Package 'httk'

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Title High-Throughput Toxicokinetics

Description Generic models and chemical-specific data for simulation and statistical analysis of chemical toxicokinetics (``TK'') as described by Pearce et al. (2017) <doi:10.18637/jss.v079.i04>. Chemical-specific in vitro data have been obtained from relatively high throughput experiments. Both physiologically-based (``PBTK'') and empirical (for example, one compartment) ``TK'' models can be parameterized with the data provided for thousands of chemicals, multiple exposure routes, and various species. The models consist of systems of ordinary differential equations which are solved using compiled (C-based) code for speed. A Monte Carlo sampler is included, which allows for simulating human biological variability (Ring et al., 2017 <doi:10.1016/j.envint.2017.06.004>) and propagating parameter uncertainty. Calibrated methods are included for predicting tissue:plasma partition coefficients and volume of distribution (Pearce et al., 2017 <doi:10.1007/s10928-017-9548-7>). These functions and data provide a set of tools for in vitro-in vivo extrapolation (``IVIVE'') of high throughput screening data (for example, Tox21, ToxCast) to real-world exposures via reverse dosimetry (also known as ``RTK'') (Wetmore et al., 2015 <doi:10.1093/toxsci/kfv171>).

Depends R (>= 2.10)

Imports deSolve, msm, data.table, survey, mvtnorm, truncnorm, stats, graphics, utils, magrittr, purrr, methods

Suggests ggplot2, knitr, rmarkdown, R.rsp, GGally, gplots, scales, EnvStats, MASS, RColorBrewer, TeachingDemos, classInt, ks, stringr, reshape, reshape2, gdata, viridis, CensRegMod, gmodels, colorspace, cowplot, ggrepel, dplyr, forcats, smatr, gtools, gridExtra

License GPL-3

LazyData true

Encoding UTF-8

VignetteBuilder knitr, R.rsp

RoxygenNote 7.1.1

URL https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research

BugReports https://github.com/USEPA/CompTox-ExpoCast-httk

NeedsCompilation yes

Author John Wambaugh [aut, cre] (<https://orcid.org/0000-0002-4024-534X>),
Robert Pearce [aut] (<https://orcid.org/0000-0003-3168-4049>),
Caroline Ring [aut] (<https://orcid.org/0000-0002-0463-1251>),
Greg Honda [aut] (<https://orcid.org/0000-0001-7713-9850>),
Mark Sfeir [aut], Matt Linakis [aut] (<https://orcid.org/0000-0003-0526-2395>),
Jimena Davis [ctb], James Sluka [ctb] (<https://orcid.org/0000-0002-5901-1404>),
Nisha Sipes [ctb] (<https://orcid.org/0000-0003-4203-6426>),
Barbara Wetmore [ctb] (<https://orcid.org/0000-0002-6878-5348>),
Woodrow Setzer [ctb] (<https://orcid.org/0000-0002-6709-9186>)

Maintainer John Wambaugh <wambaugh.john@epa.gov>

R topics documented:

`httk-package` *High-Throughput Toxicokinetics*

Description

Generic models and chemical-specific data for simulation and statistical analysis of chemical toxicokinetics ("TK") as described by Pearce et al. (2017) <doi:10.18637/jss.v079.i04>. Chemical-specific in vitro data have been obtained from relatively high throughput experiments. Both physiologically-based ("PBTK") and empirical (for example, one compartment) "TK" models can be parameterized with the data provided for thousands of chemicals, multiple exposure routes, and various species. The models consist of systems of ordinary differential equations which are solved using compiled (C-based) code for speed. A Monte Carlo sampler is included, which allows for simulating human biological variability (Ring et al., 2017 <doi:10.1016/j.envint.2017.06.004>) and propagating parameter uncertainty. Calibrated methods are included for predicting tissue:plasma partition coefficients and volume of distribution (Pearce et al., 2017 <doi:10.1007/s10928-017-9548-7>). These functions and data provide a set of tools for in vitro-in vivo extrapolation ("IVIVE") of high throughput screening data (for example, Tox21, ToxCast) to real-world exposures via reverse dosimetry (also known as "RTK") (Wetmore et al., 2015 <doi:10.1093/toxsci/kfv171>).

