User's Guide

PMOD Workflow for Dosimetry Preprocessing (PBAS, PKIN)

Version 3.8

PMOD is a software FOR RESEARCH USE ONLY (RUO) and must not be used for diagnosis or treatment of patients.

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Workflow for Dosimetry Preprocessing

Introduction

The estimation of the internal radiation dose in nuclear medicine is a common requirement for novel radiotracers. The 'Effective Dose' to the patient or volunteer, in milli-Sieverts per mega-Bequerel (mSv/MBq) of radiotracer administered, and identification of the 'dose-limiting organs', may be required by Ethical Commissions before the maximum injectable dose can be defined. Calculation of such radiation dose is commonly known as 'dosimetry'.

Prior to studies in humans, dosimetry in animals can be extrapolated to provide an initial estimate of 'Effective Dose'. The total number of disintegrations in the organs during the presence of the radionuclide in the body is required. In order to calculate the total number of disintegrations in each organ, knowledge of the radiotracer pharmacokinetics is required. Although ex vivo biodistribution studies are still performed in animals, PET and SPECT imaging allow the tracer kinetics to be quantified in single subjects, reducing the number of animals required and making human studies possible. However, accurately estimating the tracer kinetics throughout the time that the radioisotope is present in the body typically requires a substantially different protocol to that normally used in dynamic PET/SPECT.

According to International Commission on Radiation Units and Measurements report no 67 [1, 2], image acquisition starting times of 1/3, 2/3, 3/2, 3, and 5 multiples of the effective half-life are recommended to sufficiently describe the kinetics. In the case of radionuclides with longer half-lives, even F-18, this necessitates multiple scanning sessions.

Deriving time-activity curves from such data thus necessitates merging of the independent scan sessions into a dynamic series, with careful consideration of decay correction. In fact, as the total number of disintegrations in each organ is required, no decay correction should be applied to imaging data used for dosimetry. However, as decay correction to the acquisition start time is the default in clinical imaging, particularly for whole body PET with multiple fields-of-view, a pragmatic approach is to ensure that decay correction to a common time point is applied to all scans. From this starting point, decay according to the known radionuclide half-life can be applied.

The activity in each organ at each time point can be extracted from the imaging data using volume-of-interest (VOI)-based analysis. Note that due to scanning in independent sessions, these VOIs may need to adapt to changing organ positions over time (dynamic VOIs).

Once the tracer kinetics in each organ are known, the total number of disintegrations during the presence of the radionuclide can be calculated as the area-under-the-curve (AUC; y-axis: total activity in Bq in organ, x-axis: time in hours). Extension from the last data point collected to infinity (or decay of the last Bq in the body) is usually achieved by analytic integration based on the known radionuclide half-life. The total number of disintegrations is known as the 'residence time', and has the units 'Bequerel hour per Bequerel'. A number of methods have been proposed to calculate the residence time, ranging from simple rectangular or trapezoidal calculation of the AUC for the measured data portion, to fitting of exponential models and analytical calculation of AUC from injection to infinity.

These residence times are used as the input to digital 'phantoms', representing a standard model of adult male or female, within which the dose from each source region to all other target regions can be calculated (see [3]). These calculations are performed in standalone software tools, such as OLINDA/EXM [4] and IDAC [5]. The output of these programs is a table containing individual doses in mSv per organ per MBq injected, and the Effective Dose, a weighted average between critical organs (e.g. ICRP publication 60, 1991 [6]).

The recommendations for dosimetry are evaluated by the International Commission on Radiological Protection (ICRP; www.icrp.org), and updated at regular intervals. Recently, ICRP publication 103 updated the weighting factors for calculation of the Effective Dose, and introduced more sophisticated voxelized phantoms [7]. ICRP publication 89 updated the organ masses used in the calculation of residence times, and introduced reference values for both males and females of six different ages [8].

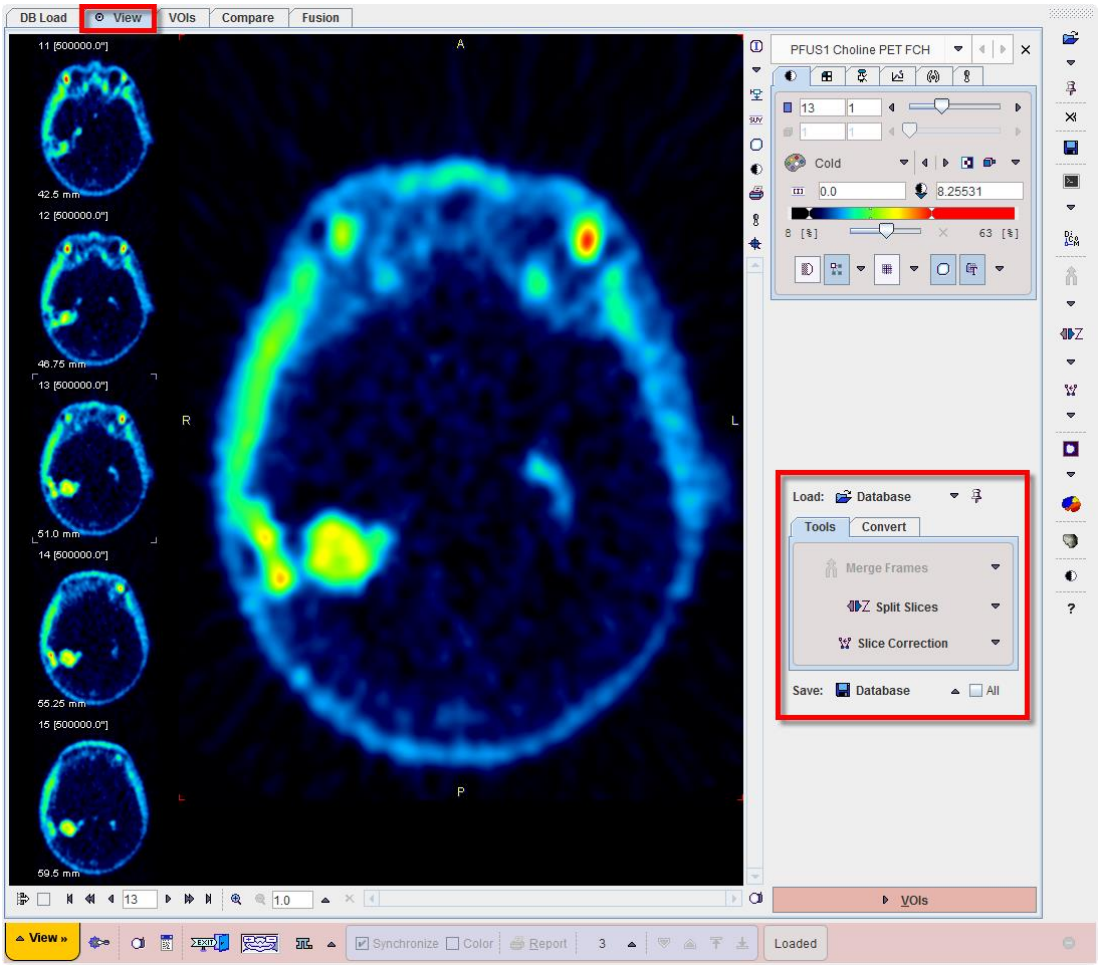
PMOD supports a tailored workflow of preprocessing steps to arrive at reliable dosimetry input data from a set of sequential image acquisitions, using the base tool PBAS and the kinetic modeling tool PKIN.

