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PACEM

SHINY BETA VERSION 0.9.

User Manual

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Abbreviations

CDF	Cumulative density function
HP	Household product
MCRA	Monte Carlo Risk Assessment
PACEM	Probabilistic Aggregate Consumer Exposure Model
PCP	Personal care product
UI	User interface

Introduction

PACEM stands for Probabilistic Aggregate Consumer Exposure Model. It is a person-oriented consumer exposure model and was developed to facilitate realistic exposure assessments of chemicals in personal care products (PCPs). Several publications described the PACEM model and its application in different case studies (Delmaar et al. 2015; Dudzina et al. 2015; Gosens et al. 2014). Also with regard to skin sensitization, case studies have been conducted (Ezendam et al. 2018; Garcia-Hidalgo et al. 2018; Jongeneel et al. 2018; Nijkamp et al. 2015). PACEM was developed in the modelling language R and some experience with R is required for using it. Therefore, it was considered desirable to develop a user interface (UI) that can be used without such experience to make PACEM available to a broader user community.

In the following paragraphs, detailed instructions are given on how the PACEM Shiny model can be started and on how an exposure assessment can be conducted in the UI.

In the following section, the methodology used in PACEM is shortly described.

Short description of PACEM

In PACEM, the central entity of the exposure calculation is the exposed individual. Individual-based exposure modelling prevents unrealistic combinations of product exposures, which might occur with product-based modelling (Delmaar et al. 2015). PACEM is based on PCP use data and general information for sets of individuals (Biesterbos et al. 2013; Garcia-Hidalgo et al. 2017; Hall et al. 2007, 2011). Also, data on the use of household products (HPs) are included (Dimitroulopoulou et al. 2015; Garcia-Hidalgo et al. 2017), either for the same set of individuals (Garcia-Hidalgo et al. 2017) or a different set (Dimitroulopoulou et al. 2015).

Based on the individual product use patterns, aggregate exposure is calculated by adding up exposures to different products (Delmaar et al. 2015). The product use is characterized by the used amounts, the use frequencies, and the body areas of product application. Related information were collected for several PCPs. The exact number of investigated product categories depends on the survey. On the basis of these data, PACEM calculates exposure by sampling individual product uses from the survey database and by combining these uses with concentration data specified for the chemical of interest (Delmaar et al. 2015).

More specifically, PACEM takes the following steps (Delmaar et al. 2015):

1) For a defined number of N individuals, a model population is built from the survey population by repeatedly sampling from the survey population data. This means that each individual in the model population is a copy of an individual in the survey population. The respective copies only differ by the days on which exposure occurs (Dudzina et al., 2015).
2) For each individual in the model population, exposure is calculated by summing up all exposures evoked by the different products. The single external exposure estimates are calculated by multiplying the number of daily product uses, the amount of product used per application, the concentration of the chemical in the product, and the exposure fraction or retention factor (for assessing systemic exposure or dermal load, respectively). For example, external systemic exposure to a substance is calculated as:

$$E_{ij} = \sum_{k=1}^{p} n_{ijk}\, A_{ik}\, C_k\, EF_k \quad [\frac{ng}{day}]$$

with E_{ij} being the external exposure of individual i on day j, n_{ijk} the number of uses of product k by individual i on day j, A_{ik} the amount of product k used by individual i, C_k the concentration of the chemical in the product k, EF_k the fraction of the chemical the individual i is externally exposed to after use of the product, and p the number of PCPs accounted for (Delmaar et al. 2015).

Exposure fractions are the fractions of a product that come into contact with the exposed individual, e.g. the fraction of a product that ends up on the skin or the fraction of a spray product that becomes airborne and gets inhaled. They are specified for the whole person and are therefore used for systemic exposure assessments. Please note that it needs to be taken into account if the remaining fractions of the substance of interest and of the product in which it is applied are different (e.g. the case for volatile substances). More detailed information about deriving exposure fractions can be found in literature (Delmaar et al. 2015; Dudzina et al. 2015; SCCS 2016). In order to calculate an exposure estimate for a specific substance the exposure fractions have to be multiplied with a concentration of the substance in the product. Retention factors are similar fractions that define the amount of a chemical remaining on the skin after product use. They can be specified separately for different body parts and are used to assess the dermal load for different body parts, e.g. for sensitizing chemicals.

