

## RevK

### Reverse dosimetry and PBPK prediction

NTUA, INERIS

OpenRiskNet: Open e-Infrastructure to Support Data Sharing, Knowledge Integration and *in silico* Analysis and Modelling in Risk Assessment  
Project Number 731075

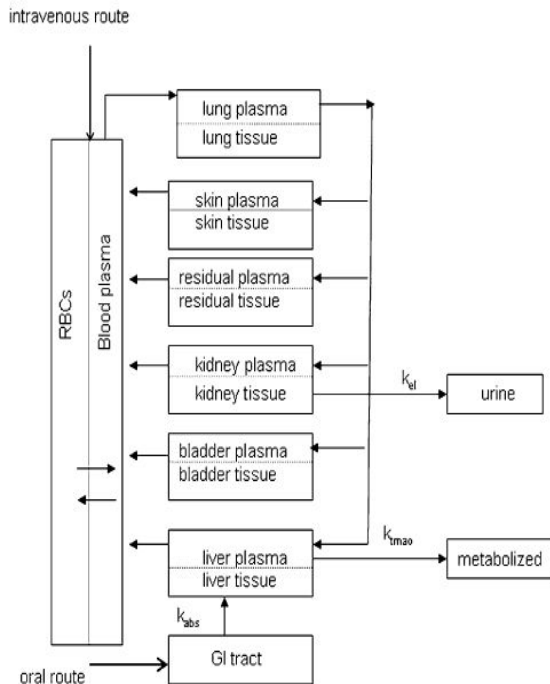


# PBPK modelling in REVK

PBPK modelling is offered through the integration of 2 modelling environments:

- **PKSIM** (over API): extensive, industry strength, open-source software, fixed model type
- **httk** (over API and Jaqpot 5 UI): R package from US EPA, more capabilities and greater modelling freedom
- **JaqpotforR**: deploy PBPK model directly from R

# PBPK model: Multi-compartment model (System of Ordinary Differential Equations, ODEs)



Non-metabolizing compartments:

$$V_{bl}^i \frac{dC_v^i(t)}{dt} = Q_i (C_{art}(t) - C_v^i(t)) - \pi_i \left( C_v^i(t) - \frac{C^i(t)}{P_i} \right)$$

$$V^i \frac{dC^i(t)}{dt} = \pi_i \left( C_v^i(t) - \frac{C^i(t)}{P_i} \right)$$

Metabolizing or excretion compartments:

$$V_{bl}^i \frac{dC_v^i(t)}{dt} = Q_i (C_{art}(t) - C_v^i(t)) - \pi_i \left( C_v^i(t) - \frac{C^i(t)}{P_i} \right) - r_{ex}^i (C_v^i(t)) V_{bl}^i$$

$$V^i \frac{dC^i(t)}{dt} = \pi_i \left( C_v^i(t) - \frac{C^i(t)}{P_i} \right) - r_{met}^i (C^i(t)) V^i$$

Blood:

$$V^{pl} \frac{dC^{pl}(t)}{dt} = u(t) + \sum_{i \in I_0 \cup I_1} Q_i C_v^i(t) + \pi_{rbc} C^{rbc}(t) - \pi_{pl} C^{pl}(t) - Q_{pl} C^{pl}(t)$$

