Package 'httk'

February 3, 2016

Title High-Throughput Toxicokinetics

Version 1.4

Date 2016-1-26

Author John Wambaugh and Robert Pearce, Schmitt method implementation by Jimena Davis, dynamic model adapted from code by R. Woodrow Setzer, Rabbit parameters from Nisha Sipes

Suggests ggplot2

Description Functions and data tables for simulation and statistical analysis of chemical toxicokinetics (``TK'') using data obtained from relatively high throughput, in vitro studies. Both physiologically-based (``PBTK'') and empirical (e.g., one compartment) ``TK'' models can be parameterized for several hundred chemicals and multiple species. These models are solved efficiently, often using compiled (C-based) code. A Monte Carlo sampler is included for simulating biological variability and measurement limitations. Functions are also provided for exporting ``PBTK'' models to ``SBML'' and ``JARNAC'' for use with other simulation software. These functions and data provide a set of tools for in vitro-in vivo extrapolation (``IVIVE'') of high throughput screening data (e.g., ToxCast) to real-world exposures via reverse dosimetry (also known as ``RTK'').

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License GPL-3

LazyData true

Imports deSolve, msm

Depends R (>= 2.10)

NeedsCompilation yes

Repository CRAN

Date/Publication 2016-02-03 01:14:25

R topics documented:

`add_chemtable` *Add a table of chemical information for use in making httk predictions.*

Description

This function adds chemical-specific information to the table chem.physical_and_invitro.data. This table is queried by the model parameterization functions when attempting to parameterize a model, so adding sufficient data to this table allows additional chemicals to be modeled.

Usage

```
add_chemtable(new.table, data.list, current.table=NULL,
              reference=NULL,species=NULL, overwrite=F)
```

Arguments

new.table	Object of class data.frame containing one row per chemical, with each chemical minimally by described by a CAS number.
data.list	This list identifies which properties are to be read from the table. Each item in the list should point to a column in the table new.table. Valid names in the list are: 'Compound', 'CAS', 'DSSTox.GSID' 'SMILES.desalt', 'Reference', 'Species', 'MW', 'logP', 'pKa_Donor', 'pKa_Accept', 'logMA', 'Clint', 'Clint.pValue', 'Funbound.plasma', 'Fgutabs', 'Rblood2plasma'. Note that Rblood2plasma (Ratio blood to plasma) is currently not used.
current.table	This is the table to which data is being added.
reference	This is the reference for the data in the new table. This may be omitted if a column in data.list gives the reference value for each chemical.
species	This is the species for the data in the new table. This may be omitted if a column in data.list gives the species value for each chemical or if the data is not species-specific (e.g., MW).
overwrite	If overwrite=TRUE then data in current.table will be replaced by any data in new.table that is for the same chemical and property. If overwrite=FALSE (DEFAULT) then new data for the same chemical and property is ignored.

Value

data.frame	A new data.frame containing the data in current.table augmented by new.table

Author(s)

John Wambaugh

Examples

```
my.new.data <- as.data.frame(c("A","B","C"),stringsAsFactors=FALSE)
my.new.data <- cbind(my.new.data,as.data.frame(c("111-11-5","222-22-0","333-33-5"),
                     stringsAsFactors=FALSE))
my.new.data <- cbind(my.new.data,as.data.frame(c(200,200,200)))
my.new.data <- cbind(my.new.data,as.data.frame(c(2,3,4)))
my.new.data <- cbind(my.new.data,as.data.frame(c(0.01,0.02,0.3)))
my.new.data <- cbind(my.new.data,as.data.frame(c(0,10,100)))
colnames(my.new.data) <- c("Name","CASRN","MW","LogP","Fup","CLint")

chem.physical_and_invitro.data <- add_chemtable(my.new.data,
                                  current.table=chem.physical_and_invitro.data,
                                  data.list=list(
                                  Compound="Name",
                                  CAS="CASRN",
                                  MW="MW",
```

```
                                    logP="LogP",
                                    Funbound.plasma="Fup",
                                    Clint="CLint"),
                                    species="Human",
                                    reference="MyPaper 2015")
parameterize_steadystate(chem.name="C")
calc_mc_oral_equiv(10,chem.name="B")
```

`calc_analytic_css` *Calculate the analytic steady state concentration.*

Description

This function calculates the analytic steady state plasma or venous blood concentrations as a result of infusion dosing for the three compartment and multiple compartment PBTK models.

Usage

```
calc_analytic_css(chem.name=NULL,chem.cas = NULL,parameters=NULL,daily.dose=1,
                  output.units='uM',model = 'pbtk',species='Human',
                  concentration='plasma',suppress.messages=F,
                  recalc.blood2plasma=F,default.to.human=F)
```

Arguments

`chem.name`	Either the chemical name, CAS number, or the parameters must be specified.
`chem.cas`	Either the chemical name, CAS number, or the parameters must be specified.
`parameters`	Chemical parameters from parameterize_pbtk (for model = 'pbtk'), parameterize_3comp (for model = '3compartment), parmeterize_1comp(for model = '3compartmentss') or parameterize_steadystate (for model = '1compartment'), overrides chem.name and chem.cas.
`daily.dose`	Total daily dose, mg/kg BW.
`output.units`	Units for returned concentrations, defaults to uM (specify units = "uM") but can also be mg/L.
`model`	Model used in calculation, 'pbtk' for the multiple compartment model,'3compartment' for the three compartment model, '3compartmentss' for the three compartment steady state model, and '1compartment' for one compartment model.
`species`	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
`suppress.messages`	Whether or not the output message is suppressed.
`concentration`	Desired concentration type, 'blood' or default 'plasma'.
`recalc.blood2plasma`	Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters, calculated with hematocrit, Funbound.plasma, and Krbc2pu.
`default.to.human`	Substitutes missing rat values with human values if true.

Details

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Value

`Steady state concentration`

Author(s)

Robert Pearce

References

Schmitt W. "General approach for the calculation of tissue to plasma partition coefficients." Toxicology In Vitro, 22, 457-467 (2008).

Examples

```
calc_analytic_css(chem.name='Bisphenol-A',output.units='mg/L',
                  model='3compartment',concentration='blood')
```

---

calc_css *Find the steady state concentration and the day it is reached.*

Description

This function finds the day a chemical comes within the specified range of the analytical steady state venous blood or plasma concentration(from calc_analytic_css) for the multiple compartment, three compartment, and one compartment models, the fraction of the true steady state value reached on that day, the maximum concentration, and the average concentration at the end of the simulation.

Usage

```
calc_css(parameters=NULL,chem.name=NULL,chem.cas=NULL,species="Human", f = .01,
         daily.dose=1, doses.per.day=3,days = 10,output.units = "uM",
       concentration='plasma',suppress.messages=F,model='pbtk',default.to.human=F,
         f.change=0.00001,...)
```

Arguments

`chem.name`	Either the chemical name, CAS number, or parameters must be specified.
`chem.cas`	Either the chemical name, CAS number, or parameters must be specified.
`f`	Fractional distance from the final steady state concentration that the average concentration must come within to be considered at steady state.

parameters	Chemical parameters from parameterize_pbtk function, overrides chem.name and chem.cas.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
daily.dose	Total daily dose, mg/kg BW.
doses.per.day	Number of doses per day.
days	Initial number of days to run simulation that is multiplied on each iteration.
output.units	Units for returned concentrations, defaults to uM (specify units = "uM") but can also be mg/L.
concentration	Desired concentration type, 'blood' or default 'plasma'.
suppress.messages	Whether or not to suppress messages.
model	Model used in calculation, 'pbtk' for the multiple compartment model,'3compartment' for the three compartment model, '3compartmentss' for the three compartment steady state model, and '1compartment' for one compartment model.
default.to.human	Substitutes missing animal values with human values if true (hepatic intrinsic clearance or fraction of unbound plasma).
f.change	Fractional change of daily steady state concentration reached to stop calculating.
...	Additional arguments passed to model solver (default of solve_pbtk).

Details

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Value

frac	Fraction of the true steady state concentration reached on the day steady state is reached.
max	The maximum concentration of the simulation.
avg	The average concentration on the final day of the simulation.
the.day	The day the average concentration comes within 100 * p percent of the true steady state concentration.

Author(s)

Robert Pearce

Examples

```
parms <- parameterize_pbtk(chem.name='Bisphenol-A')
calc_css(parms,concentration='blood')
calc_css(chem.name='Bisphenol-A',doses.per.day=5,f=.001,output.units='mg/L')
```

`calc_elimination_rate` *Calculate the elimination rate for a one compartment model.*

Description

This function calculates an elimination rate from the three compartment steady state model where elimination is entirely due to metablism by the liver and glomerular filtration in the kidneys.

Usage

```
calc_elimination_rate(chem.cas=NULL,chem.name=NULL,parameters=NULL,species="Human",
                      suppress.messages=F,default.to.human=F)
```

Arguments

`chem.name`	Either the chemical name or the cas number must be specified.
`chem.cas`	Either the cas number or the chemical name must be specified.
`parameters`	Chemical parameters from parameterize_steadystate or 1compartment function, overrides chem.name and chem.cas.
`species`	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
`suppress.messages`	Whether or not the output message is suppressed.
`default.to.human`	Substitutes missing animal values with human values if true.

Details

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Value

`Elimination rate`	Units of 1/h.

Author(s)

John Wambaugh

Examples

```
calc_elimination_rate(chem.name="Bisphenol A")
calc_elimination_rate(chem.name="Bisphenol A",species="Rat")
calc_elimination_rate(chem.name="Bisphenol A",species="Rabbit")
calc_elimination_rate(chem.cas="80-05-7")
```

calc_hepatic_clearance *Calculate the hepatic clearance.*

Description

This function calculates the hepatic clearance for a well-stirred model or other type if specified.