In the surveys, ranges of value were used to specify use amounts and frequencies (Dudzina et al. 2015). In PACEM these ranges were translated into distributions with the respective ranges. For example, for product use frequencies below once per day, a daily use of 0 or 1 is sampled with a probability based on the use frequency in the survey (Delmaar et al. 2015).

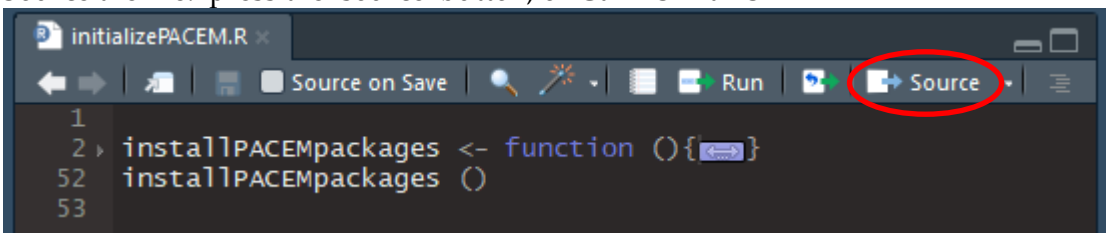
1. Installing R and R Studio

For using PACEM and the related Shiny interface, you need to install R and R Studio first. For installing R, you can go to the website https://cran.r-project.org/ and select the download for your location and operating system. Always choose the newest version available.
We recommend the R Studio development environment for working in R, but this extension is not necessary to work with PACEM. The examples and illustrations below assume you work in the R Studio environment. R Studio is a user friendly UI for R. You can find related downloads here: https://www.rstudio.com/products/rstudio/download/. The free desktop version is sufficient.

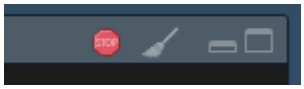
2. Installing the PACEM package

A ZIP-file containing all PACEM Shiny documents is available on Zenodo: https://zenodo.org/deposit/1475191. Please download and extract this file to a local folder.
First of all, **R packages** need to be downloaded that are a prerequisite for the PACEM package. For this you need an internet connection. Please note: The installation of these R packages only needs to be done once.

1. Start R Studio
2. In R Studio, open the file 'initializePACEM.r'
    a. Click on "File", "Open File…", and browse to the folder "PACEM_beta_15.10.18".
    b. Open the file 'initializePACEM.r'
3. Source the file: press the 'source' button, or Ctrl + Shift + S

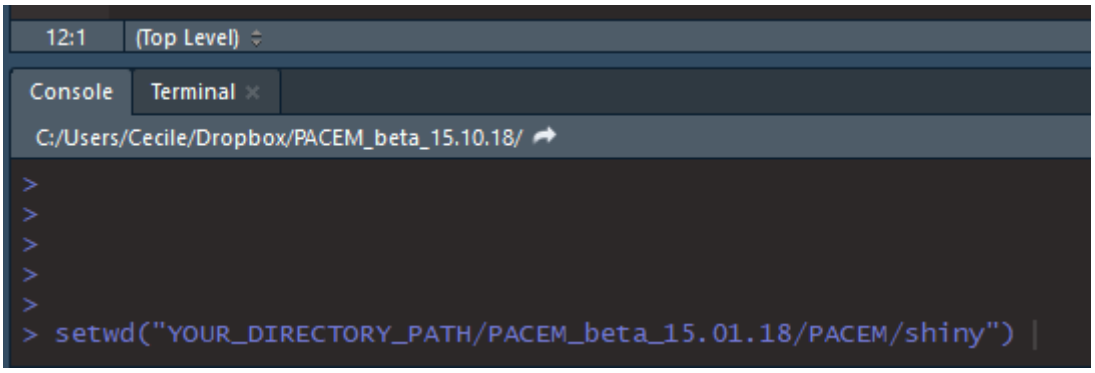


Sourcing may take some time, indicated by the "stop" icon in the upper right corner of the "Console" window:

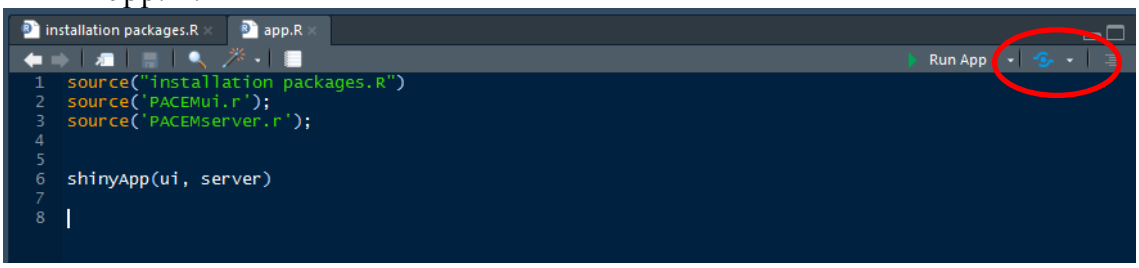


Then, for installing the PACEM package,

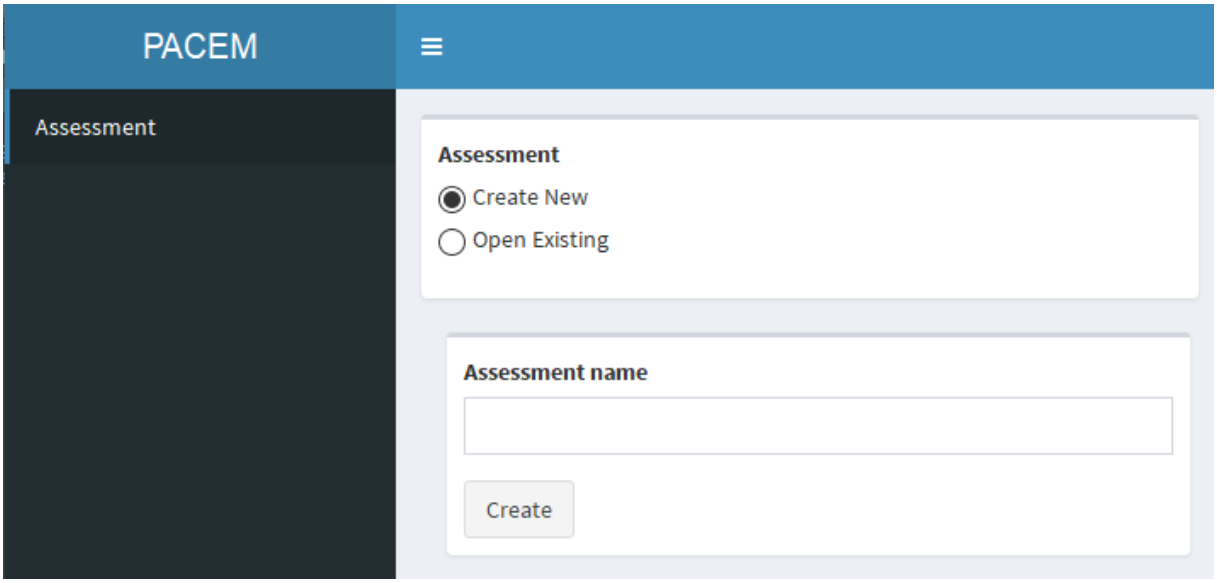
    a. Still in R studio, open the file 'app.R' by clicking on "File", "Open File…", and browse to the folder "PACEM_beta_15.10.18/PACEM/shiny"
    b. Open the file 'app.R'
4. Set the correct work directory to this file:
    a. Click on "Session", "Set Working Directory", "Choose Directory…." and browse to the directory PACEM_beta_15.10.18/PACEM/shiny.
    b. Click "Open" to set the "shiny" directory as your working directory.
    c. In the console window of RStudio (bottom left corner) the command 'setwd("YOUR_DIRECTORY_PATH/PACEM_beta_15.10.18/PACEM/shiny")' appears, confirming the chosen working directory



5. After having specified the work directory, Hit the 'run app' button for running 'app.R'.



Now, a new window should open that displays the Shiny interface of PACEM.