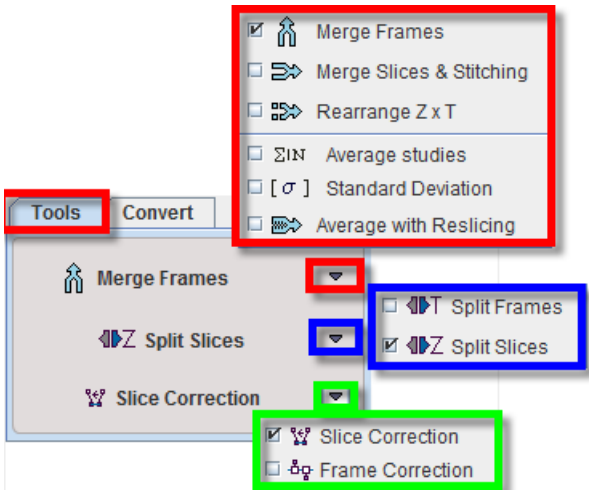
Data Preparation in PBAS

The images of multiple studies may be separated by hours or even days depending on the half-life of the isotope in question. The first task is to combine those images into a consistent dynamic series. A crucial element during data merging is the proper handling of decay correction for independently acquired series. For image formats containing sufficient header information (e.g. DICOM), PMOD's Merge tool can derive the series timing directly from the image headers and offers decay correction at the individual image and dynamic series levels.

Merge Frames Tool

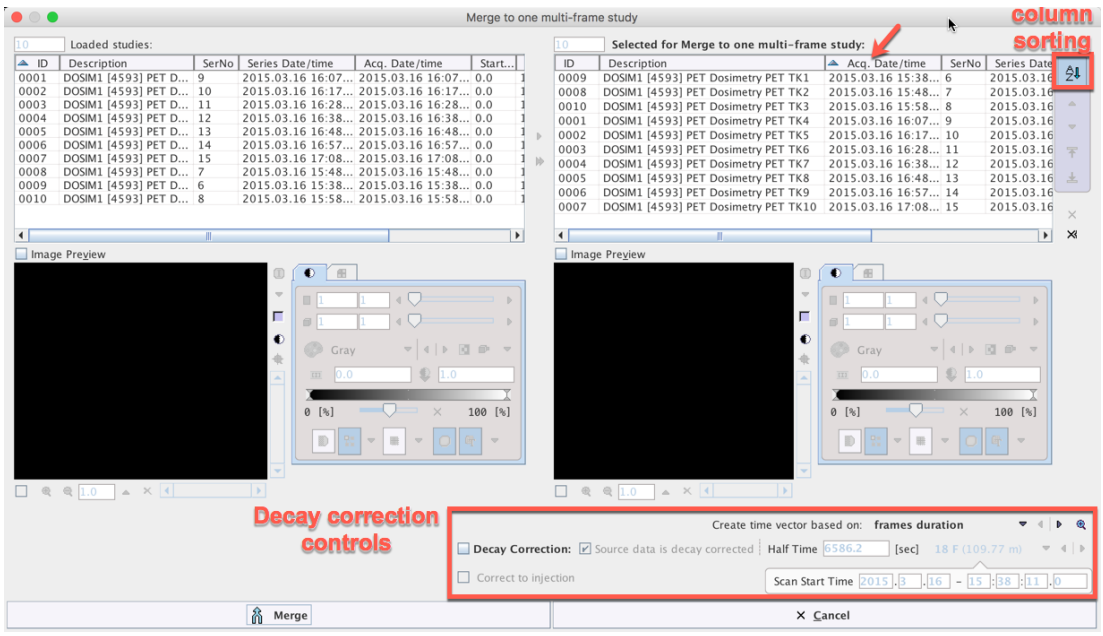
The **Merge Frames** tool is available on the *View* page of the VIEW module, below the main image controls. It is activated once multiple image series are loaded.





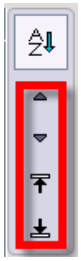
The **Merge Frames** tool allows the combination of image series with the same geometry into a joint dynamic series. Static and dynamic series may be merged.

Activating **Merge Frames** opens a dialog window as illustrated below. The list in the upper left shows the loaded image series in loading order. The list in the upper right shows the image series that will be combined into a dynamic series with the current sorting order. Initially, all series appear in the original order. The options related to applying decay correction during merging and generating the timing of the new dynamic series is located in the lower part.



Series can be copied from left to right by Double-Clicking in the left list, or selecting a list element and activating the arrow between the lists. The double arrow copies all loaded series to the right.

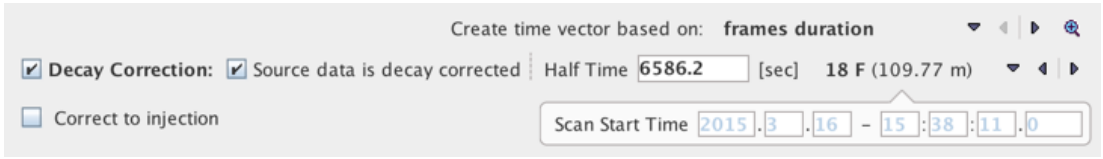
The order of the *Selected for Merge* list can be modified by selecting a list element and adjusting its position in the list using the arrows to the right.



If the columns contain information that is suitable for sorting, the sorting button **AZ** can be enabled and sorting started by clicking the appropriate column header. In the example above, the acquisition time was used to sort the static series into the proper acquisition order.

Decay Correction

When joining PET or SPECT data into a dynamic series, a consistent decay correction must be ensured. Usually, each image series is corrected to its own acquisition start time. Therefore, when joining static series into a dynamic series, later series have to be decay corrected to the start of the first acquisition by scaling them by a corresponding factor. The appropriate setting for this situation is to enable **Decay Correction**, confirm that **Source data is decay corrected**, check that the isotope **Half Time** is correct, and check that the Acquisition Start times of the series *Selected for Merge* are sorted correctly, as illustrated below. The Acquisition Start time of the first series in the list is taken as the common time for decay correction.

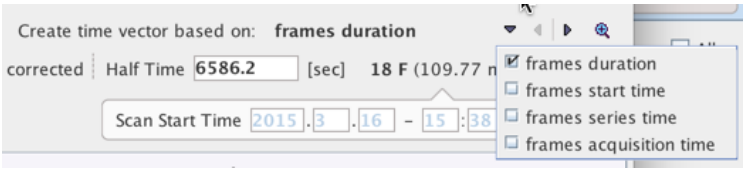


Alternatively, if the time of tracer injection varies from the start of acquisition, and this has been correctly recorded in the image header, **Correct to injection** may be activated.