Author(s)

John Wambaugh, Robert Pearce, Caroline Ring, Gregory Honda, Nisha Sipes, Jimena Davis, Barbara Wetmore, Woodrow Setzer, Mark Sfeir

See Also

PowerPoint Presentation: High-Throughput Toxicokinetics (HTTK) R package

Pearce et al. (2017): httk: R Package for High-Throughput Toxicokinetics

Wetmore et al. (2015): Incorporating High-Throughput Exposure Predictions With Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing

Wambaugh et al. (2015): Toxicokinetic Triage for Environmental Chemicals

Pearce et al. (2017): Evaluation and calibration of high-throughput predictions of chemical distribution to tissues

Ring et al. (2017): Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability

Sipes et al. (2017): An Intuitive Approach for Predicting Potential Human Health Risk with the Tox21 10k Library

Wambaugh et al. (2018): Evaluating In Vitro-In Vivo Extrapolation of Toxicokinetics

Honda et al. (2019): Using the concordance of in vitro and in vivo data to evaluate extrapolation assumptionss

Wambaugh et al. (2019): Assessing Toxicokinetic Uncertainty and Variability in Risk Prioritization

Linakis et al. (2020): Development and evaluation of a high throughput inhalation model for organic chemicals

EPA's ExpoCast (Exposure Forecasting) Project

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,
  sig.fig = 4,
  clint.pvalue.overwrite = T,
  allow.na = F
)
```

Arguments

new.table	Object of class data.frame containing one row per chemical, with each chemical minimally 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'.
current.table	This is the table to which data are 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 are 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 are ignored. Funbound.plasma values of 0 (below limit of detection) are overwritten either way.
sig.fig	Sets the number of significant figures stored (defaults to 4)
clint.pvalue.overwrite	If TRUE then the Cl_int p-value is set to NA when the Cl_int value is changed unless a new p-value is provided. (defaults to TRUE)
allow.na	If TRUE (default is FALSE) then NA values are written to the table, otherwise they are 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("111-11-2","222-22-0","333-33-5"),
                     stringsAsFactors=FALSE))
my.new.data <- cbind(my.new.data,as.data.frame(c("DTX1","DTX2","DTX3"),
                    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","DTXSID","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",
                                  DTXSID="DTXSID",
                                  MW="MW",
                                  logP="LogP",
                                  Funbound.plasma="Fup",
                                  Clint="CLint"),
                                  species="Human",
                                  reference="MyPaper 2015")
parameterize_steadystate(chem.name="C")
calc_css(chem.name="B")
```

---

age_dist_smooth *Smoothed age distributions by race and gender.*

Description

Distributions of ages in months, computed from NHANES data smoothed using survey::svysmooth(), for each combination of race/ethnicity and gender.

Usage

```
age_dist_smooth
```

Format

A data.table object with three variables:

`gender` Gender: Male or Female

`reth` Race/ethnicity

`smth` A list of `svysmooth` objects, each encoding a weighted smoothed distribution of ages.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

`age_draw_smooth` *Draws ages from a smoothed distribution for a given gender/race combination*

Description

Draws ages from a smoothed distribution for a given gender/race combination

Usage

```
age_draw_smooth(g, r, nsamp, agelim_months)
```

Arguments

`g`	Gender. Either 'Male' or 'Female'.
`r`	Race/ethnicity. One of 'Mexican American', 'Other Hispanic', 'Non-Hispanic Black', 'Non-Hispanic White', 'Other'.
`nsamp`	Number of ages to draw.
`agelim_months`	Two-element numeric vector giving the minimum and maximum ages in months to include.

Value

A named list with members 'ages_months' and 'ages_years', each numeric of length `nsamp`, giving the sampled ages in months and years.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

`armitage_estimate_sarea` *Estimate well surface area*

Description

Estimate geometry surface area of plastic in well plate based on well plate format suggested values from Corning. option.plastic == T (default) give nonzero surface area (sarea, m^2) option.bottom == T (default) includes surface area of the bottom of the well in determining sarea. Optionally include user values for working volume (v_working, m^3) and surface area.

Usage

```
armitage_estimate_sarea(
  tcdata = NA,
  this.well_number = 384,
  this.cell_yield = NA,
  this.v_working = NA
)
```

Arguments

`tcdata`	A data table with well_number corresponding to plate format, optionally include v_working, sarea, option.bottom, and option.plastic
`this.well_number`	For single value, plate format default is 384, used if is.na(tcdata)==T
`this.cell_yield`	For single value, optionally supply cell_yield, otherwise estimated based on well number
`this.v_working`	For single value, optionally supply working volume, otherwise estimated based on well number (m^3)

Value

tcdata, A data table with well_number, sarea (surface area, m^2), cell_yield (# cells), v_working (m^3), v_total (m^3) per well

Author(s)

Greg Honda

armitage_eval *Evaluate the updated Armitage model*

Description

Evaluate the Armitage model for chemical distributon in vitro. Takes input as data table or vectors of values. Outputs a data table. Updates over the model published in Armitage et al. 2014 include binding to plastic walls and lipid and protein compartments in cells.