Usage

```
calc_hepatic_clearance(chem.name=NULL,chem.cas=NULL,parameters=NULL,species='Human',
                       hepatic.model='well-stirred',suppress.messages=F)
```

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
parameters	Chemical parameters from parameterize_steadystate function, overrides chem.name and chem.cas.
hepatic.model	Model used in calculating hepatic clearance, unscaled, parallel tube, dispersion, or default well-stirred.
suppress.messages	Whether or not to suppress the output message.

Details

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Value

Hepatic Clearance
: Units of L/h/kg BW.

Author(s)

John Wambaugh

Examples

```
calc_hepatic_clearance(chem.name="Ibuprofen")
```

`calc_ionization` *Calculate the ionization.*

Description

This function calculates the ionization of a compound at a given pH. The pKa's are either entered as parameters or taken from a specific compound in the package.

Usage

```
calc_ionization(chem.cas=NULL,chem.name=NULL,pH=NULL,pKa_Donor=NA,pKa_Accept=NA)
```

Arguments

`chem.name`	Either the chemical name or the CAS number must be specified.
`chem.cas`	Either the chemical name or the CAS number must be specified.
`pH`	pH where ionization is evaluated.
`pKa_Donor`	Compound H dissociation equilibirum constant(s). Overwrites chem.name and chem.cas.
`pKa_Accept`	Compound H association equilibirum constant(s). Overwrites chem.name and chem.cas.

Details

The fractions are calculated by determining the coefficients for each species and dividing the particular species by the sum of all three. The positive, negative and zwitterionic/neutral coefficients are given by:

$$zwitter/netural = 1$$

$$for(iin1:pkabove)negative = negative + 10^(i * pH - pKa1 - ... - pKai)$$

$$for(iin1:pkbelow)positive = positive + 10^(pKa1 + ... + pKai - i * pH)$$

where i begins at 1 and ends at the number of points above(for negative) or below(for positive) the neutral/zwitterionic range. The neutral/zwitterionic range is either the pH range between 2 pKa's where the number of acceptors above is equal to the number of donors below, everything above the pKa acceptors if there are no donors, or everything below the pKa donors if there are no acceptors. Each of the terms in the sums represent a different ionization.

Value

`fraction_neutral`
: fraction of compound neutral

`fraction_charged`
: fraction of compound charged

`fraction_negative`
: fraction of compound negative

`fraction_positive`
: fraction of compound positive

`fraction_zwitter`
: fraction of compound zwitterionic

Author(s)

Robert Pearce

Examples

```
calc_ionization(chem.name='bisphenola',pH=7.4)
calc_ionization(pKa_Donor=8,pKa_Accept=c(1,4),pH=9)
```

`calc_mc_css` *Find the monte carlo steady state concentration.*

Description

This function finds the analytical steady state plasma concentration(from calc_analytic_css) for the three compartment steady state model (model = '3compartmentss') using a monte carlo simulation (monte_carlo).

Usage

```
calc_mc_css(chem.cas=NULL,chem.name=NULL,parameters=NULL,daily.dose=1,
          which.quantile=0.95,species="Human",output.units="mg/L",suppress.messages=F,
            censored.params=list(Funbound.plasma=list(cv=0.3,lod=0.01)),
            vary.params=list(BW=0.3,Vliverc=0.3,Qgfrc=0.3,Qtotal.liverc=0.3,
            million.cells.per.gliver=0.3,Clint=0.3),samples=1000,
            return.samples=F)
```

Arguments

`chem.name`	Either the chemical parameters, name, or the CAS number must be specified.
`chem.cas`	Either the CAS number, parameters, or the chemical name must be specified.
`parameters`	Parameters from parameterize_steadystate.
`daily.dose`	Total daily dose, mg/kg BW/day.
`which.quantile`	Which quantile from Monte Carlo simulation is requested. Can be a vector.
`species`	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
`output.units`	Plasma concentration units, either uM or default mg/L.
`suppress.messages`	Whether or not to suppress output message.

`censored.params`
: The parameters listed in censored.params are sampled from a normal distribution that is censored for values less than the limit of detection (specified separately for each paramter). This argument should be a list of sub-lists. Each sublist is named for a parameter in "parameters" and contains two elements: "CV" (coefficient of variation) and "LOD" (limit of detection, below which parameter values are censored. New values are sampled with mean equal to the value in "parameters" and standard deviation equal to the mean times the CV. Censored values are sampled on a uniform distribution between 0 and the limit of detection.

`vary.params`
: The parameters listed in vary.params are sampled from a normal distribution that is truncated at zero. This argument should be a list of coefficients of variation (CV) for the normal distribution. Each entry in the list is named for a parameter in "parameters". New values are sampled with mean equal to the value in "parameters" and standard deviation equal to the mean times the CV.

`samples`
: Number of samples generated in calculating quantiles.

`return.samples`
: Whether or not to return the vector containing the samples from the simulation instead of the selected quantile.

Details

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Author(s)

John Wambaugh

Examples

```
calc_mc_css(chem.name='Bisphenol A',output.units='uM',which.quantile=.9)
```

---

calc_mc_oral_equiv *Calculate Monte Carlo Oral Equivalent Dose*

Description

This functions converts a chemical plasma concetration to an oral equivalent dose using a concentration obtained from calc_mc_css.

Usage

```
calc_mc_oral_equiv(conc,chem.name=NULL,chem.cas=NULL,which.quantile=0.95,
                   species="Human",input.units='uM',output.units='mg',
                   suppress.messages=F,return.samples=F,...)
```

Arguments

conc	Bioactive in vitro concentration in units of uM.
chem.name	Either the chemical name or the CAS number must be specified.
chem.cas	Either the CAS number or the chemical name must be specified.
suppress.messages	Suppress text messages.
input.units	Units of given concentration, default of uM but can also be mg/L.
output.units	Units of dose, default of 'mg' for mg/kg BW/ day or 'mol' for mol/ kg BW/ day.
which.quantile	Which quantile from Monte Carlo simulation is requested. Can be a vector.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
return.samples	Whether or not to return the vector containing the samples from the simulation instead of the selected quantile.
...	Additional parameters passed to calc_mc_css.

Details

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Value

Equivalent dose in specified units, default of mg/kg BW/day.

Author(s)

John Wambaugh

Examples

```
calc_mc_oral_equiv(0.1,chem.cas="34256-82-1")

calc_mc_oral_equiv(0.1,chem.cas="34256-82-1",which.quantile=c(0.05,0.5,0.95))
```

---

calc_rblood2plasma *Calculate the constant ratio of the blood concentration to the plasma concentration.*

Description

This function calculates the constant ratio of the blood concentration to the plasma concentration. It uses the hematocrit and the red blood cell (RBC) parition coefficient as predicted by the Schmitt (2008) method.

Usage

```
calc_rblood2plasma(chem.cas=NULL, chem.name=NULL, default.to.human=F, species="Human")
```

Arguments

chem.name	Either the chemical name or the CAS number must be specified.
chem.cas	Either the CAS number or the chemical name must be specified.
default.to.human	Substitutes missing animal values with human values if true.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").

Details

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Author(s)

John Wambaugh

References

Schmitt W. "General approach for the calculation of tissue to plasma partition coefficients." Toxicology In Vitro, 22, 457-467 (2008).

Examples

```
calc_rblood2plasma(chem.name="Bisphenol A")
calc_rblood2plasma(chem.name="Bisphenol A",species="Rat")
```

---

calc_stats *Calculate the statistics.*

Description

This function calculates the area under the curve, the mean, and the peak values for the venous blood or plasma concentration of a specified chemical or all chemicals if none is specified for the multiple compartment model with a given number of days, dose, and number of doses per day.

Usage

```
calc_stats(days,chem.name=NULL,chem.cas=NULL,parameters=NULL,stats=c("AUC","peak","mean"),
         species='Human',exclude.fub.zero=F,daily.dose=1,dose=NULL,doses.per.day=NULL,
         output.units='uM',concentration='plasma',model='pbtk',suppress.messages=F,...)
```

Arguments

days	Length of the simulation.
chem.name	Name of desired chemical.
chem.cas	CAS number of desired chemical.
parameters	Chemical parameters from parameterize_pbtk function, overrides chem.name and chem.cas.
stats	Desired values (either 'AUC', 'mean', 'peak', or a vector containing any combination).
daily.dose	Total daily dose, mg/kg BW.
dose	Amount of a single dose, mg/kg BW. Overwrites daily.dose.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
exclude.fub.zero	Whether or not to exclude chemicals with a fraction of unbound plasma equal to zero or include them with a value of 0.005, only used when chem.name, chem.cas, and parameters are not specified.
doses.per.day	Number of doses per day.
output.units	Desired units (either "mg/L", "mg", "umol", or default "uM").
model	Model used in calculation, 'pbtk' for the multiple compartment model,'3compartment' for the three compartment model, '3compartmentss' for the three compartment steady state model, and '1compartment' for one compartment model.
concentration	Desired concentration type, 'blood' or default 'plasma'.
suppress.messages	Whether to suppress output message.
...	Arguments passed to solve function.

Details

Default value of 0 for doses.per.day solves for a single dose.

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Value

AUC	Area under the plasma concentration curve.
mean	The area under the curve divided by the number of days.
peak	The highest concentration.

Author(s)

John Wambaugh and Robert Pearce

Examples

```
calc_stats(chem.name='Bisphenol-A',days=100,stats='mean')
calc_stats(chem.name='Bisphenol-A',days=100,stats=c('peak','mean'),species='Rat')
```

`calc_total_clearance` *Calculate the total clearance.*

Description

This function calculates the total clearance rate for a one compartment model where clearance is entirely due to metablism by the liver and glomerular filtration in the kidneys, identical to clearance of three compartment steady state model.