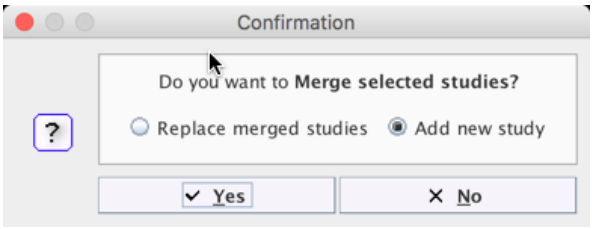
If image acquisition timing data is not available in the image header, it is recommended that the user resave their data in a format that allows the timing information to be added (e.g. DICOM), before using the **Merge Frames** tool.

Timing Vector

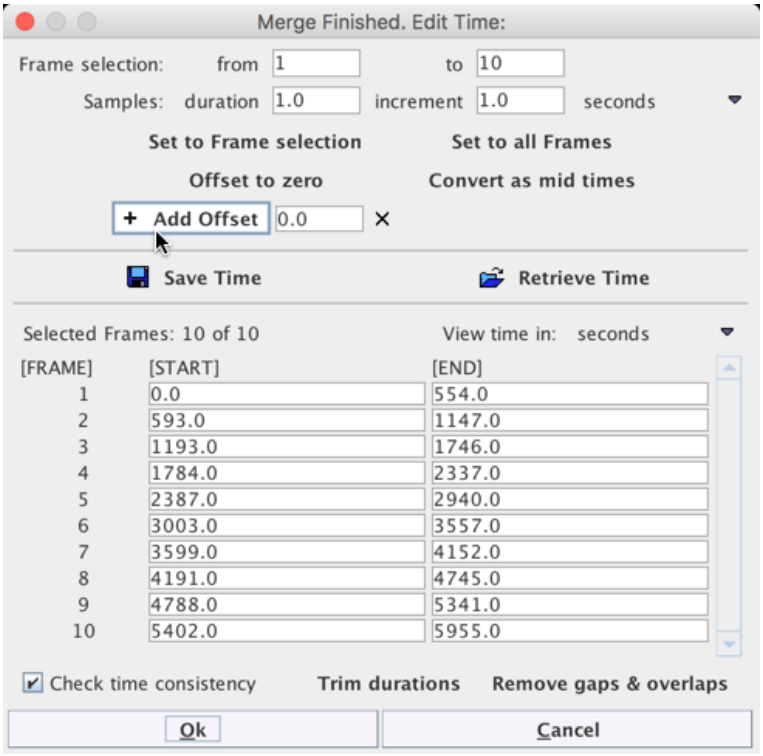
The timing of the created dynamic series must be constructed. It can be specified using the **Create time vector based on** selection.



Processing is started with the **Merge** button, and the user has a choice between replacing the currently open image series, or creating a new series.



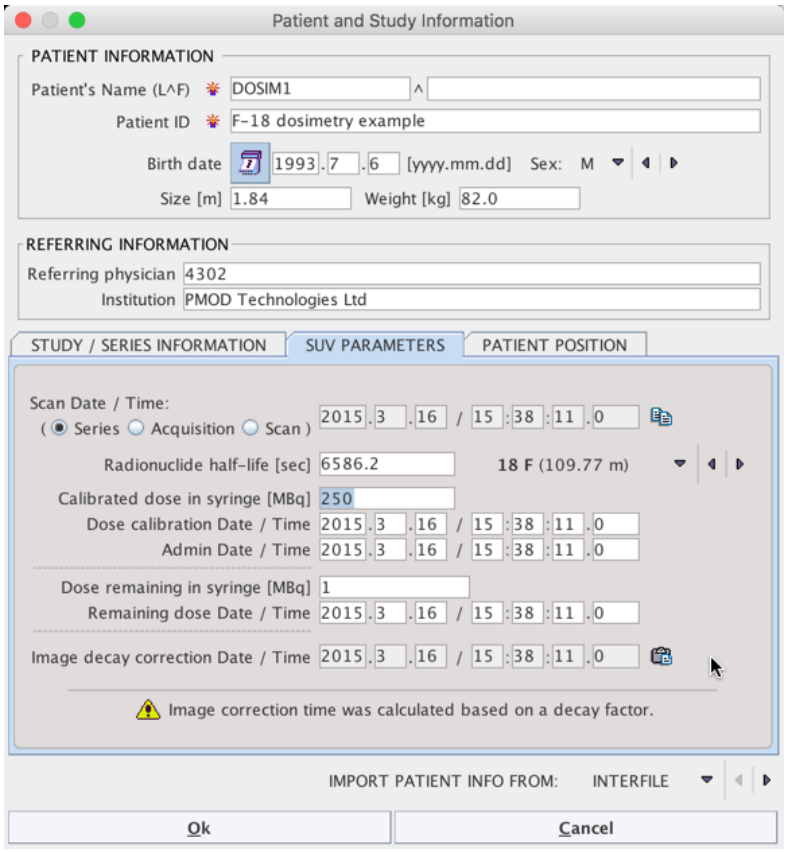
Before the new series is created and optionally decay corrected, the timing is displayed in a dialog window for confirmation and editing. In the example below, which was generated using **frames acquisition times,** there are gaps of about 40 seconds between the acquisitions. They occurred because the scanner had to be restarted for the subsequent whole-body acquisitions. Using **frames duration**, this information would have been missed.



Inspection of Dynamic Series

Once merging is complete, the user should examine the resulting dynamic series. By default, the suffix [MERGE_T] is added to the *Series Description*. This can be edited using the *Info & Edit* dialog window available with the button, then **Edit Patient / Study Info**.

Of particular importance for later residence time calculation is the injected dose of radiotracer and radionuclide half-life. These parameters can be edited on the *SUV PARAMETERS* tab. Note, the new dynamic image series must be saved in a suitable image format to maintain this information in the image header (e.g. DICOM). Radionuclide and Calibrated dose in syringe are used during the calculation of residence times in PKIN, and are written to the exported OLINDA .cas file. However, note that OLINDA does not interpret this information during loading.



Additionally, the user should check the image for movement between frames. This is particularly important where multiple scanning sessions were used, as positioning of the subject is very likely to change. The presence of movement or misalignment between organ positions across time influences the type of VOIs required in the next step.