Usage

```
armitage_eval(
  casrn.vector = NA_character_,
  nomconc.vector = 1,
  this.well_number = 384,
  this.FBSf = NA_real_,
  tcdata = NA,
  this.sarea = NA_real_,
  this.v_total = NA_real_,
  this.v_working = NA_real_,
  this.cell_yield = NA_real_,
  this.Tsys = 37,
  this.Tref = 298.15,
  this.option.kbsa2 = F,
  this.option.swat2 = F,
  this.pseudooct = 0.01,
  this.memblip = 0.04,
  this.nlom = 0.2,
  this.P_nlom = 0.035,
  this.P_dom = 0.05,
  this.P_cells = 1,
  this.csalt = 0.15,
  this.celldensity = 1,
  this.cellmass = 3,
  this.f_oc = 1
)
```

Arguments

casrn.vector	For vector or single value, CAS number
nomconc.vector	For vector or single value, micromolar nominal concentration (e.g. AC50 value)
this.well_number	For single value, plate format default is 384, used if is.na(tcdata)==T
this.FBSf	Fraction fetal bovine serum, must be entered by user.
tcdata	A data.table with casrn, nomconc, MP, gkow, gkaw, gswat, sarea, v_total, v_working. Otherwise supply single values to this.params.
this.sarea	Surface area per well (m^2)
this.v_total	Total volume per well (m^3)
this.v_working	Working volume per well (m^3)

this.cell_yield
: Number of cells per well

this.Tsys
: System temperature (oC)

this.Tref
: Reference temperature (K)

this.option.kbsa2
: Use alternative bovine-serum-albumin partitioning model

this.option.swat2
: Use alternative water solubility correction

this.pseudooct
: Pseudo-octanol cell storage lipid content

this.memblip
: Membrane lipid content of cells

this.nlom
: Structural protein conent of cells

this.P_nlom
: Proportionality constant to octanol structural protein

this.P_dom
: Proportionality constant to octnaol dom

this.P_cells
: Proportionality constant to octanol storage lipid

this.csalt
: Ionic strength of buffer, mol/L

this.celldensity
: Cell density kg/L, g/mL

this.cellmass
: Mass per cell, ng/cell

this.f_oc
: 1, everything assumed to be like proteins

Value

tcdata

Author(s)

Greg Honda

References

Armitage, J. M.; Wania, F.; Arnot, J. A. Environ. Sci. Technol. 2014, 48, 9770-9779. https://doi.org/10.1021/es501955g
Honda et al. PloS one 14.5 (2019): e0217564. https://doi.org/10.1371/journal.pone.0217564

Examples

```
temp <- armitage_eval(casrn.vector = c("80-05-7", "81-81-2"), this.FBSf = 0.1,
this.well_number = 384, nomconc = 10)
print(temp$cfree.invitro)
```

armitage_input *Armitage et al. (2014) Model Inputs from Honda et al. (2019)*

Description

Armitage et al. (2014) Model Inputs from Honda et al. (2019)

Usage

```
armitage_input
```

Format

A data frame with 53940 rows and 10 variables:

MP

MW

casrn

compound_name

gkaw

gkow

gswat

Author(s)

Greg Honda

Source

https://www.diamondse.info/

References

Armitage, J. M.; Wania, F.; Arnot, J. A. Environ. Sci. Technol. 2014, 48, 9770-9779. dx.doi.org/10.1021/es501955g

Honda, Gregory S., et al. "Using the Concordance of In Vitro and In Vivo Data to Evaluate Extrapolation Assumptions", PloS ONE 14.5 (2019): e0217564.

augment.table *Add a paramter value to the chem.physical_and_invitro.data table*

Description

This internal function is used by add_chemtable to add a single new parameter to the table of chemical parameters. It should not be typically used from the command line.