Usage

```
calc_total_clearance(chem.cas=NULL,chem.name=NULL,parameters=NULL,species="Human",
                     suppress.messages=F,default.to.human=F)
```

Arguments

`chem.name`	Either the chemical name, CAS number, or the parameters must be specified.
`chem.cas`	Either the chemical name, CAS number, or the parameters must be specified.
`parameters`	Chemical parameters from parameterize_steadystate function, overrides chem.name and chem.cas.
`species`	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
`suppress.messages`	Whether or not the output message is suppressed.
`default.to.human`	Substitutes missing animal values with human values if true.

Details

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Value

`Total Clearance`
Units of L/h/kg BW.

Author(s)

John Wambaugh

Examples

```
calc_total_clearance(chem.name="Ibuprofen")
```

`calc_vdist` *Calculate the volume of distribution for a one compartment model.*

Description

This function predicts partition coefficients for all tissues, then lumps them into a single compartment. The effective volume of distribution is calculated by summing each tissues volume times it's partition coefficient relative to plasma. Plasma, and the paritioning into RBCs are also added to get the total volume of distribution in L/KG BW. Partition coefficients are calculated using Schmitt's (2008) method.

Usage

```
calc_vdist(chem.cas=NULL, chem.name=NULL, parameters=NULL,
                        default.to.human=F,species="Human", suppress.messages=F)
```

Arguments

`chem.name`	Either the chemical name or the CAS number must be specified.
`chem.cas`	Either the CAS number or the chemical name must be specified.
`parameters`	Parameters from parameterize_3comp or parameterize_pbtk.
`default.to.human`	Substitutes missing animal values with human values if true.
`species`	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
`suppress.messages`	Whether or not the output message is suppressed.

Details

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Value

`Volume of distribution`
Units of L/ kg BW.

Author(s)

John Wambaugh

References

Schmitt W. "General approach for the calculation of tissue to plasma partition coefficients." Toxicology In Vitro, 22, 457-467 (2008). Peyret, T., Poulin, P., Krishnan, K., "A unified algorithm for predicting partition coefficients for PBPK modeling of drugs and environmental chemicals." Toxicology and Applied Pharmacology, 249, 197-207 (2010).

Examples

```
calc_vdist(chem.cas="80-05-7")
calc_vdist(chem.name="Bisphenol A")
calc_vdist(chem.name="Bisphenol A",species="Rat")
calc_vdist(chem.name="Bisphenol A",species="Rabbit")
```

---

chem.invivo.PK.data *Published toxicokinetic time course measurements*

Description

This data set includes time and dose specific measurements of chemical concentration in tissues taken from animals administered control doses of the chemicals either orally or intravenously. This plasma concentration-time data is from rat experiments reported in public sources. Toxicokinetic data were retrieved from those studies by the Netherlands Organisation for Applied Scientific Research (TNO) using curve stripping (TechDig v2). This data is provided for statistical analysis as in Wambaugh (2014).

Usage

```
chem.invivo.PK.data
```

Format

A data.frame containing 597 rows and 13 columns.

Author(s)

Sieto Bosgra

Source

Wambaugh et al. (2014), in preparation

References

Aanderud L, Bakke OM (1983). Pharmacokinetics of antipyrine, paracetamol, and morphine in rat at 71 ATA. Undersea Biomed Res. 10(3):193-201. PMID: 6636344

Aasmoe L, Mathiesen M, Sager G (1999). Elimination of methoxyacetic acid and ethoxyacetic acid in rat. Xenobiotica. 29(4):417-24. PMID: 10375010

Ako RA. Pharmacokinetics/pharmacodynamics (PK/PD) of oral diethylstilbestrol (DES) in recurrent prostate cancer patients and of oral dissolving film (ODF)-DES in rats. PhD dissertation, College of Pharmacy, University of Houston, USA, 2011.

Anadon A, Martinez-Larranaga MR, Fernandez-Cruz ML, Diaz MJ, Fernandez MC, Martinez MA (1996). Toxicokinetics of deltamethrin and its 4'-HO-metabolite in the rat. Toxicol Appl Pharmacol. 141(1):8-16. PMID: 8917670

Binkerd PE, Rowland JM, Nau H, Hendrickx AG (1988). Evaluation of valproic acid (VPA) developmental toxicity and pharmacokinetics in Sprague-Dawley rats. Fundam Appl Toxicol. 11(3):485-93. PMID: 3146521

Boralli VB, Coelho EB, Cerqueira PM, Lanchote VL (2005). Stereoselective analysis of metoprolol and its metabolites in rat plasma with application to oxidative metabolism. J Chromatogr B Analyt Technol Biomed Life Sci. 823(2):195-202. PMID: 16029965

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`chem.invivo.PK.summary.data`

Summary of published toxicokinetic time course experiments

Description

This data set summarizes the time course data in the chem.invivo.PK.data table. Maximum concentration (Cmax), time integrated plasma concentration for the duration of treatment (AUC.treatment) and extrapolated to zero concentration (AUC.infinity) as well as half-life are calculated. Summary values are given for each study and dosage. These data can be used to evaluate toxicokinetic model predictions.

Usage

```
chem.invivo.PK.summary.data
```

Format

A data.frame containing 100 rows and 25 columns.

Author(s)

John Wambaugh

Source

Wambaugh et al. (2014), in preparation

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`chem.lists` *Chemical membership in different research projects*

Description

A static list of lists identifying chemical membership in different research projects. While it is our intent to keep these lists up-to-date, the information here is only for convenience and should not be considered to be definitive.

Usage

```
chem.lists
```

Format

A list containing ten lists.

Author(s)

John Wambaugh

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chem.physical_and_invitro.data

Physico-chemical properties and in vitro measurements for toxicokinetics

---

Description

This data set contains the necessary information to make basic, high-throughput toxicokinetic (HTTK) predictions for compounds, including Funbound.plasma, molecular weight, logP, logMA (membrane affinity), and pKa. These data have been compiled from multiple sources, and can be used to parameterize a variety of toxicokinetic models.

Usage

```
chem.physical_and_invitro.data
```

Format

A data.frame containing 565 rows and 33 columns.

Author(s)

John Wambaugh

Source

Wambaugh et al. (2014), in preparation

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DSStox database (http:// www.epa.gov/ncct/dsstox

EPI Suite, http://www.epa.gov/opptintr/exposure/pubs/episuite.htm

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`export_pbtk_jarnac` *Export model to jarnac.*

Description

This function exports the multiple compartment PBTK model to a jarnac file.

Usage

```
export_pbtk_jarnac(chem.cas=NULL,chem.name=NULL,species="Human",
                initial.amounts=list(Agutlumen=0),filename="default.jan",digits = 4)
```

Arguments

`chem.cas`	Either the chemical name or CAS number must be specified.
`chem.name`	Either the chemical name or CAS number must be specified.
`species`	Species desired (either "Rat", "Rabbit", "Dog", or default "Human").
`initial.amounts`	Must specify initial amounts in units of choice.
`filename`	The name of the jarnac file containing the model.
`digits`	Desired number of decimal places to round the parameters.

Details

Compartments to enter into the initial.amounts list includes Agutlumen, Aart, Aven, Alung, Agut, Aliver, Akidney, and Arest.

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Author(s)

Robert Pearce

Examples

```
export_pbtk_jarnac(chem.name='Nicotine',initial.amounts=list(Agutlumen=1),filename='PBTKmodel.jan')
```

`export_pbtk_sbml` *Export model to sbml.*

Description

This function exports the multiple compartment PBTK model to an sbml file.

Usage

```
export_pbtk_sbml(chem.cas=NULL,chem.name=NULL,species="Human",
              initial.amounts=list(Agutlumen=0),filename="default.xml",digits = 4)
```

Arguments

`chem.cas`	Either the chemical name or CAS number must be specified.
`chem.name`	Either the chemical name or CAS number must be specified.
`species`	Species desired (either "Rat", "Rabbit", "Dog", or default "Human").
`initial.amounts`	Must specify initial amounts in units of choice.
`filename`	The name of the jarnac file containing the model.
`digits`	Desired number of decimal places to round the parameters.

Details

Compartments to enter into the initial.amounts list includes Agutlumen, Aart, Aven, Alung, Agut, Aliver, Akidney, and Arest.

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Author(s)

Robert Pearce

Examples

```
export_pbtk_sbml(chem.name='Nicotine',initial.amounts=list(Agutlumen=1),filename='PBTKmodel.xml')
```

get_cheminfo *Retrieve chemical information from HTTK package*

Description

This function provides the information specified in "info=" (can be single entry or vector) for all chemicals for which a pharmacokinetic model can be paramterized for a given species.

Usage

```
get_cheminfo(info="CAS",species="Human",exclude.fub.zero=NA,fub.lod.default=0.005,
             model='3compartmentss',default.to.human=F)
```

Arguments

info	A single character vector (or collection of character vectors) from "Compound", "CAS", "logP", "pKa_Donor"," pKa_Accept", "MW", "Clint", "Clint.pValue", or "Funbound.plasma". info="all" gives all information for the model and species.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
exclude.fub.zero	Whether or not to exclude chemicals with a fraction of unbound plasma equal to zero or include them with a value of fub.lod.default. Defaults to TRUE for 1compartment and FALSE for pbtk models.
fub.lod.default	Default value used for fraction of unbound plasma for chemicals where measured value was below the limit of detection. Default value is 0.0005.
model	Model used in calculation, 'pbtk' for the multiple compartment model, '1compartment' for the one compartment model, '3compartment' for three compartment model, '3compartmentss' for the three compartment model without partition coefficients, or 'schmitt' for chemicals with logP and fraction unbound (used in predict_partitioning_schmitt).
default.to.human	Substitutes missing values with human values if true.