VOI Definition in PBAS/Fuse It

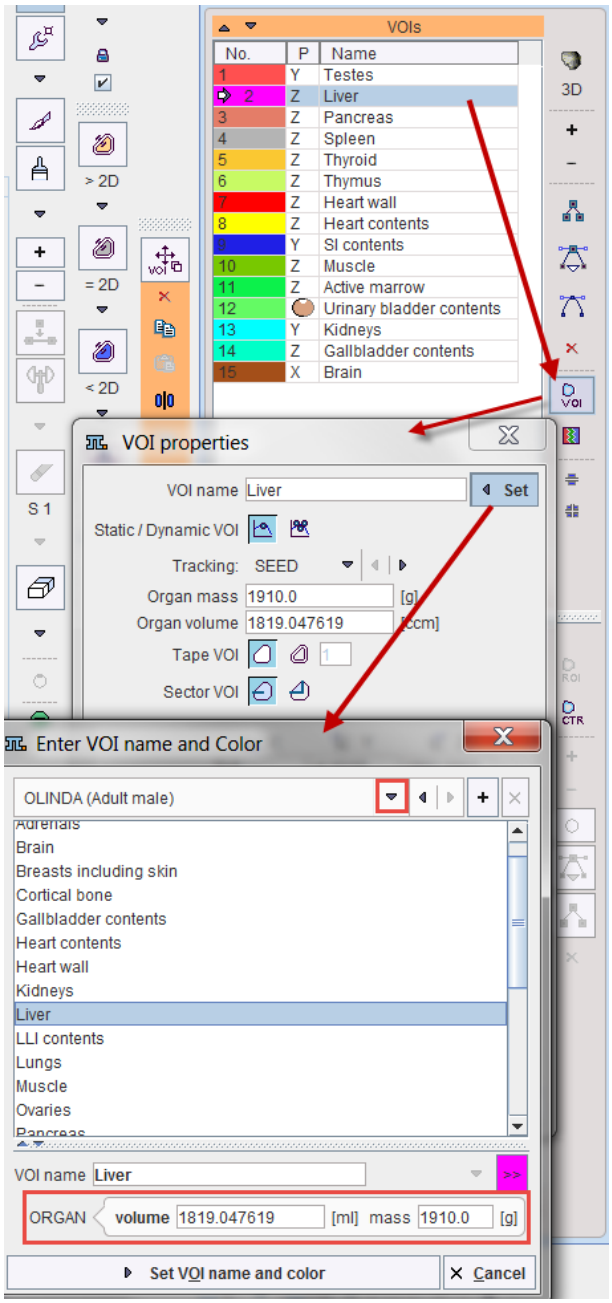
As a next step organ outlines (VOIs) need to be defined. PMOD offers various flexible approaches to overcome the challenges of this task. Organs with clear uptake can be addressed via iso-contouring. Others may require manual or semi-automatic outlining, or recourse to a matched anatomical data set. Thanks to the 4D-capabilites of PMOD VOIs, organ position and even shape changes between sequential acquisitions can be precisely tracked. Finally, using a drop-down list, each VOI can easily be assigned to an organ with properties corresponding to a particular dosimetry phantom anatomy.
The basics of VOI analysis and descriptions of the tools available are available in a dedicated section of the PMOD online manual: http://doc.pmod.com/pbas/640.htm, and are thus not covered in detail here. The relevant aspects of VOI Properties are described below.

VOI Properties

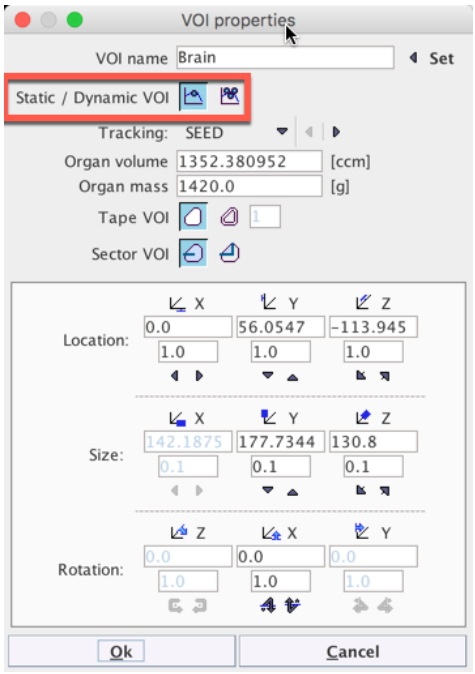
In the case of many organs and tissues required for dosimetry analysis it is not possible to make a complete delineation, because the organ/tissue is not clearly visible, or because (as in the case of muscle), it is not compact. In this case, standard organ volumes can be used in order to extrapolate VOI uptake to organ uptake. An organ can be assigned to a defined VOI as illustrated below:

1) Select the VOI in the list.
2) Open the VOI properties editor using the  button, and select the **Set** button.
3) Select an appropriate name list. For instance, the **OLINDA (Adult male)** contains the organ definitions (name, volume, mass) for the adult male phantom in OLINDA.
4) Choose the organ from the list. The predefined **ORGAN volume** and **mass** are shown and may be edited.
5) Close with the **Set VOI name and color** button.

An additional advantage of this workflow is that the VOI names correspond exactly to those required for export of an OLINDA/EXM case file at the end of the overall dosimetry analysis.



In the event of body/organ movement between frames, a dynamic (4D) VOI may be necessary. An initial VOI should be created, typically on the first time frame, then the *VOI Properties* should be set to *Dynamic*.



Static VOI  : If a VOI is static, the same VOI definition is applied and shown at all times.

Dynamic VOI  : For dynamic VOIs, a different VOI definition can be used at different times. Note that a dynamic VOI is only shown when viewing the images of the time frame it was defined on. As long as only one VOI is defined, statistics calculation will apply this VOI at all times as with a static VOI. However, as soon as VOIs have been defined at more than one time, it is required that VOIs are defined at all times. Here the VOI propagate functionality may be helpful (available on the *VOI Adjustment* tool bar).

Propagate option button  : Propagation for VOIs means copying a VOI from one time frame to another. This function is only available for dynamic series and VOIs set to dynamic in *VOI Properties*.

Dosimetry Organ List

Organs available in the OLINDA (Adult male), with default mass and volume, are listed below:

OLINDA (Adult male)	Organ volume (ml)	Organ mass (g)
Adrenals	15.52380952	16.3
Brain	1352.380952	1420.0
Breasts_including_skin	NA	NA

Gallbladder_contents	53.04761905	55.7
LLI_contents	136.1904762	143.0
SI_contents	1047.619048	1100.0
Stomach_contents	247.6190476	260.0
ULI_contents	220.952381	232.0
Heart_contents	432.3809524	454.0
Heart_wall	300.952381	316.0
Kidneys	284.7619048	299.0
Liver	1819.047619	1910.0
Lungs*	952.3809524	1000.0
Muscle	26923.0	28000.0
Ovaries	NA	NA
Pancreas	89.80952381	94.3
Red_marrow	1066.666667	1120.0
Cortical_bone	3809.52381	4000.0
Trabecular_bone	952.3809524	1000.0
Spleen	174.2857143	183.0
Testes	37.23809524	39.1
Thymus	19.9047619	20.9
Thyroid	19.71428571	20.7
Urinary_bladder_contents	200.952381	211.0
Uterus	NA	NA
Fetus	NA	NA
Placenta	NA	NA

Organ masses were taken from Stabin & Siegel (2003) [3]. Note: a tissue density of 1.05 g/ml was assumed for conversion of all organ masses to volume. Users may choose to use the lower density of 0.4 g/ml for lung.