3. Performing a PACEM model run in the Shiny interface

To perform a PACEM model run, one has to prepare several input tables and select settings. The workflow for performing an exposure assessment is displayed in Figure 1. The presentation '18-08-21-presentationCecileKarrerEuroTox.pdf' (available in the same Zenodo directory as this user manual) shows an example assessment with detailed screenshots.

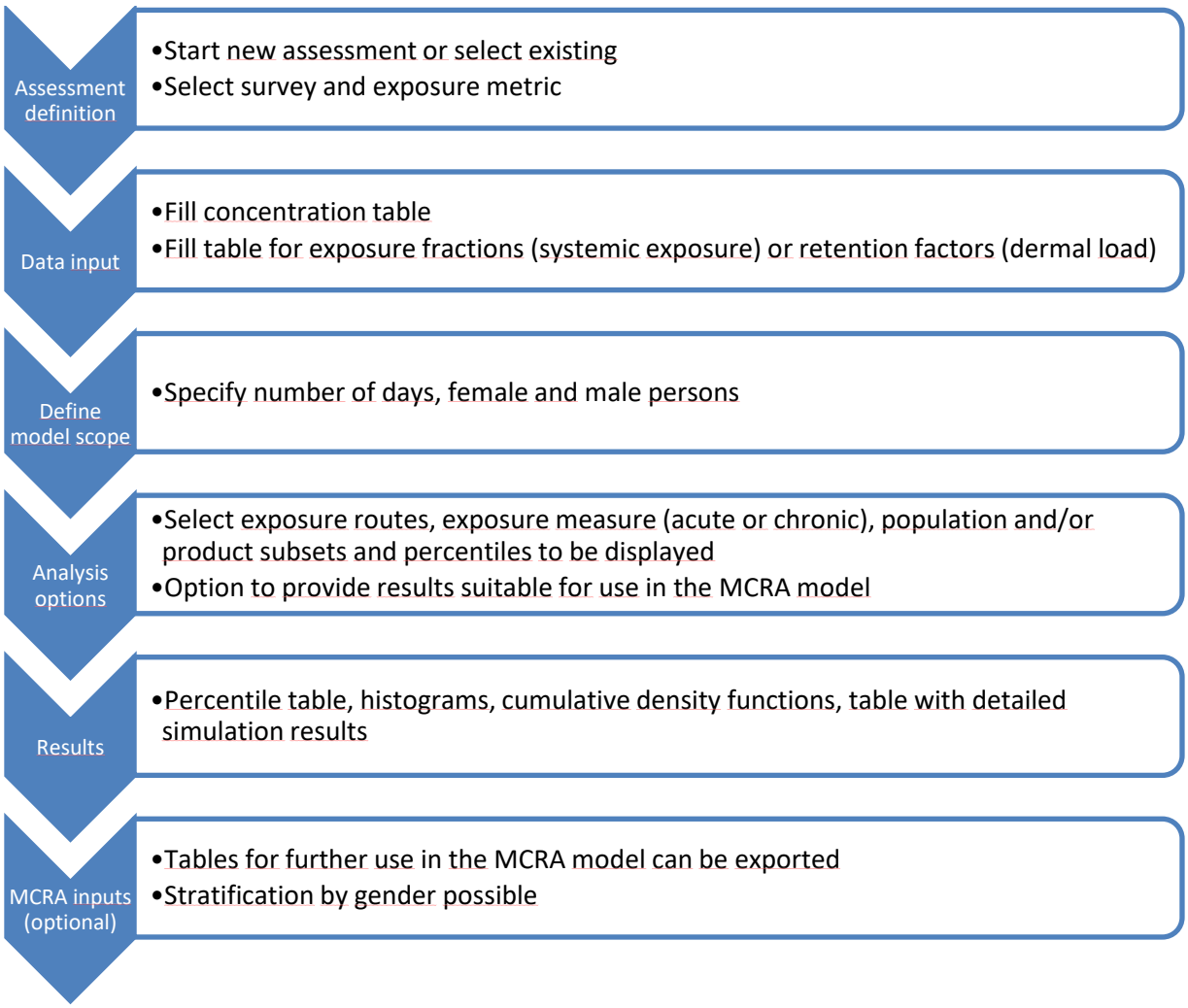


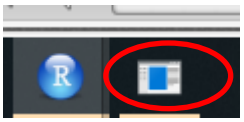
Figure 1. Workflow of the PACEM model.