Details

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Value

info	Table/vector containing values specified in "info" for valid chemicals.

Author(s)

John Wambaugh

Examples

```
# List all CAS numbers for which the 1compartment model can be run in humans:
get_cheminfo()
# List all compound names for which the 1compartment model can be run in rats,
# excluding those chemicals that were below the limit of detection in the
# plasma binding assay:
get_cheminfo(info='Compound',exclude.fub.zero=TRUE,species='Rat')
# List all CAS numbers for which the 1compartment model can be run in humans:
get_cheminfo(info=c('compound','funbound.plasma','logP'))
get_cheminfo(model="pbtk")
# See all the data for humans:
get_cheminfo(info="all")

TPO.cas <- c("741-58-2", "333-41-5", "51707-55-2", "30560-19-1", "5598-13-0",
"35575-96-3", "142459-58-3", "1634-78-2", "161326-34-7", "133-07-3", "533-74-4",
"101-05-3", "330-54-1", "6153-64-6", "15299-99-7", "87-90-1", "42509-80-8",
"10265-92-6", "122-14-5", "12427-38-2", "83-79-4", "55-38-9", "2310-17-0",
"5234-68-4", "330-55-2", "3337-71-1", "6923-22-4", "23564-05-8", "101-02-0",
"140-56-7", "120-71-8", "120-12-7", "123-31-9", "91-53-2", "131807-57-3",
"68157-60-8", "5598-15-2", "115-32-2", "298-00-0", "60-51-5", "23031-36-9",
"137-26-8", "96-45-7", "16672-87-0", "709-98-8", "149877-41-8", "145701-21-9",
"7786-34-7", "54593-83-8", "23422-53-9", "56-38-2", "41198-08-7", "50-65-7",
"28434-00-6", "56-72-4", "62-73-7", "6317-18-6", "96182-53-5", "87-86-5",
"101-54-2", "121-69-7", "532-27-4", "91-59-8", "105-67-9", "90-04-0",
"134-20-3", "599-64-4", "148-24-3", "2416-94-6", "121-79-9", "527-60-6",
"99-97-8", "131-55-5", "105-87-3", "136-77-6", "1401-55-4", "1948-33-0",
"121-00-6", "92-84-2", "140-66-9", "99-71-8", "150-13-0", "80-46-6", "120-95-6",
"128-39-2", "2687-25-4", "732-11-6", "5392-40-5", "80-05-7", "135158-54-2",
"29232-93-7", "6734-80-1", "98-54-4", "97-53-0", "96-76-4", "118-71-8",
"2451-62-9", "150-68-5", "732-26-3", "99-59-2", "59-30-3", "3811-73-2",
"101-61-1", "4180-23-8", "101-80-4", "86-50-0", "2687-96-9", "108-46-3",
"95-54-5", "101-77-9", "95-80-7", "420-04-2", "60-54-8", "375-95-1", "120-80-9",
"149-30-4", "135-19-3", "88-58-4", "84-16-2", "6381-77-7", "1478-61-1",
"96-70-8", "128-04-1", "25956-17-6", "92-52-4", "1987-50-4", "563-12-2",
"298-02-2", "79902-63-9", "27955-94-8")
httk.TPO.rat.table <- subset(get_cheminfo(info="all",species="rat"),
 CAS %in% TPO.cas)

httk.TPO.human.table <- subset(get_cheminfo(info="all",species="human"),
 CAS %in% TPO.cas)
```

`get_wetmore_cheminfo` *Get Wetmore Chemical Information.*

Description

This function provides the information specified in "info=" for all chemicals with data from the Wetmore et al. (2012) and (2013) publications.

Usage

```
get_wetmore_cheminfo(info="CAS",species="Human")
```

Arguments

info	A single character vector (or collection of character vectors) from "Compound","CAS","MW","Raw.Expe ,"r2","p.val","Concentration..uM.","Css_lower_5th_perc.mg.L.","Css_median_perc.mg.L.","Css_upper_ and "Species".
species	Species desired (either "Rat" or default "Human").

Value

info	Table/vector containing values specified in "info" for valid chemicals.

Author(s)

John Wambaugh

References

Wetmore, B.A., Wambaugh, J.F., Ferguson, S.S., Sochaski, M.A., Rotroff, D.M., Freeman, K., Clewell, H.J., Dix, D.H., Andersen, M.E., Houck, K.A., Allen, B., Judson, R.S., Sing, R., Kavlock, R.J., Richard, A.M., and Thomas, R.S., "Integration of Dosimetry, Exposure and High-Throughput Screening Data in Chemical Toxicity Assessment," Toxicological Sciences 125 157-174 (2012)

Wetmore, B.A., Wambaugh, J.F., Ferguson, S.S., Li, L., Clewell, H.J. III, Judson, R.S., Freeman, K., Bao, W, Sochaski, M.A., Chu T.-M., Black, M.B., Healy, E, Allen, B., Andersen M.E., Wolfinger, R.D., and Thomas R.S., "The Relative Impact of Incorporating Pharmacokinetics on Predicting in vivo Hazard and Mode-of-Action from High-Throughput in vitro Toxicity Assays" Toxicological Sciences, 132:327-346 (2013).

Wetmore, B. A., Wambaugh, J. F., Allen, B., Ferguson, S. S., Sochaski, M. A., Setzer, R. W., Houck, K. A., Strope, C. L., Cantwell, K., Judson, R. S., LeCluyse, E., Clewell, H.J. III, Thomas, R.S., and Andersen, M. E. (2015). "Incorporating High-Throughput Exposure Predictions with Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing" Toxicological Sciences, kfv171.

Examples

```
get_wetmore_cheminfo()

get_wetmore_cheminfo(info=c('CAS','MW'))
```

get_wetmore_css *Get Wetmore Css*

Description

This function retrives a steady-state plasma concentration as a result of infusion dosing from the Wetmore et al. (2012) and (2013) publications.

Usage

```
get_wetmore_css(chem.cas=NULL,chem.name=NULL,daily.dose=1,which.quantile=0.95,
                species="Human",clearance.assay.conc=NULL,output.units="mg/L",
                suppress.messages=F)
```

Arguments

chem.name	Either the chemical name or the CAS number must be specified.
chem.cas	Either the cas number or the chemical name must be specified.
which.quantile	Which quantile from the SimCYP Monte Carlo simulation is requested. Can be a vector.
species	Species desired (either "Rat" or default "Human").
clearance.assay.conc	Concentration of chemical used in measureing intrinsic clearance data, 1 or 10 uM.
daily.dose	Total daily dose infused in units of mg/kg BW/day. Defaults to 1 mg/kg/day.
output.units	Returned units for function, defaults to mg/L but can also be uM (specify units = "uM").
suppress.messages	Whether or not the output message is suppressed.

Author(s)

John Wambaugh

References

Wetmore, B.A., Wambaugh, J.F., Ferguson, S.S., Sochaski, M.A., Rotroff, D.M., Freeman, K., Clewell, H.J., Dix, D.H., Andersen, M.E., Houck, K.A., Allen, B., Judson, R.S., Sing, R., Kavlock, R.J., Richard, A.M., and Thomas, R.S., "Integration of Dosimetry, Exposure and High-Throughput Screening Data in Chemical Toxicity Assessment," Toxicological Sciences 125 157-174 (2012)

Wetmore, B.A., Wambaugh, J.F., Ferguson, S.S., Li, L., Clewell, H.J. III, Judson, R.S., Freeman, K., Bao, W, Sochaski, M.A., Chu T.-M., Black, M.B., Healy, E, Allen, B., Andersen M.E., Wolfinger, R.D., and Thomas R.S., "The Relative Impact of Incorporating Pharmacokinetics on Predicting in vivo Hazard and Mode-of-Action from High-Throughput in vitro Toxicity Assays" Toxicological Sciences, 132:327-346 (2013).

Wetmore, B. A., Wambaugh, J. F., Allen, B., Ferguson, S. S., Sochaski, M. A., Setzer, R. W., Houck, K. A., Strope, C. L., Cantwell, K., Judson, R. S., LeCluyse, E., Clewell, H.J. III, Thomas, R.S., and Andersen, M. E. (2015). "Incorporating High-Throughput Exposure Predictions with Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing" Toxicological Sciences, kfv171.

Examples

```
get_wetmore_css(chem.cas="34256-82-1")


get_wetmore_css(chem.cas="34256-82-1",species="Rat",which.quantile=0.5)
```

`get_wetmore_oral_equiv` *Get Wetmore Oral Equivalent Dose*

Description

This function converts a chemical plasma concetration to an oral equivalent dose using the values from the Wetmore et al. (2012) and (2013) publications.

Usage

```
get_wetmore_oral_equiv(conc,chem.name=NULL,chem.cas=NULL,suppress.messages=F,
                       which.quantile=0.95,species="Human",input.units='uM',
                       output.units='mg',clearance.assay.conc=NULL,...)
```

Arguments

`conc`	Bioactive in vitro concentration in units of specified input.units, default of uM.
`chem.name`	Either the chemical name or the CAS number must be specified.
`chem.cas`	Either the CAS number or the chemical name must be specified.
`input.units`	Units of given concentration, default of uM but can also be mg/L.
`output.units`	Units of dose, default of 'mg' for mg/kg BW/ day or 'mol' for mol/ kg BW/ day.
`suppress.messages`	Suppress output messages.
`which.quantile`	Which quantile from the SimCYP Monte Carlo simulation is requested. Can be a vector. Papers include 0.05, 0.5, and 0.95 for humans and 0.5 for rats.
`species`	Species desired (either "Rat" or default "Human").
`clearance.assay.conc`	Concentration of chemical used in measureing intrinsic clearance data, 1 or 10 uM.
`...`	Additional parameters passed to get_wetmore_css.