Organs available in the OLINDA (Adult female), with default mass and volume, are listed below:

OLINDA (Adult female)	Organ volume (ml)	Organ mass (g)
Adrenals	13.33	14.0
Brain	1142.86	1200.0
Breasts_including_skin	392.38	412.0
Gallbladder_contents	47.62	50.0
LLI_contents	128.57	135.0
SI_contents	357.14	375.0
Stomach_contents	219.05	230.0
ULI_contents	200.0	210.0
Heart_contents	390.48	410.0
Heart_wall	228.57	240.0
Kidneys	261.9	275.0
Liver	1333.33	1400.0
Lungs*	761.9	800.0
Muscle	16346.0	17000.0
Ovaries	10.48	11.0
Pancreas	80.95	85.0
Red_marrow	1000.0	1050.0
Cortical_bone	2857.14	3000.0
Trabecular_bone	714.29	750.0
Spleen	142.86	150.0
Testes	NA	NA
Thymus	19.05	20.0
Thyroid	16.19	17.0
Urinary_bladder_contents	152.38	160.0

Uterus	75.24	79.0
Fetus	NA	NA
Placenta	NA	NA

Residence Times Calculation in PKIN

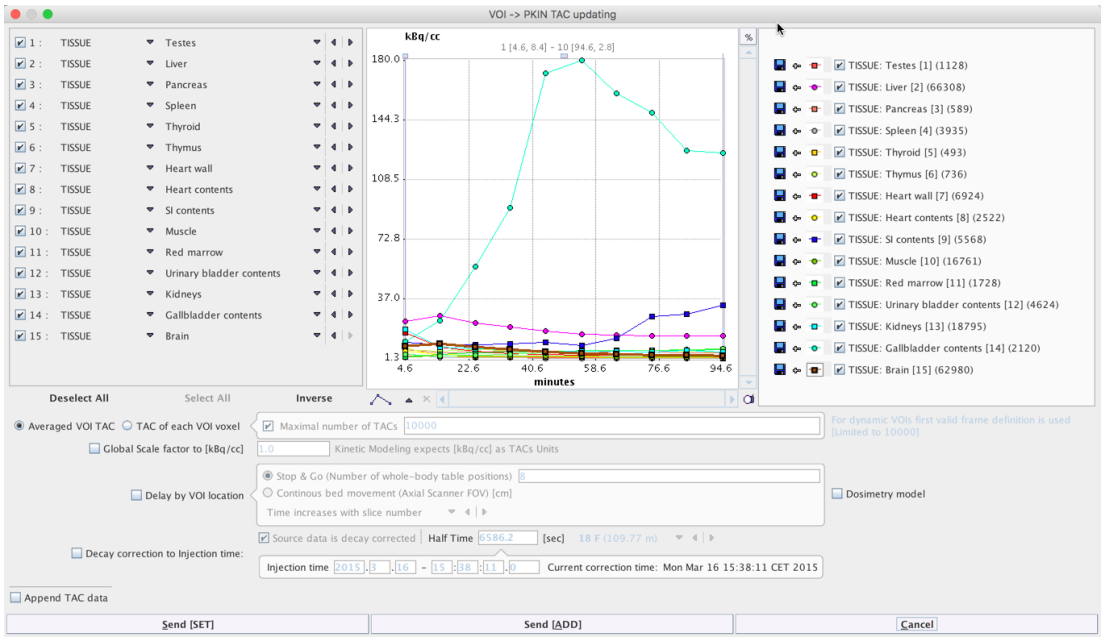
The radioactivity in each organ VOI is then averaged and transferred to PKIN, PMOD's kinetic modeling tool, as a time-activity curve (TAC). The TACs may feature time shifts to account for acquisitions with multiple bed positions. Before the actual number of disintegrations in the organs can be estimated, decay correction – if applied – has to be undone, and activity concentration data needs to be converted into total organ uptake. PMOD's workflow allows this process to be automated. Several integration approaches can be applied to the count rate curves generated: Discrete rectangular or trapezoidal integration followed by isotope decay, fitting of the declining part of the data with exponentials and algebraic integration, or a combination of both.

The OLINDA Residence Times model performs pre-processing steps for the calculation of the absorbed dose from diagnostic or therapeutic radiopharmaceuticals. Given the time-course of the activity in a volume of tissue, it calculates the Residence Time, which could in fact better be called the Normalized Cumulated Activity [9] to avoid confusion of its meaning. However, as it is widely used in literature, the notion Residence Time will be used in the remainder of this section. The residence time represents the total number of disintegrations occurring during an integration time, per unit of administered activity. Ideally, integration is performed from the time of administration to infinity.

The organ residence times resulting from the **OLINDA Residence Times** model can serve as input to a program such as OLINDA [4] for the actual calculation of the absorbed organ doses.

Time-Activity Curve Transfer

Following the definition of VOIs and assignment of VOI Properties as described in the previous section, the tracer time-activity curves (TACs) for each organ are calculated using the *TAC Export* button  . The *TAC Export dialog* window is opened.



The TACs are displayed in the central curve display area, and their inclusion in the transfer to PKIN can be toggled using the menu on the left.

Below the curve display area the time shift between actual acquisition of each organ can be configured. Such a time shift can be used to correct for the acquisition of multiple fields-of-view to create a whole body PET image.

Activating the **Delay by VOI location** button makes two options for time shift application available.

Stop & Go is intended for data acquired with multiple fields-of-view. The number of table positions used during whole body acquisition must be entered by the user, and the direction of scanning defined by setting **Time increases with slice number** or **Time decreases with slice number** (representing whether the subject was scanned from head to feet, or vice versa). Once activated, the time shift for each organ is calculated and displayed in the curve display area.

Continuous bed movement is applicable when the scanner supports whole body image acquisition through a continuously moving bed, such as the Siemens Biograph mCT Flow.

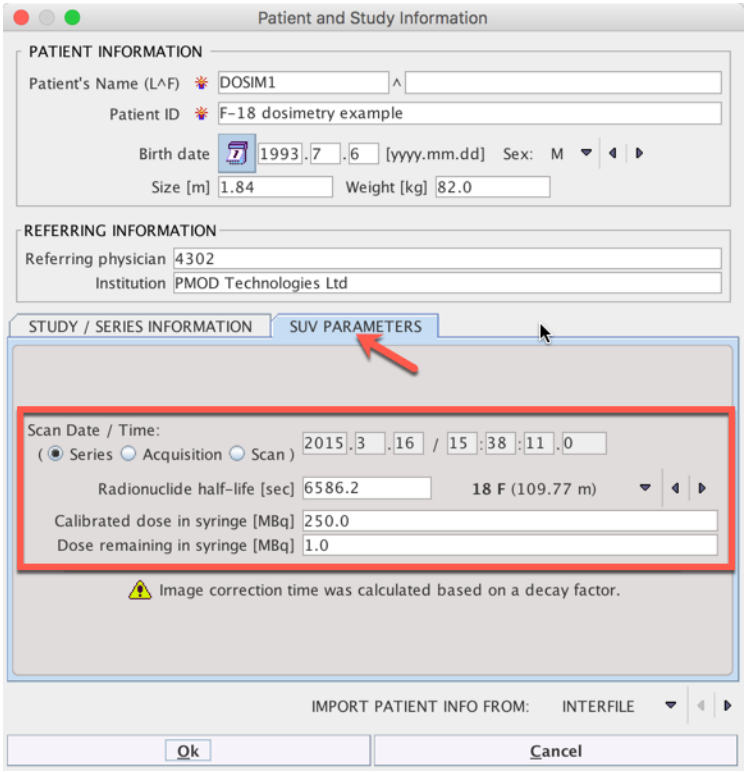
To the right of the time-shift dialog, the **Dosimetry model** button enables automated selection of the **Residence Times** model in PKIN following TAC transfer.