In the following paragraphs, the different steps for using the PACEM model will be elaborated in more detail.

3.1. Opening an existing assessment or starting a new assessment

On the first page, the user can either start a new assessment or open an existing assessment to continue working on it. Please note that an assessment can be saved under another name in the following steps. This way, one can open an existing assessment, use already defined specifications (e.g. the concentration table, the exposure fraction table or the retention factor table), and change some specifications to yield a different exposure assessment. Please note: When you create a new assessment, provide an assessment name and click 'Create', a folder dialog is opened to specify the location where the assessment should be saved. Sometimes this

dialog does not pop up, but it just appears in the task bar and needs to be brought into focus by the user by clicking the icon in the task bar. The same applies when you click 'Save as' in any step of using PACEM shiny to save your assessment under another name.

Task bar:  *click to bring folder dialog into focus*

3.2. Selection of use survey and exposure metric

In the following step, the user can select the survey on the use of PCPs and optionally HPs. One can select from the following surveys on PCP use:

a) Dutch population: 516 persons, 18 to 71 years of age (Biesterbos et al. (2013))
b) Swiss population: 759 persons, 0 to 91 years of age (Garcia-Hidalgo et al. (2017))
c) Mixed European population (Colipa survey): European population adjusted based on survey data from France, Germany, Great Britain and Spain (Hall et al. 2007, 2011)

The user can select whether or not exposure from HPs should be modelled additionally. As mentioned previously, the Swiss survey includes information on both PCPs and HPs for the same individuals. For the other two surveys, another survey (Dimitroulopoulou et al. 2015) can be used to model exposure from HPs (based on a different set of individuals).
Afterwards, the exposure metric needs to be selected. The user can choose between systemic exposure and the assessment of the dermal load (e.g. when focusing on sensitization).

3.3. Filling the concentration table

In the following step, concentrations of the studied substance in the products need to be specified in a table. Please note that the input tables are customized for the respective use surveys (because different product categories are included in the surveys). Therefore, if you have opened an existing assessment, but changed the use survey in the next step, a blank concentration table will be displayed even if you had filled a table in your previous assessment.
The concentration table contains rows for each PCP investigated in the chosen survey. If exposure to HPs is to be modelled, all HPs are appended to the table as well. For each product in the list, concentration information can be added. Please note that concentrations need to be entered in the unit '**ng/g**'. An empty line is treated as if the concentration in the corresponding product is zero. Explanations of the different columns and required inputs are given in Table 1.

Table 1. Required inputs for the concentration data table.

Column name	Description	Type	Default
Sample size	How many different concentrations are available and should be sampled for the product	Positive integer	0
Distribution	Distribution to be used for drawing the concentrations. One of the following can be selected: point, uniform, lognormal, triangular, truncated lognormal, trapezoidal	Factor	point
Fraction of zeroes	Share of the product that does not contain the chemical	Positive number in between 0 and 1.	0
Distribution parameter 1-4	Parameters needed for specifying the distributions. The parameters required are specified in the Shiny interface below the concentration table	Positive numbers	0

Please note that the decimal separator is a point "." and not a comma.

3.4. Filling the tables for exposure fractions (systemic exposure) and retention factors (dermal load)

Next, a table needs to be filled for specifying exposure fractions (for the systemic exposure assessment) or retention factors (for the dermal load assessment).

3.4.1. Exposure fractions

Exposure fractions are the fractions of a product that come into contact with the exposed person, e.g. the fraction of a product that ends up on the skin or the fraction of a spray product that becomes airborne and gets inhaled. Thus, the use of exposure fractions yields external exposure estimates. If the user wants to obtain internal exposure estimates as model results, the exposure fractions specified in PACEM should additionally contain absorption fractions, e.g. the fraction of a substance in a product on the skin that is eventually absorbed. The goal of the assessment and the definition of exposure fractions for the respective assessment needs to be decided and consequently kept in mind by the user.

Exposure fractions can be provided for the different exposure routes *dermal*, *oral* and *inhalation*. Per product considered in the assessment, at least one exposure fraction (for one route) should be specified. Please note that the exposure fractions need to be specified as fractions, not as percentages (all values must be below or equal to 1).