Value

Equivalent dose in specified units, default of mg/kg BW/day.

Author(s)

John Wambaugh

References

Wetmore, B.A., Wambaugh, J.F., Ferguson, S.S., Sochaski, M.A., Rotroff, D.M., Freeman, K., Clewell, H.J., Dix, D.H., Andersen, M.E., Houck, K.A., Allen, B., Judson, R.S., Sing, R., Kavlock, R.J., Richard, A.M., and Thomas, R.S., "Integration of Dosimetry, Exposure and High-Throughput Screening Data in Chemical Toxicity Assessment," Toxicological Sciences 125 157-174 (2012)

Wetmore, B.A., Wambaugh, J.F., Ferguson, S.S., Li, L., Clewell, H.J. III, Judson, R.S., Freeman, K., Bao, W, Sochaski, M.A., Chu T.-M., Black, M.B., Healy, E, Allen, B., Andersen M.E., Wolfinger, R.D., and Thomas R.S., "The Relative Impact of Incorporating Pharmacokinetics on Predicting in vivo Hazard and Mode-of-Action from High-Throughput in vitro Toxicity Assays" Toxicological Sciences, 132:327-346 (2013).

Wetmore, B. A., Wambaugh, J. F., Allen, B., Ferguson, S. S., Sochaski, M. A., Setzer, R. W., Houck, K. A., Strope, C. L., Cantwell, K., Judson, R. S., LeCluyse, E., Clewell, H.J. III, Thomas, R.S., and Andersen, M. E. (2015). "Incorporating High-Throughput Exposure Predictions with Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing" Toxicological Sciences, kfv171.

Examples

```
table <- NULL
for(this.cas in sample(get_wetmore_cheminfo(),50)) table <- rbind(table,cbind(
as.data.frame(this.cas),as.data.frame(get_wetmore_oral_equiv(conc=1,chem.cas=this.cas))))




get_wetmore_oral_equiv(0.1,chem.cas="34256-82-1")

get_wetmore_oral_equiv(0.1,chem.cas="34256-82-1",which.quantile=c(0.05,0.5,0.95))
```

---

in.list *Convenience Boolean (yes/no) functions to idnetify chemical membership in several key lists.*

Description

These functions allow easy identification of whether or not a chemical CAS is included in various research projects. While it is our intent to keep these lists up-to-date, the information here is only for convenience and should not be considered to be definitive.

Usage

```
in.list(chem.cas=NULL, which.list="ToxCast")
is.nhanes(chem.cas)
is.nhanes.serum.parent(chem.cas)
is.nhanes.serum.analyte(chem.cas)
is.nhanes.blood.parent(chem.cas)
is.nhanes.blood.analyte(chem.cas)
is.nhanes.urine.parent(chem.cas)
is.nhanes.urine.analyte(chem.cas)
is.tox21(chem.cas)
is.toxcast(chem.cas)
is.expocast(chem.cas)
is.httk(chem.cas,species="Human",model="3compartmentss")
```

Arguments

chem.cas	The Chemical Abstracts Service Resgistry Number (CAS-RN) corresponding to the chemical of interest.
which.list	A character string that can take the following values: "ToxCast", "Tox21", "ExpoCast", "NHANES", ""NHANES.serum.parent", "NHANES.serum.analyte","NHANES.blood.parent","NHANES.urine.parent","NHANES.urine.analyte"
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
model	Model used in calculation, 'pbtk' for the multiple compartment model, '1compartment' for the one compartment model, '3compartment' for three compartment model, '3compartmentss' for the three compartment model without partition coefficients, or 'schmitt' for chemicals with logP and fraction unbound (used in predict_partitioning_schmitt).

Details

Tox21: Toxicology in the 21st Century (Tox21) is a U.S. federal High Throughput Screening (HTS) collaboration among EPA, NIH, including National Center for Advancing Translational Sciences and the National Toxicology Program at the National Institute of Environmental Health Sciences, and the Food and Drug Administration. (Bucher et al., 2008)

ToxCast: The Toxicity Forecaster (ToxCast) is a HTS screening project led by the U.S. EPA to perform additional testing of a subset of Tox21 chemicals. (Judson et al. 2010)

ExpoCast: ExpoCast (Exposure Forecaster) is an U.S. EPA research project to generate tenetative exposure estimates (e.g., mg/kg BW/day) for thousands of chemicals that have little other information using models and informatics. (Wambaugh et al. 2014)

NHANES: The U.S. Centers for Disease Control (CDC) National Health and Nutrition Examination Survery (NHANES) is an on-going survey to characterize the health and biometrics (e.g., weight, height) of the U.S. population. One set of measurments includes the quantification of xenobiotic chemicals in various samples (blood, serum, urine) of the thousands of surveyed individuals. (CDC, 2014)

Value

logical	A Boolean (1/0) value that is TRUE if the chemical is in the list.

Author(s)

John Wambaugh

References

Bucher, J. R. (2008). Guest Editorial: NTP: New Initiatives, New Alignment. Environ Health Perspect 116(1).

Judson, R. S., Houck, K. A., Kavlock, R. J., Knudsen, T. B., Martin, M. T., Mortensen, H. M., Reif, D. M., Rotroff, D. M., Shah, I., Richard, A. M. and Dix, D. J. (2010). In Vitro Screening of Environmental Chemicals for Targeted Testing Prioritization: The ToxCast Project. Environmental Health Perspectives 118(4), 485-492.

Wambaugh, J. F., Wang, A., Dionisio, K. L., Frame, A., Egeghy, P., Judson, R. and Setzer, R. W. (2014). High Throughput Heuristics for Prioritizing Human Exposure to Environmental Chemicals. Environmental Science & Technology, 10.1021/es503583j.

CDC (2014). National Health and Nutrition Examination Survey. Available at: http://www.cdc.gov/nchs/nhanes.htm.

Examples

```
httk.table <- get_cheminfo(info=c("CAS","Compound"))
httk.table[,"Rat"] <- ""
httk.table[,"NHANES"] <- ""
httk.table[,"Tox21"] <- ""
httk.table[,"ToxCast"] <- ""
httk.table[,"ExpoCast"] <- ""
httk.table[,"PBTK"] <- ""
# To make this example run quickly, this loop is only over the first fifty
# chemicals. To build a table with all available chemicals use:
# for (this.cas in httk.table$CAS)
for (this.cas in httk.table$CAS[1:50])
{
  this.index <- httk.table$CAS==this.cas
  if (is.nhanes(this.cas)) httk.table[this.index,"NHANES"] <- "Y"
  if (is.tox21(this.cas)) httk.table[this.index,"Tox21"] <- "Y"
  if (is.toxcast(this.cas)) httk.table[this.index,"ToxCast"] <- "Y"
  if (is.expocast(this.cas)) httk.table[this.index,"ExpoCast"] <- "Y"
  if (is.httk(this.cas,model="PBTK")) httk.table[this.index,"PBTK"] <- "Y"
  if (is.httk(this.cas,species="rat")) httk.table[this.index,"Rat"] <- "Y"
}
```

lump_tissues *Lump tissue parameters*

Description

This function takes the parameters from predict_partitioning_schmitt and lumps the partition coefficients along with the volumes and flows based on the given tissue list. It is useful in Monte Carlo simulation of individual partition coefficients when calculating the rest of body partition coefficient.

Usage

```
lump_tissues(Ktissue2pu.in, tissuelist=NULL, species="Human")
```

Arguments

Ktissue2pu.in	List of partition coefficients from predict_partitioning_schmitt.
tissuelist	Specifies compartment names and tissues groupings. Remaining tissues in tissue.data are lumped in the rest of the body.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").

Value

Krbc2pu	Ratio of concentration of chemical in red blood cells to unbound concentration in plasma.
Krest2pu	Ratio of concentration of chemical in rest of body tissue to unbound concentration in plasma.
Vrestc	Volume of the rest of the body per kg body weight, L/kg BW.
Vliverc	Volume of the liver per kg body weight, L/kg BW.
Qtotal.liverf	Fraction of cardiac output flowing to the gut and liver, i.e. out of the liver.
Qgutf	Fraction of cardiac output flowing to the gut.
Qkidneyf	Fraction of cardiac output flowing to the kidneys.

Author(s)

John Wambaugh

Examples

```
pcs <- predict_partitioning_schmitt(chem.name='bisphenola')
tissuelist <- list(liver=c("liver"),kidney=c("kidney"),lung=c("lung"),gut=c("gut")
,muscle.bone=c('muscle','bone'))
lump_tissues(pcs,tissuelist=tissuelist)
```

`monte_carlo` *Monte Carlo for pharmacokinetic models*

Description

This function performs Monte Carlo to assess uncertainty and variability for pharmacokinetic models.

Usage

```
monte_carlo(params,which.quantile=0.95,cv.params=NULL,censored.params=NULL,samples=1000,
          name.model='calc_analytic_css',output.col.model=NA,return.samples=F,...)
```

Arguments

`params`	All parameters needed by the function indicated by the argument "name.model". These paramters that are also listed in either cv.params or censored.params are sampled using Monte Carlo.
`which.quantile`	This argument specifies which quantiles are to be calculated. It can be a vector or a single value. It defaults to the 0.95 quantile (95%).
`cv.params`	The parameters listed in cv.params are sampled from a normal distribution that is truncated at zero. This argument should be a list of coefficients of variation (cv) for the normal distribution. Each entry in the list is named for a parameter in "params". New values are sampled with mean equal to the value in "params" and standard deviation equal to the mean times the cv.
`censored.params`	The parameters listed in censored.params are sampled from a normal distribution that is censored for values less than the limit of detection (specified separately for each paramter). This argument should be a list of sub-lists. Each sublist is named for a parameter in "params" and contains two elements: "cv" (coefficient of variation) and "LOD" (limit of detection), below which parameter values are censored. New values are sampled with mean equal to the value in "params" and standard deviation equal to the mean times the cv.Censored values are sampled on a uniform distribution between 0 and the limit of detection.
`samples`	This argument is the number of samples to be generated for calculating quantiles.
`name.model`	This argument is a character vector giving the name of the model to be sampled. Defaults to 'calc_analytic_css'.
`output.col.model`	If the evaluation of the function indicated by "model" returns a list, then model.output.col is the element from that list that is sampled and is used for calculating quantiles. Defaults to NA (i.e., the function returns a single value).
`return.samples`	Whether or not to return the vector containing the samples from the simulation instead of the selected quantile.
`...`	Additional arguments passed to name.model.