If decay correction was applied during merging, as described above, activation of **Decay correction to injection time** is unnecessary.

Finally, the TACs can be transferred to PKIN using either **Send (Set)** or **Send (Add)** buttons. **Send (Add)** will create a new tab if PKIN is already open.

Edit Patient

Depending on the method used to import the TACs into PKIN, isotope and activity information may or may not be available. **Radionuclide half-life** and C**alibrated dose in syringe** are necessary for *residence time* calculation. Transfer of TACs from VOI analysis in another PMOD module will also transfer patient data including SUV information. Loading of pre-saved TACs or TACs prepared as a text file will not include patient and SUV information. These parameters can be edited in the **Patient and Study Information** window as illustrated below. Activate **Edit Patient** in the **Tools** list, select **SUV PARAMETERS**, and enter **Radionuclide half-life** and **Pre-injected tracer activity**. Note that the activity needs to be calibrated to time 0 of the activity curve.

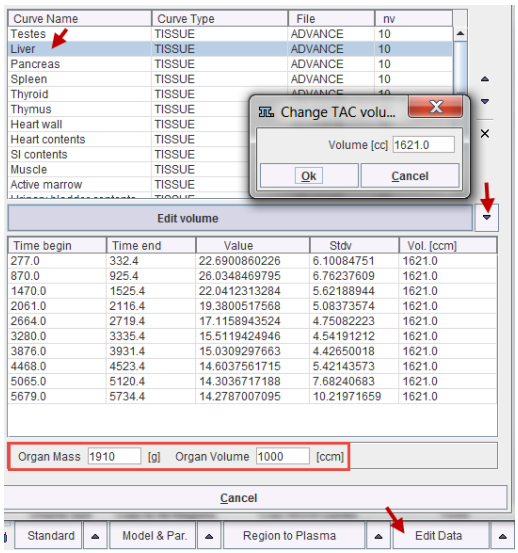


Edit Data

The regional VOI volume is available if the TAC was generated in PMOD's View tool and transferred to PKIN.

An alternative approach is to edit the VOI and organ volumes as follows:

1) Activate **Edit Data** in the **Tools** list
2) Select a region in the upper list.
3) Choose **Edit volume** from the curve tools
4) Enter the **Volume** of the VOI in the dialog window.
5) Change The **Organ Volume** in the lower part. (currently, Organ mass is not used for the calculation).
6) Close the **PKIN data explorer** with **Ok**.



Operational Equations

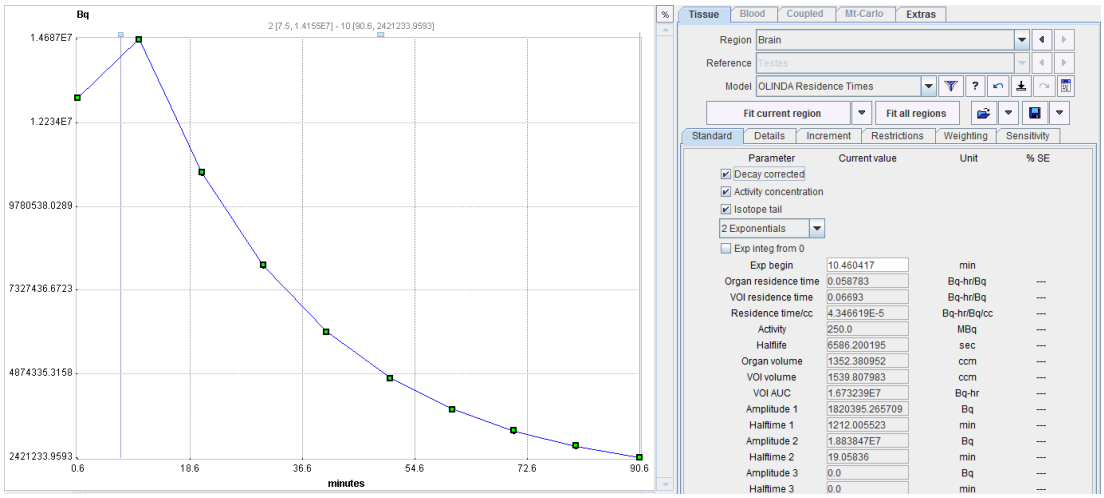
Given an activity A_0 applied to a subject, and a measured (not decay corrected) activity A(t) in an organ, the residence time t is calculated by

$$\tau = \frac{\int_0^\infty A(t)dt}{A_0}$$

Note that the unit of t is usually given as [Bq×hr/Bq]. The measured part of the organ activity can easily be numerically integrated by the trapezoidal rule. For the unknown remainder of A(t) until infinity it is a conservative assumption to apply the radioactive decay of the isotope. This exponential area can easily be calculated and added to the trapezoidal area. Alternatively, if the measured activity curve has a dominant washout shape, a sum of exponentials can be fitted to the to the measured data and the entire integral algebraically calculated.

Model Input Parameters

The **OLINDA Residence Times** model in PKIN supports both the trapezoidal integration approach as well as the use of fitted exponentials. It furthermore supports some practicalities such as conversion of an average activity concentration in [kBq/cc] to activity in [Bq], by multiplication with the VOI volume, and reversion of decay correction.



The **OLINDA Residence Times** model has 4 input parameters that need to be specified interactively by the user. These settings can easily be propagated from one region to all others with the **Model & Par** button.

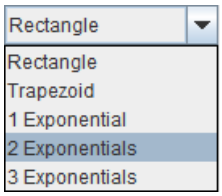
Decay corrected — Check this box if the loaded curves were decay corrected, as is usually the case for PET imaging studies. The **Halflife** of the radioisotope will be used to undo the decay correction.

Activity concentration — Check this box if the loaded curves represent activity concentration, rather than the total activity in a region. The **volume** of the region will be multiplied with the signal to calculate activity in [Bq].

Isotope tail — Check this box to use the radioactive decay shape for the integration from the end of the last frame to infinity. This option is only relevant if exponentials are fitted to the measurement.

For the **Rectangle** and **Trapezoid** methods it will always be enabled. For the exponentials it will also be enabled if the exponential halftime is longer than the isotope half-life (a warning will be recorded in the log).

Integration — The integration method can be selected in the option list:



The **Rectangle** method is the natural selection for PET values that represent the time average during the frame duration. If there are gaps between the PET frames, the uncovered area is approximated by the trapezoidal rule.

The **Trapezoid** method uses trapezoidal areas between the frame mid-times.

With an **Exponential** selection, the specified number of decaying exponentials is fitted to the measurements, and used for analytical integration. Note that samples marked as invalid are neglected in the fit.