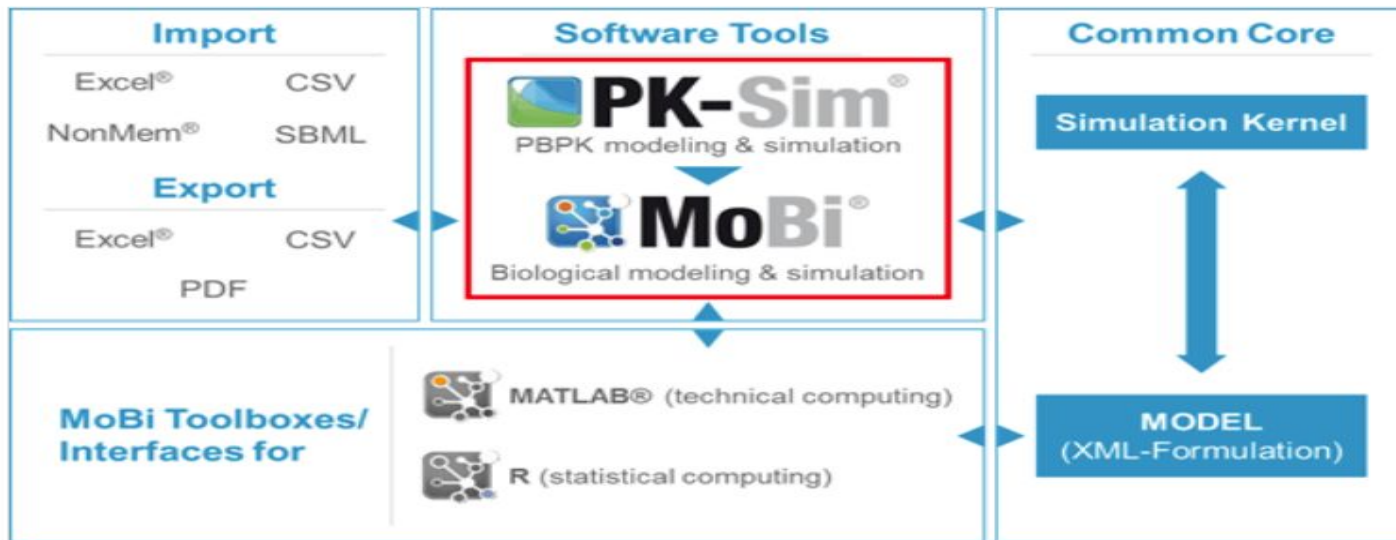
$$V^{rbc} \frac{dC^{rbc}(t)}{dt} = \pi_{pl} C^{pl}(t) - \pi_{rbc} C^{rbc}(t)$$

Lung:

$$V_{bl}^{lu} \frac{dC_{art}^{lu}(t)}{dt} = Q_{lu} (C^{pl}(t) - C_{art}^{lu}(t)) - \pi_{lu} \left( C_{art}^{lu}(t) - \frac{C^{lu}(t)}{P_{lu}} \right)$$

$$V^{lu} \frac{dC^{lu}(t)}{dt} = \pi_{lu} \left( C_{art}^{lu}(t) - \frac{C^{lu}(t)}{P_{lu}} \right)$$

# Open Systems Pharmacology Suite with PK-Sim and MoBi



<http://www.systems-biology.com/products/pk-sim.html>

# PKSIM modelling in Jaqpot API

The screenshot displays the Swagger UI for the Jaqpot API. The browser address bar shows the URL: `api-jaqpot.prod.openrisknet.org/jaqpot/swagger/#/biokinetics/trainBiokineticsModel`. The interface lists several API endpoints:

- PUT** `/services/bibtex/{id}`: Places a new BibTeX entry at a particular URI.
- DELETE** `/services/bibtex/{id}`: Deletes a particular BibTeX resource.

The **biokinetics** section is expanded, showing a **POST** endpoint:

- POST** `/services/biokinetics/pksim/createmodel`: Creates Biokinetics model with PKSim.

Description: Creates a biokinetics model given a pksim .xml file and demographic data.

**Parameters**

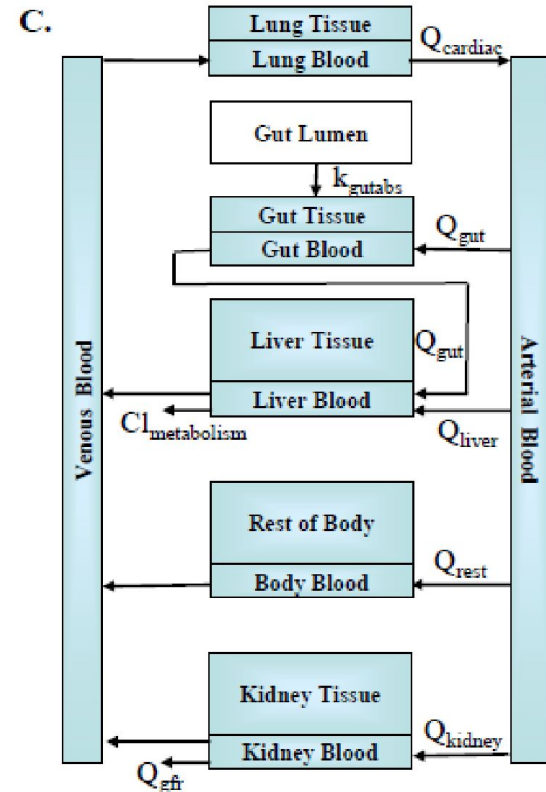
Name	Description
Authorization <code>string</code> (header)	Authorization token

**Request body** (multipart/form-data)

<https://api-jaqpot.prod.openrisknet.org/jaqpot/swagger/#/biokinetics>

# The htk R package

- Four toxicokinetic models have been created in this package, ranging from single-compartmental models to full PBTK models.
- Structure-derived physicochemical properties and species-specific physiological data.
- The package can currently use human *in vitro* data to make predictions for 553 chemicals in humans, rats, mice, dogs, and rabbits, including 94 pharmaceuticals and 415 ToxCast chemicals.
- The package contains tools for Monte Carlo sampling and reverse dosimetry along with functions for the analysis of concentration vs. time simulations.
- htk support oral or iv dosing.