Author(s)

John Wambaugh

Examples

```
# Fig 1 SimCYP vs. our predictions:
## Not run:
library(httk)
library(ggplot2)

vary.params <- list(BW=0.3)
vary.params[["Vliverc"]]<-0.3
vary.params[["Qgfrc"]]<-0.3
vary.params[["Qtotal.liverc"]]<-0.3
vary.params[["million.cells.per.gliver"]]<-0.3
vary.params[["Clint"]]<-0.3
censored.params<-list(Funbound.plasma=list(cv=0.3,lod=0.01))

pValues <- get_cheminfo(c("Compound","CAS","Clint.pValue"))
pValues.rat <- get_cheminfo(c("Compound","CAS","Clint.pValue"),species="Rat")



Wetmore.table <- NULL
for (this.CAS in get_cheminfo(model="3compartmentss"))
  if (this.CAS %in% get_wetmore_cheminfo())
  {
    print(this.CAS)
    these.params <- parameterize_steadystate(chem.cas=this.CAS)
    if (these.params[["Funbound.plasma"]] == 0.0)
    {
      these.params[["Funbound.plasma"]] <- 0.005
    }
    vLiver.human.values <- monte_carlo(these.params,
                                       cv.params=vary.params,
                                       censored.params=censored.params,
                                       which.quantile=c(0.05,0.5,0.95),
                                       output.units="mg/L",
                                       model='3compartmentss',
                                       suppress.messages=T,
                                       fu.hep.correct=F)
    percentiles <- c("5","50","95")
    for (this.index in 1:3)
    {
      this.row <- as.data.frame(get_wetmore_css(chem.cas=this.CAS,
                                which.quantile=as.numeric(percentiles[this.index])/100))
      this.row <- cbind(this.row, as.data.frame(vLiver.human.values[this.index]))
      this.row <- cbind(this.row, as.data.frame(percentiles[this.index]))
      this.row <- cbind(this.row, as.data.frame("Human"))
      this.row <- cbind(this.row, as.data.frame(this.CAS))
      this.row <- cbind(this.row, as.data.frame(pValues[pValues$CAS==this.CAS,
                                                "Human.Clint.pValue"]<0.05))
```

```
      colnames(this.row) <- c("Wetmore", "Predicted", "Percentile", "Species",
                              "CAS", "Systematic")
      if (is.na(this.row["Systematic"])) this.row["Systematic"] <- F
      Wetmore.table <- Wetmore.table <- rbind(Wetmore.table,this.row)
    }
  }

scientific_10 <- function(x) {
  out <- gsub("1e", "10^", scientific_format()(x))
  out <- gsub("\+","",out)
  out <- gsub("10^01","10",out)
  out <- parse(text=gsub("10^00","1",out))
}


Fig1 <- ggplot(Wetmore.table, aes(Predicted,Wetmore,group = CAS)) +
  geom_line() +
  geom_point(aes(colour=factor(Percentile),shape=factor(Percentile))) +
  scale_colour_discrete(name="Percentile") +
  scale_shape_manual(name="Percentile", values=c("5"=21, "50"=22,"95"=24)) +
  scale_x_log10(expression(paste(C[ss]," Predicted (mg/L) with Refined Assumptions")),
                label=scientific_10) +
  scale_y_log10(expression(paste(C[ss]," Wetmore ",italic("et al."),"(2012) (mg/L)")),
                label=scientific_10) +
  geom_abline(intercept = 0, slope = 1,linetype="dashed")+
  theme_bw()+
  theme(legend.position="bottom", text  = element_text(size=18))

print(Fig1)

Fig1a.fit <- lm(log(Wetmore) ~ log(Predicted)*Percentile, Wetmore.table)
## End(**Not run**)

## End(Not run)
```

---

parameterize_1comp *Parameterize_1comp*

Description

This function initializes the parameters needed in the function solve_1comp.

Usage

```
parameterize_1comp(chem.cas=NULL,chem.name=NULL,species="Human",
                   default.to.human=F)
```

Arguments

chem.name	Either the chemical name or the CAS number must be specified.
chem.cas	Either the chemical name or the CAS number must be specified.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
default.to.human	Substitutes missing rat values with human values if true.

Details

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Value

Vdist	Volume of distribution, units of L/kg BW.
Fgutabs	Fraction of the oral dose absorbed, i.e. the fraction of the dose that enters the gutlumen.
kelim	Elimination rate, units of 1/h.
hematocrit	Percent volume of red blood cells in the blood.
kgutabs	Rate chemical is absorbed, 1/h.
million.cells.per.gliver	Millions cells per gram of liver tissue.
MW	Molecular Weight, g/mol.
Rblood2plasma	The ratio of the concentration of the chemical in the blood to the concentration in the plasma.

Author(s)

John Wambaugh

Examples

```
parameters <- parameterize_1comp(chem.name='Bisphenol-A',species='Rat')
parameters <- parameterize_1comp(chem.cas='80-05-7')
```

parameterize_3comp *Parameterize_3comp*

Description

This function initializes the parameters needed in the function solve_3comp.

Usage

```
parameterize_3comp(chem.cas=NULL,chem.name=NULL,species="Human",
                   default.to.human=F,force.human.clint.fub = F,
                   clint.pvalue.threshold=0.05)
```

Arguments

chem.name	Either the chemical name or the CAS number must be specified.
chem.cas	Either the chemical name or the CAS number must be specified.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
default.to.human	Substitutes missing animal values with human values if true.
force.human.clint.fub	Forces use of human values for hepatic intrinsic clearance and fraction of unbound plasma if true.
clint.pvalue.threshold	Hepatic clearances with clearance assays having p-values greater than the threshold are set to zero.

Details

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Value

BW	Body Weight, kg.
Clmetabolismc	Hepatic Clearance, L/h/kg BW.
Fgutabs	Fraction of the oral dose absorbed, i.e. the fraction of the dose that enters the gutlumen.
Funbound.plasma	Fraction of plasma that is not bound.
Fhep.assay.correction	The fraction of chemical unbound in hepatocyte assay using the method of Kilford et al. (2008)
hematocrit	Percent volume of red blood cells in the blood.

Kgut2pu	Ratio of concentration of chemical in gut tissue to unbound concentration in plasma.
Kliver2pu	Ratio of concentration of chemical in liver tissue to unbound concentration in plasma.
Krbc2pu	Ratio of concentration of chemical in red blood cells to unbound concentration in plasma.
Krest2pu	Ratio of concentration of chemical in rest of body tissue to unbound concentration in plasma.
million.cells.per.gliver	Millions cells per gram of liver tissue.
MW	Molecular Weight, g/mol.
Qcardiacc	Cardiac Output, L/h/kg BW^3/4.
Qgfrc	Glomerular Filtration Rate, L/h/kg BW^3/4, volume of fluid filtered from kidney and excreted.
Qgutf	Fraction of cardiac output flowing to the gut.
Qliverf	Fraction of cardiac output flowing to the liver.
Rblood2plasma	The ratio of the concentration of the chemical in the blood to the concentration in the plasma.
Vgutc	Volume of the gut per kg body weight, L/kg BW.
Vliverc	Volume of the liver per kg body weight, L/kg BW.
Vrestc	Volume of the rest of the body per kg body weight, L/kg BW.

Author(s)

Robert Pearce and John Wambaugh

References

Kilford, P. J., Gertz, M., Houston, J. B. and Galetin, A. (2008). Hepatocellular binding of drugs: correction for unbound fraction in hepatocyte incubations using microsomal binding or drug lipophilicity data. Drug Metabolism and Disposition 36(7), 1194-7, 10.1124/dmd.108.020834.

Examples

```
parameters <- parameterize_3comp(chem.name='Bisphenol-A',species='Rat')
parameters <- parameterize_3comp(chem.cas='80-05-7')
```

parameterize_pbtk *Parameterize_PBTK*

Description

This function initializes the parameters needed in the functions solve_pbtk, calc_css, and others using the multiple compartment model.

Usage

```
parameterize_pbtk(chem.cas=NULL,chem.name=NULL,species="Human",default.to.human=F,
tissuelist=list(liver=c("liver"),kidney=c("kidney"),lung=c("lung"),gut=c("gut")),
force.human.clint.fub = F,clint.pvalue.threshold=0.05)
```

Arguments

chem.name	Either the chemical name or the CAS number must be specified.
chem.cas	Either the chemical name or the CAS number must be specified.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
default.to.human	Substitutes missing animal values with human values if true (hepatic intrinsic clearance or fraction of unbound plasma).
tissuelist	Specifies compartment names and tissues groupings. Remaining tissues in tissue.data are lumped in the rest of the body. However, solve_pbtk only works with the default parameters.
force.human.clint.fub	Forces use of human values for hepatic intrinsic clearance and fraction of unbound plasma if true.
clint.pvalue.threshold	Hepatic clearances with clearance assays having p-values greater than the threshold are set to zero.

Details

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Value

BW	Body Weight, kg.
Clmetabolismc	Hepatic Clearance, L/h/kg BW.
Fgutabs	Fraction of the oral dose absorbed, i.e. the fraction of the dose that enters the gutlumen.