Exp integ from 0 Check this box to use the exponential from time zero for the integration. If the box is unchecked, rectangular integration is used for samples before **Exp begin**.

Exp begin Defines the time (frame mid), from which point onwards the exponentials are fitted to the measurement.

Model Output Parameters

As soon as the **Fit Region** button is activated, the fits and calculations are performed, resulting in a list of parameters:

Organ residence time [Bq×hr/Bq] Total number of disintegrations in the organ volume from time 0 until infinity per unit injected activity. This is the main result and equal to **Residence time/cc*Organ Volume**. Note that it is zero as long as the **Organ volume** is not defined.

VOI residence time [Bq×hr/Bq] Total number of disintegrations in the regional VOI volume from time 0 until infinity per unit of injected activity, calculated as **VOI AUC/Activity**.

Residence Time/cc [Bq/cc×hr/Bq] Total number of disintegrations per unit volume in the region. Equal to **VOI residence time/VOI Volume**.

Activity [MBq] Administered activity. Shown for verification only.

Halflife [sec] Isotope halflife. Shown for verification only.

Organ Volume [ccm] Volume of the organ which corresponds to the regional VOI. Shown for verification only.

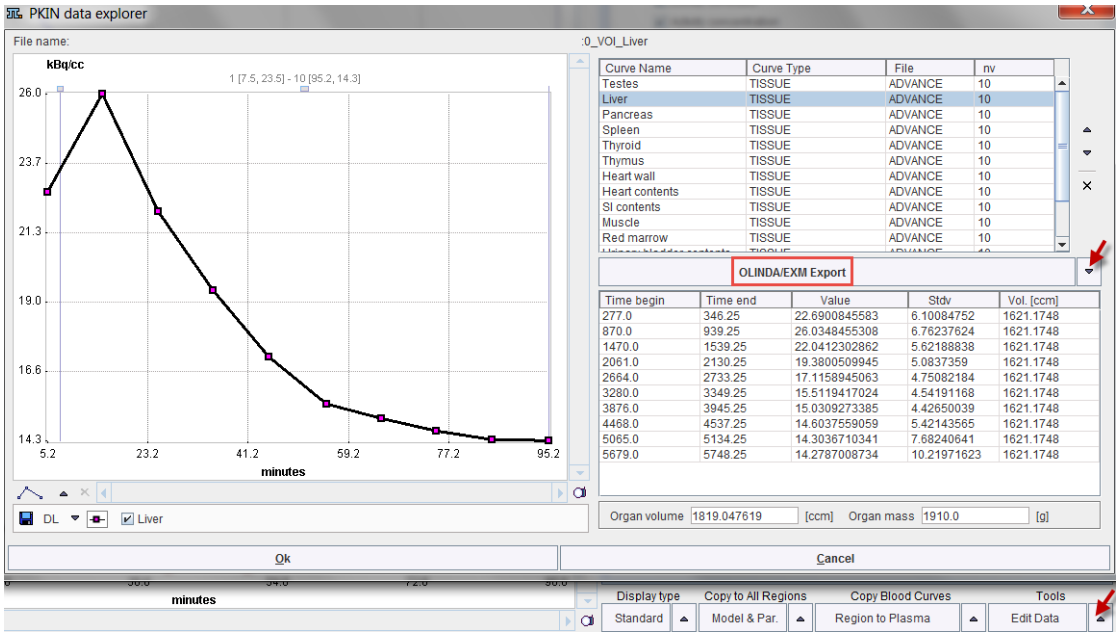
VOI Volume [ccm]	Volume of the VOI in which the uptake is measured. Shown for verification only.
VOI AUC [Bq×hr]	Integral of the activity curve from time 0 till infinity.
Amplitude 1, 2, 3 [Bq] **Halftime 1, 2, 3 [min]**	Amplitudes and halftimes of the fitted exponentials. In the case of 1 exponential a linear regression is applied, whereas iterative fitting is used with 2 or 3 exponentials.

OLINDA Case File Export

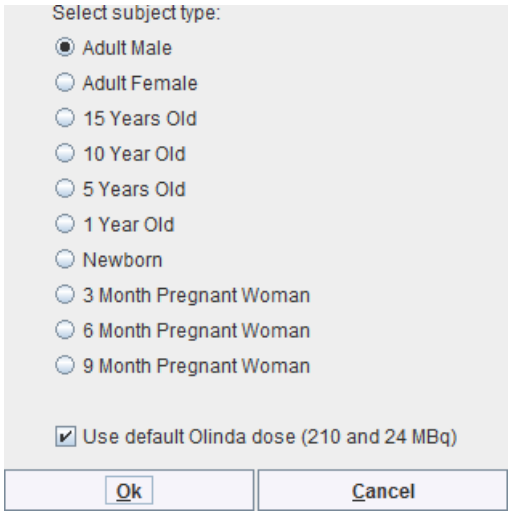
Using a dedicated facility in PKIN, the resulting residence times may be directly exported into an OLINDA/EXM case file. During this process, the complementary "Remainder in the Body" residence time is automatically calculated and added. OLINDA/EXM can then be started, the case retrieved, and the doses readily calculated.

After the **OLINDA Residence Times** model has been configured and fitted for all organs, a .cas file for direct import into OLINDA/EXM can be created as follows:

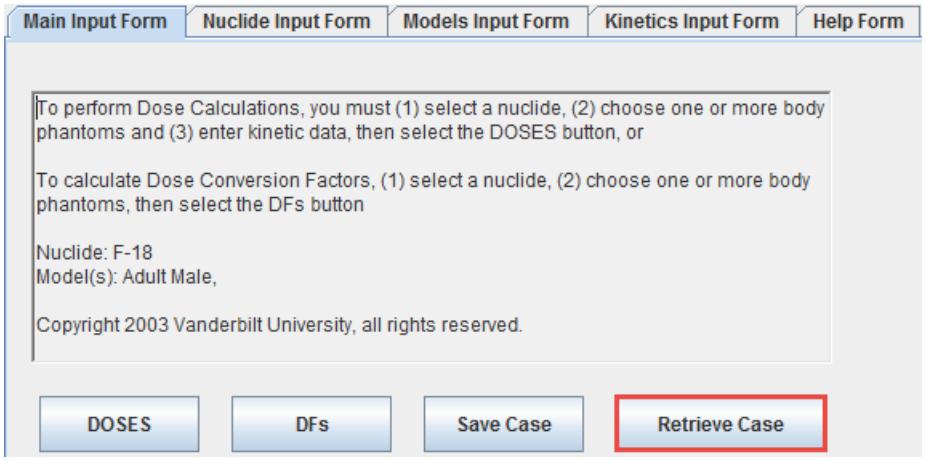
1) Select **Edit Data** from the **Tools** list in the lower right.
2) Switch the operation below the curve list to **OLINDA/EXM Export**.



3) The dialog window opened lists the phantoms supported by OLINDA/EXM. Please select the appropriate phantom, but note that OLINDA/EXM does not actually interpret this information during loading of the .cas file (as for radionuclide and injected dose). The option **Use default Olinda dose** should normally be on. Otherwise, the dose information in the patient SUV panel will be used. This will most probably cause problems upon import of the .cas file into OLINDA/EXM, because OLINDA/EXM crashes when the dose values are not integer values.