<https://cran.r-project.org/web/packages/htk/index.ht>

# httk modelling workflow in Jaqpot API (example)

This example uses the Jaqpot httk service to create a concentration-time simulation and the AUC curve for 10 days after administering a single dose of 0.1mg/Kg of bisphenolA to a human (weight 70 Kg)

The screenshot shows the 'biokinetics' API interface. It features two POST endpoints: '/services/biokinetics/pksim/createmodel' and '/services/biokinetics/httk/createmodel'. The second endpoint is selected, showing its description 'Creates an httk biokinetics Model'. Below this, there is a 'Parameters' section with a table for 'Name' and 'Description'. The table has one entry: 'Authorization token' with the description 'Authorization token'. The 'Request body' section is at the bottom, showing 'application/x-www-form-urlencoded' as the selected format.

Name	Description
Authorization token (header)	Authorization token

Input dataset:

```
{"chem.name":["bisphenolA"],"species":["Human"],"days":[10],"dose":[0.1]}
```

Output dataset

```
"Substance","Agutlumen","Atubules","Cplasma","Cart","Ckidney","Crest","Cliver","Cgut","Ametabolized","Cven","time","Clung","AUC"
"1","2355.4749","0","0","0","0","0","0","0","0","0","0","0","0"
"2","1365.8025","0.1105","13.1333","9.2261","59.1467","2.8637","277.1605","258.6781","0","9.5873","0.0104","9.3056","0.0598"
"3","791.9496","0.5618","20.3668","14.7784","106.6832","11.1376","356.6631","205.9325","0","14.8678","0.0208","14.501","0.2427"
"4","459.2054","1.1426","21.3648","15.6043","115.3854","19.338","318.4675","156.002","0","15.5963","0.0312","15.2265","0.4629"
```

Tutorial available at: <https://drive.google.com/drive/u/0/folders/1mA2xudmZXeHcav60NpDeJubzvwFHkKwI>

# JaqpotforR


```
> library(JaqpotforR)




> deploy.pbpk.jaqpot(dataframe = user_input, covariate_model = covariates,
  odes = odes, comp = comp_names)
Base path of jaqpot *etc: https://api.jaqpot.org/ : https://api.jaqpot.org/

[1] "Model created. The id is: sjXlNK6Ts0TfdfB7q4wP"
```




# PBPK modelling through Jaqpot GUI

 Jaqpote



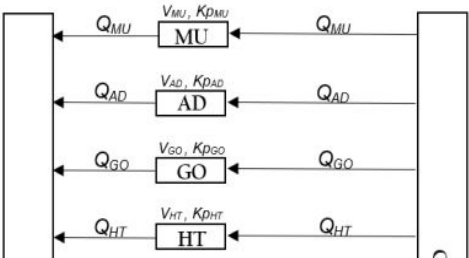
OverviewDataPredict / ValidateDiscussion



**MODEL**  
Title:  
**Diazepam**  
**PBPK**  
Owner: pantelispanka  
**Description:**  
A 14 compartment model with permeability-limited assumption of DIAZEPAM for Human

**Diazepam PBPK model**

The detailed description of the PBPK model used can be found in [Gueorgueiva et al., 2006](#). Its schematic representation can be seen in the following figure. It consists of 11 compartments describing the concentration of the drug in various tissues, namely liver (*LI*), kidney (*KI*), brain (*BR*), intestine (*IN*), stomach (*ST*), muscle (*MU*), adipose (*AD*), skin (*SK*), gonads (*GO*), heart (*HT*) and lungs (*LU*), one compartment to model the rest of the body (*RE*) as well as two blood pools; venous (*VEN*) and arterial (*ART*). The parameters of the model are divided into drug-dependent and physiological (drug-independent) parameters. The first category comprises eleven tissue-to-plasma partition coefficients ( $K_p$ ), fraction unbound in plasma ( $f_u$ ), blood-to-plasma ratio ( $R$ ), and intrinsic hepatic clearance ( $CL_{int}$ , in L/h). The physiological parameters of the model are simply the regional tissue blood flows ( $Q$ ) and tissue volumes ( $V$ ).



# PBPK modelling through Jaqpot GUI