Exposure fractions are dependent on the product and its use (e.g. taking into account dilution for calculating dermal exposure from using shower gel). Additionally, they can also depend on the substance (e.g. taking into account substance loss due to volatility). For further information about exposure fractions and suitable parametrizations, please have a look at relevant documents such as the Notes of Guidance of the Scientific Committee on Consumer Safety (SCCS 2016).

3.4.2. Retention factors

A retention factor defines the amount of a product that remains on the skin after the use of the product. The retention factors can be specified separately for the body parts trunk, head, arms, hand, legs, and feet. At minimum, one retention factor (for one body part) should be specified per product that is considered in the assessment.
Please note that the retention factors need to be specified as fractions, not as percentages (all values most be below, or equal to 1).

3.5. Simulation settings

Next, settings of the simulation need to be selected:

- The number of days over which the simulation should be conducted (*1-14*)
- The number of women and men for which exposure should be modelled.

Please note that the modelling time increases with increasing the number of days, and number of females and males. One should bear in mind the size of the survey population and the goal of the assessment. Also, the number of days and the number of women or men should be above 1 so that results can be generated. If the number of women and men are too low, results can be generated, but might not be meaningful. The user can select whether modelled results should be saved to the assessment file. If this is selected, the exposure assessment does not need to be modelled a second time when opened another time, but the user can proceed directly to the analysis step. However, the results can increase the file size significantly. This can lead to PACEM Shiny reacting slower or even to the problem that previous assessments cannot be re-opened if they are too large.

3.6. Output analysis options

In the following step, the options for the output analysis can be selected:

- Selection of exposure measure: *acute* or *chronic*
- Selection for which individuals the results should be displayed: *only exposed individuals* or *whole population*
- Selection for which products the results should be displayed: *all products* or definition of *sub-selection (please note that sub-selections are not possible in the current beta version)*
- Selection for which percentiles exposure estimates should be displayed

In case of systemic exposure:

- Selection for which exposure routes the results should be displayed: *dermal* and/or *oral* and/or *inhalation* and/or *total*. Please note: One should only select routes for which exposure fractions were defined in the exposure fraction table. *Total* cannot be selected by itself.
- Selection if specific exposure result tables should be created that can be used as inputs for aggregate exposure calculations in the MCRA model. More information about the MCRA model and this output option can be found in paragraph 3.8 Generation of MCRA tables.

3.7. Display of results

In the next step, the results are displayed and can be interpreted by the user:

- A table of the exposure estimates for the percentiles specified in paragraph 3.6 Output analysis options
- Separate histograms for all routes selected in paragraph 3.6 Output analysis options
- One plot including all cumulative density functions (CDFs) for all routes selected in paragraph 3.6 Output analysis options
- A table with the detailed simulation results

For the histograms, the number of bins can be modified and for the CDFs, the scale can be selected (*linear* or *logarithmic*). The histogram and CDF plots can be copied and/or saved; for this export option, one has to right-click onto the respective figure.
The table with detailed simulation results can be searched and ordered in different ways. Additionally, it can be saved by the user as a CSV-file for further use outside of PACEM shiny.

3.8. Generation of MCRA tables

When conducting systemic exposure assessments, the user can choose in paragraph 3.6 Output analysis options if result tables suitable for the use in the MCRA model should be generated. MCRA stands for Monte Carlo Risk Assessment. It is a web-based exposure model with a focus on exposure estimations from dietary exposure and was initially developed for the risk assessments of pesticides (van der Voet et al. 2015). MCRA is available at mcra.rivm.nl and access can be requested free of charge. MCRA provides functionalities for aggregate exposure modelling, i.e. the assessment of exposure of one chemical via multiple sources and routes. For conducting aggregate exposure assessments, the user has to upload a table that contains the exposure estimates for the source(s) and route(s) that are supposed to be aggregated with dietary exposure in the assessment. With PACEM, Shiny beta version 0.9, such tables can be generated automatically for exposure from PCPs (and HPs, if this is selected).