4) Finally, specify a location and a name for saving of the .cas file. This file can be loaded in OLINDA/EXM using the **Retrieve Case** button.



Note that the region names must be spelled exactly as below for the export/import to work properly:

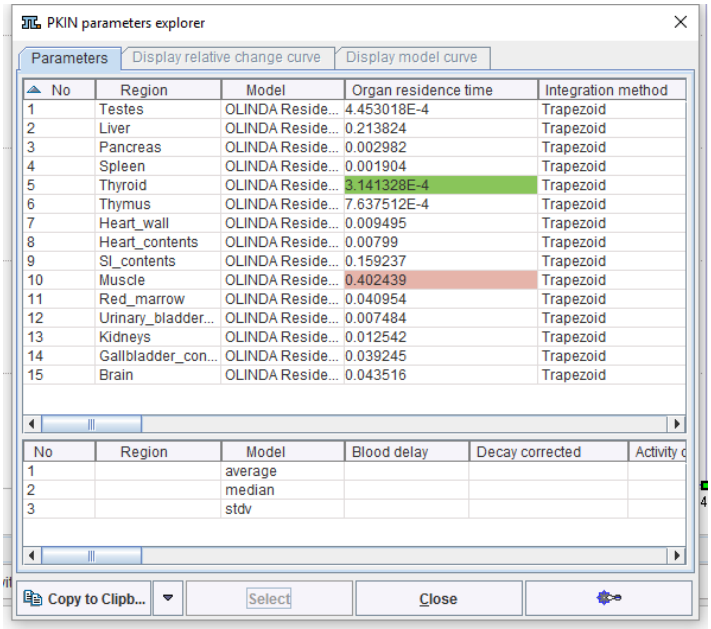
Adrenals
Brain
Breasts_including_skin
Gallbladder_contents
LLI_contents
SI_contents
Stomach_contents
ULI_contents
Heart_contents
Heart_wall
Kidneys
Liver
Lungs
Muscle
Ovaries

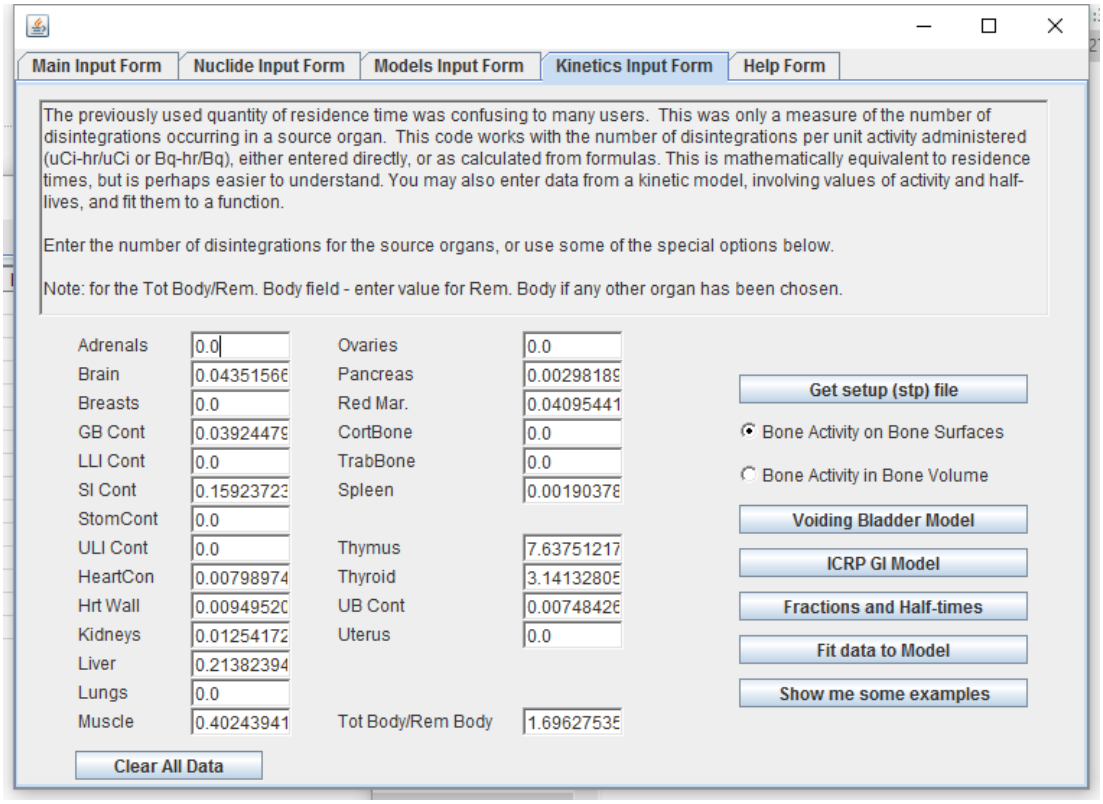
Pancreas
Red_marrow
Cortical_bone
Trabecular_bone
Spleen
Testes
Thymus
Thyroid
Urinary_bladder_contents
Uterus
Fetus
Placenta

Use of the *Dosimetry Organs list* in *VOI Properties*, as described earlier in this manual, ensures that the correct format is followed.

The difference between the injected activity and the activity accumulated in all organs is treated as the Remainder.

Residence times can be compared between PMOD and OLINDA using the View Parameters tool:




Main Input Form
Nuclide Input Form
Models Input Form
Kinetics Input Form
Help Form
The previously used quantity of residence time was confusing to many users. This was only a measure of the number of disintegrations occurring in a source organ. This code works with the number of disintegrations per unit activity administered (uCi-hr/uCi or Bq-hr/Bq), either entered directly, or as calculated from formulas. This is mathematically equivalent to residence times, but is perhaps easier to understand. You may also enter data from a kinetic model, involving values of activity and half-lives, and fit them to a function.
Enter the number of disintegrations for the source organs, or use some of the special options below.
Note: for the Tot Body/Rem. Body field - enter value for Rem. Body if any other organ has been chosen.
Adrenals 0.0
Brain 0.04351566
Breasts 0.0
GB Cont 0.03924479
LLI Cont 0.0
SI Cont 0.15923723
StomCont 0.0
ULI Cont 0.0
HeartCon 0.00798974
Hrt Wall 0.00949520
Kidneys 0.01254172
Liver 0.21382394
Lungs 0.0
Muscle 0.40243941
Ovaries 0.0
Pancreas 0.00298189
Red Mar. 0.04095441
CortBone 0.0
TrabBone 0.0
Spleen 0.00190378
Thymus 7.63751217
Thyroid 3.14132805
UB Cont 0.00748426
Uterus 0.0
Tot Body/Rem Body 1.69627535
Clear All Data
Get setup (stp) file
Bone Activity on Bone Surfaces
Bone Activity in Bone Volume
Voiding Bladder Model
ICRP GI Model
Fractions and Half-times
Fit data to Model
Show me some examples

References

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