Funbound.plasma
: Fraction of plasma that is not bound.

Fhep.assay.correction
: The fraction of chemical unbound in hepatocyte assay using the method of Kilford et al. (2008)

hematocrit
: Percent volume of red blood cells in the blood.

kdermabs
: Rate that chemical is transferred from the skin to the blood, 1/h.

Kgut2pu
: Ratio of concentration of chemical in gut tissue to unbound concentration in plasma.

kgutabs
: Rate that chemical enters the gut from gutlumen, 1/h.

kinhabs
: Rate that the chemical is transferred from the lungs to the blood, 1/h.

Kkidney2pu
: Ratio of concentration of chemical in kidney tissue to unbound concentration in plasma.

Kliver2pu
: Ratio of concentration of chemical in liver tissue to unbound concentration in plasma.

Klung2pu
: Ratio of concentration of chemical in lung tissue to unbound concentration in plasma.

Krbc2pu
: Ratio of concentration of chemical in red blood cells to unbound concentration in plasma.

Krest2pu
: Ratio of concentration of chemical in rest of body tissue to unbound concentration in plasma.

million.cells.per.gliver
: Millions cells per gram of liver tissue.

MW
: Molecular Weight, g/mol.

Qcardiacc
: Cardiac Output, L/h/kg BW^3/4.

Qgfrc
: Glomerular Filtration Rate, L/h/kg BW^3/4, volume of fluid filtered from kidney and excreted.

Qgutf
: Fraction of cardiac output flowing to the gut.

Qkidneyf
: Fraction of cardiac output flowing to the kidneys.

Qliverf
: Fraction of cardiac output flowing to the liver.

Rblood2plasma
: The ratio of the concentration of the chemical in the blood to the concentration in the plasma.

Vartc
: Volume of the arteries per kg body weight, L/kg BW.

Vgutc
: Volume of the gut per kg body weight, L/kg BW.

Vkidneyc
: Volume of the kidneys per kg body weight, L/kg BW.

Vliverc
: Volume of the liver per kg body weight, L/kg BW.

Vlungc
: Volume of the lungs per kg body weight, L/kg BW.

Vrestc
: Volume of the rest of the body per kg body weight, L/kg BW.

Vvenc
: Volume of the veins per kg body weight, L/kg BW.

Author(s)

John Wambaugh and Robert Pearce

References

Kilford, P. J., Gertz, M., Houston, J. B. and Galetin, A. (2008). Hepatocellular binding of drugs: correction for unbound fraction in hepatocyte incubations using microsomal binding or drug lipophilicity data. Drug Metabolism and Disposition 36(7), 1194-7, 10.1124/dmd.108.020834.

Examples

```
parameters <- parameterize_pbtk(chem.cas='80-05-7')

parameters <- parameterize_pbtk(chem.name='Bisphenol-A',species='Rat')

# Change the tissue lumping (note, these model parameters will not work with our current solver):
compartments <- list(liver=c("liver"),fast=c("heart","brain","muscle","kidney"),
                     lung=c("lung"),gut=c("gut"),slow=c("bone"))
parameterize_pbtk(chem.name="Bisphenol a",species="Rat",default.to.human=TRUE,
                  tissuelist=compartments)
```

---

parameterize_schmitt *Parameterize Schmitt's method.*

Description

This function provides the necessary parameters to run predict_partitioning_schmitt, excluding the data in tissue.data.

Usage

```
parameterize_schmitt(chem.cas=NULL,chem.name=NULL,species="Human",default.to.human=F)
```

Arguments

chem.name	Either the chemical name or the CAS number must be specified.
chem.cas	Either the chemical name or the CAS number must be specified.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
default.to.human	Substitutes missing fraction of unbound plasma with human values if true.

Details

When species is specified as rabbit, dog, or mouse, the human unbound fraction is substituted.

Value

Funbound.plasma	unbound fraction in plasma
Pow	octonol:water partition coefficient (not log transformed)
pKa_Donor	compound H dissociation equilibirum constant(s)
pKa_Accept	compound H association equilibirum constant(s)
MA	phospholipid:water distribution coefficient, membrane affinity
Fprotein.plasma	protein fraction in plasma - from Gardner 1980
plasma.pH	pH of the plasma
temperature	body temperature of species

Author(s)

Robert Pearce

Examples

```
parameterize_schmitt(chem.name='bisphenola')
```

---

parameterize_steadystate

Parameterize_SteadyState

Description

This function initializes the parameters needed in the functions calc_mc_css, calc_mc_oral_equiv, and calc_analytic_css for the three compartment steady state model ('3compartmentss').

Usage

```
parameterize_steadystate(chem.cas=NULL,chem.name=NULL,species="Human",
                         clint.pvalue.threshold=0.05,default.to.human=F,
                         human.clint.fub=F)
```

Arguments

chem.name	Either the chemical name or the CAS number must be specified.
chem.cas	Either the chemical name or the CAS number must be specified.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
clint.pvalue.threshold	Hepatic clearances with clearance assays having p-values greater than the threshold are set to zero.
default.to.human	Substitutes missing rat values with human values if true.

`human.clint.fub`
: Uses human hepatic intrinsic clearance and fraction of unbound plasma in calculation of partition coefficients for rats if true.

Details

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Value

`Clint`
: Hepatic Intrinsic Clearance, uL/min/10^6 cells.

`Fgutabs`
: Fraction of the oral dose absorbed, i.e. the fraction of the dose that enters the gutlumen.

`Funbound.plasma`
: Fraction of plasma that is not bound.

`Qtotal.liverc`
: Flow rate of blood exiting the liver, L/h/kg BW^3/4.

`Qgfrc`
: Gromerular Filtration Rate, L/h/kg BW^3/4, volume of fluid filtered from kidney and excreted.

`BW`
: Body Weight, kg

`MW`
: Molecular Weight, g/mol

`million.cells.per.gliver`
: Millions cells per gram of liver tissue.

`Vliverc`
: Volume of the liver per kg body weight, L/kg BW.

`liver.density`
: Liver tissue density, kg/L.

`Fhep.assay.correction`
: The fraction of chemical unbound in hepatocyte assay using the method of Kilford et al. (2008)

Author(s)

John Wambaugh

Examples

```
parameters <- parameterize_steadystate(chem.name='Bisphenol-A',species='Rat')
parameters <- parameterize_steadystate(chem.cas='80-05-7')
```

physiology.data *Species-specific physiology parameters*

Description

This data set contains values from Davies and Morris (1993) necessary to paramaterize a toxicokinetic model for human, mouse, rat, dog, or rabbit. The temperature for each species are taken from Robertshaw et al. (2004), Gordon (1993), and Stammers(1926).

Usage

```
physiology.data
```

Format

A data.frame containing 11 rows and 7 columns.

Author(s)

John Wambaugh and Nisha Sipes

Source

Wambaugh et al. (2014), in preparation

References

Davies, B. and Morris, T. (1993). Physiological Parameters in Laboratory Animals and Humans. Pharmaceutical Research 10(7), 1093-1095, 10.1023/a:1018943613122.

Robertshaw, D., Temperature Regulation and Thermal Environment, in Dukes' Physiology of Domestic Animals, 12th ed., Reece W.O., Ed. Copyright 2004 by Cornell University. Stammers (1926) The blood count and body temperature in normal rats Gordon (1993) Temperature Regulation in Laboratory Rodents

predict_partitioning_schmitt *Predict partition coefficients using the method from Schmitt (2008).*

Description

This function implements the method from Schmitt (2008) in predicting the tissue to unbound plasma partition coefficients from for the tissues contained in the tissue.data table.

Usage

```
predict_partitioning_schmitt(chem.name=NULL,chem.cas=NULL,species="Human",
                             default.to.human=F,parameters=NULL)
```

Arguments

chem.name	Either the chemical name or the CAS number must be specified.
chem.cas	Either the chemical name or the CAS number must be specified.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
default.to.human	Substitutes missing animal values with human values if true (hepatic intrinsic clearance or fraction of unbound plasma).
parameters	Chemical parameters from the parameterize_schmitt function, overrides chem.name and chem.cas.

Details

A regression is used for MA when not provided.

Value

Returns tissue to unbound plasma partition coefficients for each tissue.

Author(s)

Robert Pearce

Examples

```
predict_partitioning_schmitt(chem.name='ibuprofen')
```

---

solve_1comp *Solve one compartment TK model*

Description

This function solves for the amount or concentration of a chemical in plasma or blood for a one compartment model as a function of time based on the dose and dosing frequency.

Usage

```
solve_1comp(chem.cas=NULL,chem.name=NULL,times=NULL,parameters=NULL,daily.dose=1,
          dose=NULL,doses.per.day=NULL, days=10,tsteps = 4, suppress.messages=F,
            species='Human',output.units='uM',plots=F,initial.values=NULL,
            iv.dose=F,method="lsoda",rtol=1e-8,atol=1e-12,
            default.to.human=F,dosing.matrix=NULL,recalc.elimination=F,...)
```

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
times	Optional time sequence for specified number of days.
parameters	Chemical parameters from parameterize_1comp function, overrides chem.name and chem.cas.
days	Length of the simulation.
tsteps	The number time steps per hour.
daily.dose	Total daily dose, mg/kg BW.
dose	Amount of a single dose, mg/kg BW. Overwrites daily.dose.
doses.per.day	Number of doses per day.
species	Species desired (either "Rat", "Rabbit", "Dog", or default "Human").
iv.dose	Simulates a single i.v. dose if true.
output.units	Desired units (either "mg/L", "mg", "umol", or default "uM").
initial.values	Vector containing the initial concentrations or amounts of the chemical in specified tissues with units corresponding to output.units. Defaults are zero.
suppress.messages	Whether or not the output message is suppressed.
plots	Plots all outputs if true.
method	Method used by integrator (deSolve).
rtol	Argument passed to integrator (deSolve).
atol	Argument passed to integrator (deSolve).
default.to.human	Substitutes missing rat values with human values if true.
dosing.matrix	Vector of dosing times or a matrix consisting of two columns or rows named "dose" and "time" containing the time and amount, in mg/kg BW, of each dose.
recalc.elimination	Whether or not to recalculate the elimination rate.
...	Additional arguments passed to the integrator.