3.8.1. Settings for MCRA table generation

Prior to the table generation, different settings need to be made by the user:

- Specification of a compound ID. This alpha-numeric character string is the unique identification code of the chemical. The compound ID should be used consistently for all tables to be used in MCRA.
- Stratification: The user can select if the exposure results should be stratified by gender. This way, exposure estimates from PCPs and HPs can be allocated to individuals of the dietary survey used in MCRA in a more targeted way.
- Specification of deterministic absorption factors for the different routes, if external exposure estimates have been calculated with PACEM, Shiny.

3.8.2. MCRA table display and export

In the following step, three or four tables are displayed that are needed for using the generated exposure estimates in MCRA:

- The table *NonDietarySurveys* provides details about the survey(s): description, location, date and unit of exposure
- The table *NonDietarySurveyProperties* specifies demographic criteria for the assignment of non-dietary exposure values to individuals in the food survey(s). These criteria are defined by the user in step 3.8.1 Settings for MCRA table generation. If demographic criteria are defined, only those individuals in the dietary survey who meet the criteria for the PACEM survey will be assigned non-dietary exposures.
- The table *NonDietaryExposures* lists the non-dietary exposure values for the individuals within the PACEM survey. Each exposure entry comprises the non-dietary survey (PACEM), a string identifying an individual (unique alpha-numeric character string), a compound (compound ID specified in step 3.8.1 Settings for MCRA table generation), and dermal, oral and inhalation exposure values (if specified). The exposure values refer to acute or chronic exposure, depending on what exposure measure has been specified by the user in step 3.6 Output analysis options. Acute exposures are the exposures on one randomly selected day and chronic exposures are the average exposure values over all days considered.
- The table *NonDietaryAbsorptionFactors* is only provided if the assessment in PACEM Shiny has yielded external exposure estimates. It lists deterministic absorption factors specified for the different routes.

All three or four tables can only be saved separately as CSV-files from PACEM Shiny. In the following step, they need to be merged into one excel file.
To do this, please open all tables. Save the *NonDietaryExposures* table as excel file and use this as basis for adding the other tables. In each table (separately), select the first column and split the text into multiple columns:

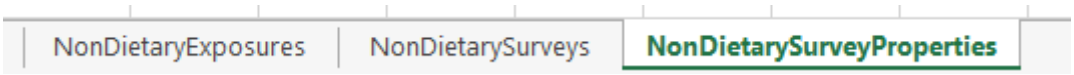
- Go to the tab 'data' > select 'text to columns'. This starts the Convert Text to Columns Wizard.
- Click 'Delimited' > 'Next', then check 'Comma' as separator, click 'next' and 'finish' without setting the data formats in this wizard.

Next, the data formats need to be specified for each column of the three tables as required for use in MCRA. To do this, mark the respective column(s) entirely > right click > choose 'format cells' and format the columns as specified in Table 2.

Table 2. Data formats required for the columns of the four tables needed for use in MCRA.

Table	Column	Type
NonDietary Exposures	idIndividual	Text
	idNonDietarySurvey	
	idSubstance	
	Dermal	Number (specify decimal places so that it is suitable)
	Oral	
	Inhalation	
NonDietary SurveyProperties	IndividualPropertyName	Text
	idNonDietarySurvey	
	IndividualPropertyTextValue	
	IndividualPropertyDoubleValueMin	Number
	IndividualPropertyDoubleValueMax	
NonDietarySurveys	idNonDietarySurvey	Text
	Description	
	NonDietaryIntakeUnit	
	PercentageZeros	Number (please note, that by default entries with zero exposures are included in the dataset, so that the percentage of zeroes is 0)
NonDietary AbsorptionFactors	idNonDietarySurvey	Text
	idCompound	Text
	DermalAbsorptionFactor	Number between 0 and 1
	OralAbsorptionFactor	Number between 0 and 1
	InhalationAbsorptionFactor	Number between 0 and 1

Next, two or three additional sheets need to be added to the excel file that contains the *NonDietaryExposures* table. The sheets containing the tables *NonDietarySurveyProperties, NonDietarySurveys* (and optionally *NonDietaryAbsorptionFactors)* need to be copied into these empty sheets. In the last step, the sheets need to be renamed to '*NonDietaryExposures*', '*NonDietarySurveyProperties'*, '*NonDietarySurveys'*, and optionally '*NonDietaryAbsorptionFactors'* respectively.



After these steps, the excel table can be uploaded to MCRA and used in aggregate exposure assessments.

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