Usage

```
augment.table(
  this.table,
  this.CAS,
  compound.name = NULL,
  this.property,
  value,
  species = NULL,
  reference,
  overwrite = F,
  sig.fig = 4,
  clint.pvalue.overwrite = T,
  allow.na = F
)
```

Arguments

this.table	Object of class data.frame containing one row per chemical.
this.CAS	The Chemical Abstracts Service registry number (CAS-RN) correponding to the parameter value
compound.name	A name associated with the chemical (defaults to NULL)
this.property	The property being added/modified.
value	The value being assigned to this.property.
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 are not species-specific (e.g., MW).
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.
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 are ignored. Funbound.plasma values of 0 (below limit of detection) are overwritten either way.
sig.fig	Sets the number of significant figures stored (defaults to 4)
clint.pvalue.overwrite	If TRUE then the Cl_int p-value is set to NA when the Cl_int value is changed unless a new p-value is provided. (defaults to TRUE)
allow.na	If TRUE (default is FALSE) then NA values are written to the table, otherwise they are ignored.

Value

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

Author(s)

John Wambaugh

`available_rblood2plasma` *Find the best available ratio of the blood to plasma concentration constant.*

Description

This function finds the best available constant ratio of the blood concentration to the plasma concentration, using get_rblood2plasma and calc_rblood2plasma.

Usage

```
available_rblood2plasma(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
  adjusted.Funbound.plasma = T,
  suppress.messages = F
)
```

Arguments

`chem.cas`	Either the CAS number or the chemical name must be specified.
`chem.name`	Either the chemical name or the CAS number must be specified.
`dtxsid`	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
`species`	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
`adjusted.Funbound.plasma`	Whether or not to use Funbound.plasma adjustment if calculating Rblood2plasma.
`suppress.messages`	Whether or not to display relevant warning messages to user.

Details

Either retrieves a measured blood:plasma concentration ratio from the chem.physical_and_invitro.data table or calculates it using the red blood cell partition coefficient predicted with Schmitt's method

If available, in vivo data (from chem.physical_and_invitro.data) for the given species is returned, substituting the human in vivo value when missing for other species. In the absence of in vivo data, the value is calculated with calc_rblood2plasma for the given species. If Funbound.plasma is unvailable for the given species, the human Funbound.plasma is substituted. If none of these are available, the mean human Rblood2plasma from chem.physical_and_invitro.data is returned. details than the description above ~~

Author(s)

Robert Pearce

Examples

```
available_rblood2plasma(chem.name="Bisphenol A",adjusted.Funbound.plasma=FALSE)
available_rblood2plasma(chem.name="Bisphenol A",species="Rat")
```

---

blood_mass_correct *Find average blood masses by age.*

Description

If blood mass from blood_weight is negative or very small, then just default to the mean blood mass by age. (Geigy Scientific Tables, 7th ed.)

Usage

```
blood_mass_correct(blood_mass, age_months, age_years, gender, weight)
```

Arguments

blood_mass	A vector of blood masses in kg to be replaced with averages.
age_months	A vector of ages in months.
age_years	A vector of ages in years.
gender	A vector of genders (either 'Male' or 'Female').
weight	A vector of body weights in kg.

Value

A vector of blood masses in kg.

Author(s)

Caroline Ring

References

Geigy Pharmaceuticals, "Scientific Tables", 7th Edition, John Wiley and Sons (1970)

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

blood_weight *Predict blood mass.*

Description

Predict blood mass based on body surface area and gender, using equations from Bosgra et al. 2012

Usage

```
blood_weight(BSA, gender)
```

Arguments

BSA	Body surface area in m^2. May be a vector.
gender	Either 'Male' or 'Female'. May be a vector.

Value

A vector of blood masses in kg the same length as BSA and gender.

Author(s)

Caroline Ring

References

Bosgra, Sieto, et al. "An improved model to predict physiologically based model parameters and their inter-individual variability from anthropometry." Critical reviews in toxicology 42.9 (2012): 751-767.

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

bmiage *CDC BMI-for-age charts*

Description

Charts giving the BMI-for-age percentiles for boys and girls ages 2-18

Usage

```
bmiage
```

Format

A data.table object with variables

Sex 'Male' or 'Female'

Agemos Age in months

L, M, S LMS parameters; see https://www.cdc.gov/growthcharts/percentile_data_files.htm

P3, P5, P10, P25, P50, P75, P85, P90, P95, **and** P97 BMI percentiles

Details

For children ages 2 to 18, weight class depends on the BMI-for-age percentile.

