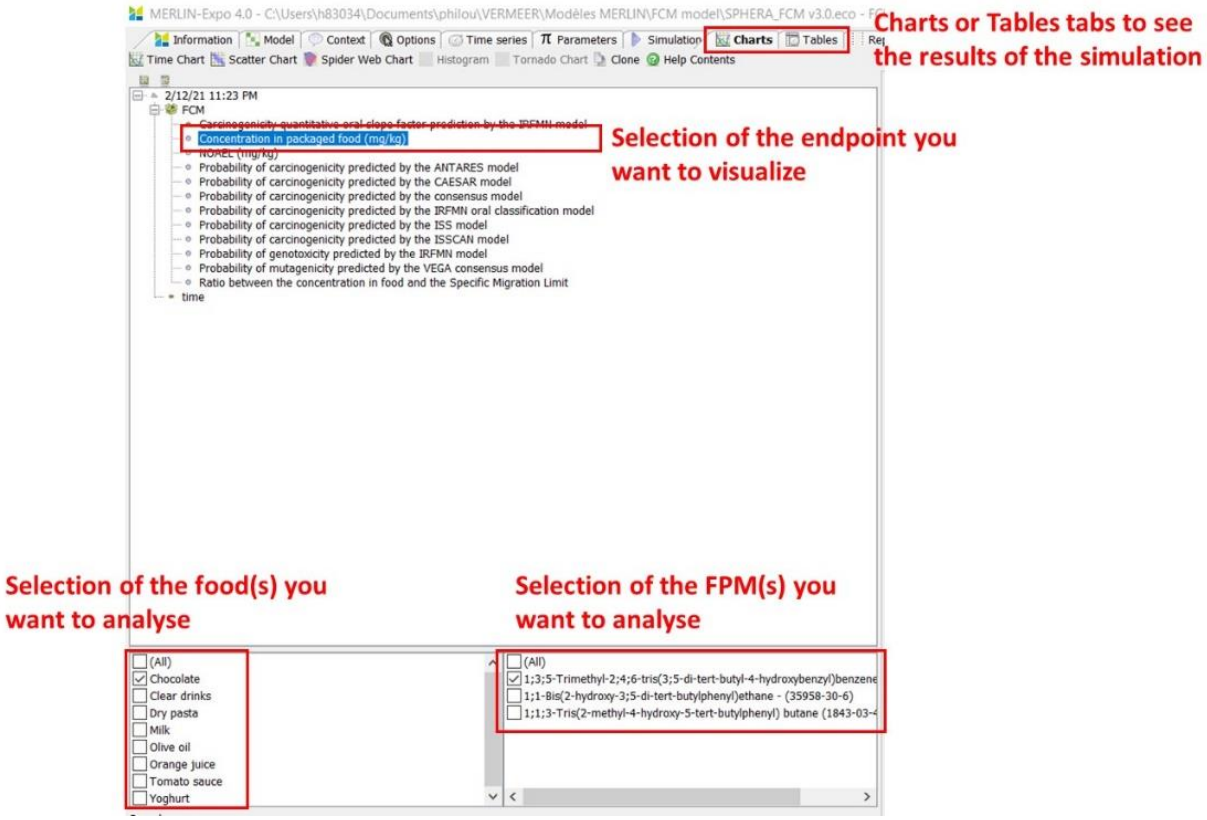
Results can be analysed in the Charts or in the Tables tabs. Whatever results are displayed on the Charts or Tables tabs, the process in the selection of endpoints is similar.

4.8.1 Selecting the endpoints

To analyse the results of the simulation, you have first to select which results are relevant for you. For this purpose:

- Select the targeted endpoint in the list of endpoints you have selected in 4.7.2;
- Select the food(s) you want to analyse;
- Select the compound(s) you want to analyse.

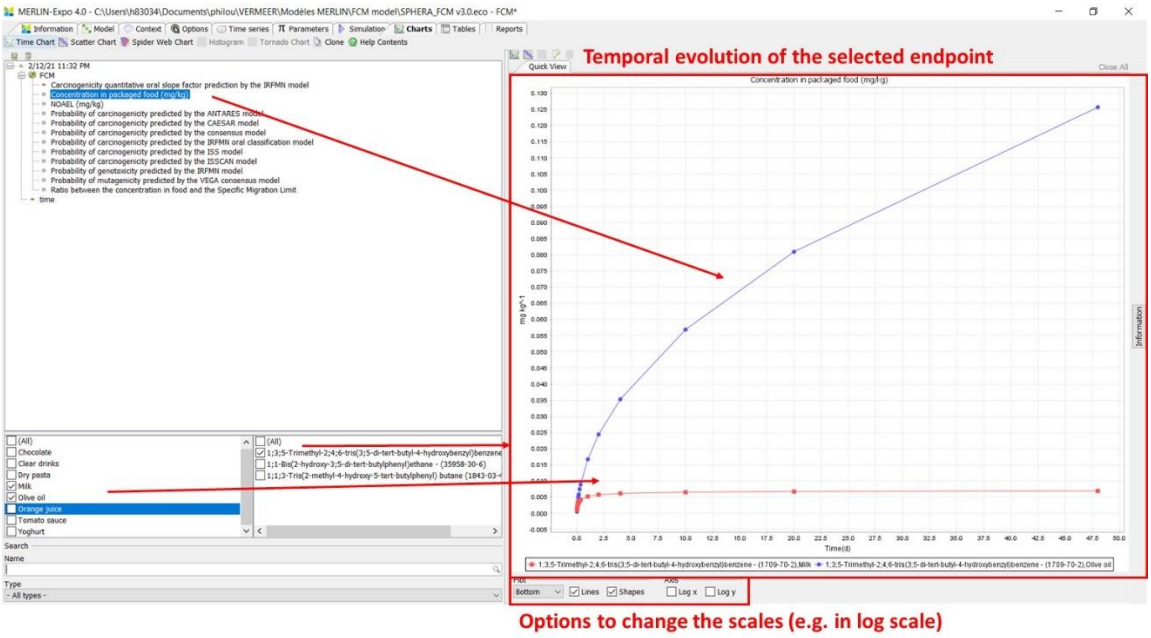
You can create all the possible endpoint-food(s)-compound(s) combinations simultaneously (i.e. all together) or sequentially (one by one).



4.8.2 Creating a chart

The VERMEER FCM tool generates figures to visualize results. For example, temporal figures can be generated as shown below.

All the options to generate the figure (generic options for all the models included in the MERLIN-Expo platform) are described in detail on https://wiki.merlin-expo.eu/doku.php?id=charts_screen.



4.8.3 Creating tables

The VERMEER FCM tool generates tables to visualize results. For example, tables describing the evaluation of the selected endpoint in time can be generated as shown below.

All the options to generate tables (generic options for all the models included in the MERLIN-Expo platform) are described in detail on https://wiki.merlin-expo.eu/doku.php?id=tables_screen.

Note that you can export data for a given table either to a text or an Excel file. Right-click the table and select 'Export data…'.