Details

Note that the model parameters have units of hours while the model output is in days.

Default value of NULL for doses.per.day solves for a single dose.

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

AUC is area under plasma concentration curve.

Value

A matrix with a column for time(in days) and a column for the compartment and the area under the curve (concentration only).

Author(s)

Robert Pearce

Examples

```
solve_1comp(chem.name='Bisphenol-A')
## Not run:
solve_1comp(chem.name='Bisphenol-A',doses.per.day=3,tsteps=50,days=20)

## End(Not run)
```

---

solve_3comp *Solve_3comp*

Description

This function solves for the amounts or concentrations of a chemical in different tissues as functions of time based on the dose and dosing frequency. It uses a three compartment model with partition coefficients.

Usage

```
solve_3comp(chem.name = NULL, chem.cas = NULL, times=NULL,
            parameters=NULL, days=10, tsteps = 4, daily.dose = 1,dose=NULL,
           doses.per.day=NULL, initial.values=NULL,plots=F, suppress.messages=F,
            species="Human", iv.dose=F,output.units='uM',
            method="lsoda",rtol=1e-8,
            atol=1e-12,default.to.human=F,recalc.blood2plasma=F,
            recalc.clearance=F,dosing.matrix=NULL,...)
```

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
times	Optional time sequence for specified number of days. The dosing sequence begins at the beginning of times.
parameters	Chemical parameters from parameterize_3comp function, overrides chem.name and chem.cas.
days	Length of the simulation.
tsteps	The number time steps per hour.
daily.dose	Total daily dose, mg/kg BW.
dose	Amount of a single dose, mg/kg BW. Overwrites daily.dose.
doses.per.day	Number of doses per day.
initial.values	Vector containing the initial concentrations or amounts of the chemical in specified tissues with units corresponding to output.units. Defaults are zero.

plots	Plots all outputs if true.
suppress.messages	Whether or not the output message is suppressed.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
iv.dose	Simulates a single i.v. dose if true.
output.units	Desired units (either "mg/L", "mg", "umol", or default "uM").
method	Method used by integrator (deSolve).
rtol	Argument passed to integrator (deSolve).
atol	Argument passed to integrator (deSolve).
default.to.human	Substitutes missing animal values with human values if true (hepatic intrinsic clearance or fraction of unbound plasma).
recalc.blood2plasma	Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters, calculated with hematocrit, Funbound.plasma, and Krbc2pu.
recalc.clearance	Recalculates the the hepatic clearance (Clmetabolism) with new million.cells.per.gliver parameter.
dosing.matrix	Vector of dosing times or a matrix consisting of two columns or rows named "dose" and "time" containing the time and amount, in mg/kg BW, of each dose.
...	Additional arguments passed to the integrator.

Details

Note that the model parameters have units of hours while the model output is in days.

Default of NULL for doses.per.day solves for a single dose.

The compartments used in this model are the small intestine, portal vein, liver, and systemic compartment.

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Value

A matrix of class deSolve with a column for time(in days) and each compartment, the plasma concentration, area under the curve, and a row for each time point.

Author(s)

John Wambaugh and Robert Pearce

Examples

```
solve_3comp(chem.name='Bisphenol-A',doses.per.day=3,dose=1/3)
 solve_3comp(chem.name='Nicotine',doses.per.day=2)
```

solve_pbtk *Solve_PBTK*

Description

This function solves for the amounts or concentrations in uM of a chemical in different tissues as functions of time based on the dose and dosing frequency.

Usage

```
solve_pbtk(chem.name = NULL, chem.cas = NULL, times=NULL, parameters=NULL,
           days=10, tsteps = 4, daily.dose=1,dose = NULL,doses.per.day=NULL,
           initial.values=NULL,plots=F,suppress.messages=F,species="Human",
           iv.dose=F,output.units='uM',method="lsoda",rtol=1e-8,atol=1e-12,
           default.to.human=F,recalc.blood2plasma=F,recalc.clearance=F,
           dosing.matrix=NULL,...)
```

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
times	Optional time sequence for specified number of days. Dosing sequence begins at the beginning of times.
parameters	Chemical parameters from parameterize_pbtk function, overrides chem.name and chem.cas.
days	Length of the simulation.
tsteps	The number time steps per hour.
daily.dose	Total daily dose, mg/kg BW.
dose	Amount of a single dose, mg/kg BW. Overwrites daily.dose.
doses.per.day	Number of doses per day.
initial.values	Vector containing the initial concentrations or amounts of the chemical in specified tissues with units corresponding to output.units. Defaults are zero.
plots	Plots all outputs if true.
suppress.messages	Whether or not the output message is suppressed.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
iv.dose	Simulates a single i.v. dose if true.
output.units	Desired units (either "mg/L", "mg", "umol", or default "uM").
method	Method used by integrator (deSolve).
rtol	Argument passed to integrator (deSolve).
atol	Argument passed to integrator (deSolve).

`default.to.human`
: Substitutes missing animal values with human values if true (hepatic intrinsic clearance or fraction of unbound plasma).

`recalc.blood2plasma`
: Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters, calculated with hematocrit, Funbound.plasma, and Krbc2pu.

`recalc.clearance`
: Recalculates the the hepatic clearance (Clmetabolism) with new million.cells.per.gliver parameter.

`dosing.matrix`
: Vector of dosing times or a matrix consisting of two columns or rows named "dose" and "time" containing the time and amount, in mg/kg BW, of each dose.

`...`
: Additional arguments passed to the integrator.

Details

Note that the model parameters have units of hours while the model output is in days.

Default NULL value for doses.per.day solves for a single dose.

The compartments used in this model are the gutlumen, gut, liver, kidneys, veins, arteries, lungs, and the rest of the body.

The extra compartments include the amounts or concentrations metabolized by the liver and excreted by the kidneys through the tubules.

AUC is the area under the curve of the plasma concentration.

When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Value

A matrix of class deSolve with a column for time(in days), each compartment, the area under the curve, and plasma concentration and a row for each time point.

Author(s)

John Wambaugh and Robert Pearce

Examples

```
solve_pbtk(chem.name='Bisphenol-A',plots=TRUE,doses.per.day=3,dose=1/3)
 solve_pbtk(chem.name='Nicotine',doses.per.day=2)
```

tissue.data *Tissue composition and species-specific physiology parameters*

Description

This data set contains values from Schmitt (2008) describing the composition of specific tissues and from Birnbaum et al. (1994) describing volumes of and blood flows to those tissues, allowing parameterization of toxicokinetic models for human, mouse, rat, dog, or rabbit.

Usage

```
tissue.data
```

Format

A data.frame containing 13 rows and 20 columns.

Author(s)

John Wambaugh and Nisha Sipes

Source

Wambaugh et al. (2014), in preparation

References

Birnbaum, L and Brown, R and Bischoff, K and Foran, J and Blancato, J and Clewell, H and Dedrick, R (1994). Physiological parameter values for PBPK model. International Life Sciences Institute, Risk Science Institute, Washington, DC

Schmitt, W. (2008). General approach for the calculation of tissue to plasma partition coefficients. Toxicology in vitro : an international journal published in association with BIBRA 22(2), 457-67, 10.1016/j.tiv.2007.09.010.

Wetmore.data *Published toxicokinetic predictions based on in vitro data*

Description

This data set gives the chemical specific predictions for serum concentration at steady state resulting from constant infusion exposure, as published in a series of papers from Barbara Wetmore's group at the Hamner Institutes for Life Sciences. Predictions include the median and 90% interval in uM and mg/L. Calculations were made using the 1 and 10 uM in vitro measured clearances.

Usage

```
Wetmore.data
```

Format

A data.frame containing 577 rows and 20 columns.

Source

Wambaugh et al. (2014), in preparation

References

Wetmore, B.A., Wambaugh, J.F., Ferguson, S.S., Sochaski, M.A., Rotroff, D.M., Freeman, K., Clewell, H.J., Dix, D.H., Andersen, M.E., Houck, K.A., Allen, B., Judson, R.S., Sing, R., Kavlock, R.J., Richard, A.M., and Thomas, R.S., "Integration of Dosimetry, Exposure and High-Throughput Screening Data in Chemical Toxicity Assessment," Toxicological Sciences 125 157-174 (2012)

Wetmore, B.A., Wambaugh, J.F., Ferguson, S.S., Li, L., Clewell, H.J. III, Judson, R.S., Freeman, K., Bao, W, Sochaski, M.A., Chu T.-M., Black, M.B., Healy, E, Allen, B., Andersen M.E., Wolfinger, R.D., and Thomas R.S., "The Relative Impact of Incorporating Pharmacokinetics on Predicting in vivo Hazard and Mode-of-Action from High-Throughput in vitro Toxicity Assays" Toxicological Sciences, 132:327-346 (2013).

Wetmore, B. A., Wambaugh, J. F., Allen, B., Ferguson, S. S., Sochaski, M. A., Setzer, R. W., Houck, K. A., Strope, C. L., Cantwell, K., Judson, R. S., LeCluyse, E., Clewell, H.J. III, Thomas, R.S., and Andersen, M. E. (2015). "Incorporating High-Throughput Exposure Predictions with Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing" Toxicological Sciences, kfv171.

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