Underweight <5th percentile

Normal weight 5th-85th percentile

Overweight 85th-95th percentile

Obese >=95th percentile

Author(s)

Caroline Ring

Source

https://www.cdc.gov/growthcharts/percentile_data_files.htm

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

`body_surface_area` *Predict body surface area.*

Description

Predict body surface area from weight, height, and age, using Mosteller's formula for age>18 and Haycock's formula for age<18

Usage

```
body_surface_area(BW, H, age_years)
```

Arguments

`BW`	A vector of body weights in kg.
`H`	A vector of heights in cm.
`age_years`	A vector of ages in years.

Value

A vector of body surface areas in cm^2.

Author(s)

Caroline Ring

References

Mosteller, R. D. "Simplified calculation of body surface area." N Engl J Med 317 (1987): 1098..

Haycock, George B., George J. Schwartz, and David H. Wisotsky. "Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults." The Journal of pediatrics 93.1 (1978): 62-66.

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

`bone_mass_age` *Predict bone mass*

Description

Predict bone mass from age_years, height, weight, gender, using logistic equations fit to data from Baxter-Jones et al. 2011, or for infants < 1 year, using equation from Koo et al. 2000 (See Price et al. 2003)

Usage

```
bone_mass_age(age_years, age_months, height, weight, gender)
```

Arguments

`age_years`	Vector of ages in years.
`age_months`	Vector of ages in months.
`height`	Vector of heights in cm.
`weight`	Vector of body weights in kg.
`gender`	Vector of genders, either 'Male' or 'Female'.

Value

Vector of bone masses.

Author(s)

Caroline Ring

References

Baxter-Jones, Adam DG, et al. "Bone mineral accrual from 8 to 30 years of age: an estimation of peak bone mass." Journal of Bone and Mineral Research 26.8 (2011): 1729-1739.

Koo, Winston WK, and Elaine M. Hockman. "Physiologic predictors of lumbar spine bone mass in neonates." Pediatric research 48.4 (2000): 485-489.

Price, Paul S., et al. "Modeling interindividual variation in physiological factors used in PBPK models of humans." Critical reviews in toxicology 33.5 (2003): 469-503.

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

brain_mass *Predict brain mass.*

Description

Predict brain mass from gender and age.

Usage

```
brain_mass(gender, age_years)
```

Arguments

gender	Vector of genders, either 'Male' or 'Female'
age_years	Vector of ages in years.

Value

A vector of brain masses in kg.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

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,
  dtxsid = NULL,
  parameters = NULL,
  species = "human",
  daily.dose = 1,
  output.units = "uM",
  model = "pbtk",
  concentration = "plasma",
  suppress.messages = F,
```

```
  tissue = NULL,
  restrictive.clearance = T,
  bioactive.free.invivo = F,
  IVIVE = NULL,
  parameterize.args = list(default.to.human = F, adjusted.Funbound.plasma = T,
    regression = T, minimum.Funbound.plasma = 1e-04),
  ...
)
```

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.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_pbtk (for model = 'pbtk'), parameterize_3comp (for model = '3compartment), parmeterize_1comp(for model = '1compartment') or parameterize_steadystate (for model = '3compartmentss'), 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.
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.
concentration	Desired concentration type, 'blood','tissue', or default 'plasma'.
suppress.messages	Whether or not the output message is suppressed.
tissue	Desired tissue conentration (defaults to whole body concentration.)
restrictive.clearance	If TRUE (default), then only the fraction of chemical not bound to protein is available for metabolism in the liver. If FALSE, then all chemical in the liver is metabolized (faster metabolism due to rapid off-binding).
bioactive.free.invivo	If FALSE (default), then the total concentration is treated as bioactive in vivo. If TRUE, the the unbound (free) plasma concentration is treated as bioactive in vivo. Only works with tissue = NULL in current implementation.
IVIVE	Honda et al. (2019) identified four plausible sets of assumptions for *in vitro-in vivo* extrapolation (IVIVE) assumptions. Argument may be set to "Honda1" through "Honda4". If used, this function overwrites the tissue, restrictive.clearance, and bioactive.free.invivo arguments. See Details below for more information.
parameterize.args	List of arguments passed to model's associated parameterization function, including default.to.human, adjusted.Funbound.plasma, regression, and minimum.Funbound.plasma. The default.to.human argument substitutes missing animal values with human values if true, adjusted.Funbound.plasma returns adjusted Funbound.plasma when set to TRUE along with parition coefficients calculated with this value, regression indicates whether or not to use the regressions in calculating partition coefficients, and minimum.Funbound.plasma is the value to which Monte Carlo

draws less than this value are set (default is 0.0001 – half the lowest measured Fup in our dataset).

... Additional parameters passed to parameterize function if parameters is NULL.

Details

Concentrations are calculated for the specifed model with constant oral infusion dosing. All tissues other than gut, liver, and lung are the product of the steady state plasma concentration and the tissue to plasma partition coefficient.

	in vivo Conc.	Metabolic Clearance	Bioactive Chemical Conc.	TK Statistic Used*
Honda1	Veinous (Plasma)	Restrictive	Free	Mean Conc.
Honda2	Veinous	Restrictive	Free	Max Conc.
Honda3	Veinous	Non-restrictive	Total	Mean Conc.
Honda4	Veinous	Non-restrictive	Total	Max Conc.
Honda5	Target Tissue	Non-restrictive	Total	Mean Conc.
Honda6	Target Tissue	Non-restrictive	Total	Max Conc.

*Assumption is currently ignored because analytical steady-state solutions are currently used by this function.

Value

Steady state concentration

Author(s)

Robert Pearce, John Wambaugh, and Greg Honda

References

Honda, Gregory S., et al. "Using the Concordance of In Vitro and In Vivo Data to Evaluate Extrapolation Assumptions." 2019. PLoS ONE 14(5): e0217564.

Examples

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

calc_analytic_css(chem.name='Bisphenol-A',tissue='liver',species='rabbit',
                parameterize.args = list(
                              default.to.human=TRUE,
                              adjusted.Funbound.plasma=TRUE,
                              regression=TRUE,
                              minimum.Funbound.plasma=1e-4),daily.dose=2)

calc_analytic_css(chem.name="bisphenol a",model="1compartment")

calc_analytic_css(chem.cas="80-05-7",model="3compartmentss")

params <- parameterize_pbtk(chem.cas="80-05-7")

calc_analytic_css(parameters=params,model="pbtk")
```

`calc_analytic_css_1comp` *Calculate the analytic steady state concentration for the one compartment model.*

Description

This function calculates the analytic steady state plasma or venous blood concentrations as a result of infusion dosing.

Usage

```
calc_analytic_css_1comp(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  hourly.dose = 1/24,
  concentration = "plasma",
  suppress.messages = F,
  recalc.blood2plasma = F,
  tissue = NULL,
  restrictive.clearance = T,
  bioactive.free.invivo = 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.
`dtxsid`	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
`parameters`	Chemical parameters from parameterize_pbtk (for model = 'pbtk'), parameterize_3comp (for model = '3compartment), parmeterize_1comp(for model = '1compartment') or parameterize_steadystate (for model = '3compartmentss'), overrides chem.name and chem.cas.
`hourly.dose`	Hourly dose rate mg/kg BW/h.
`concentration`	Desired concentration type, 'blood' or default 'plasma'.
`suppress.messages`	Whether or not the output message is suppressed.
`recalc.blood2plasma`	Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters. Use this if you have altered hematocrit, Funbound.plasma, or Krbc2pu.
`tissue`	Desired tissue conentration (defaults to whole body concentration.)
`restrictive.clearance`	If TRUE (default), then only the fraction of chemical not bound to protein is available for metabolism in the liver. If FALSE, then all chemical in the liver is metabolized (faster metabolism due to rapid off-binding).

bioactive.free.invivo
: If FALSE (default), then the total concentration is treated as bioactive in vivo. If TRUE, the the unbound (free) plasma concentration is treated as bioactive in vivo. Only works with tissue = NULL in current implementation.

...
: Additional parameters passed to parameterize function if parameters is NULL.

Value

Steady state concentration in uM units

Author(s)

Robert Pearce and John Wambaugh

---

calc_analytic_css_3comp

Calculate the analytic steady state concentration for model 3comp

---

Description

This function calculates the analytic steady state plasma or venous blood concentrations as a result of infusion dosing.

Usage

```
calc_analytic_css_3comp(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  hourly.dose = 1/24,
  concentration = "plasma",
  suppress.messages = F,
  recalc.blood2plasma = F,
  tissue = NULL,
  restrictive.clearance = T,
  bioactive.free.invivo = FALSE,
  ...
)
```

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.

dtxsid
: EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs

parameters
: Chemical parameters from parameterize_pbtk (for model = 'pbtk'), parameterize_3comp (for model = '3compartment), parmeterize_1comp(for model = '1compartment') or parameterize_steadystate (for model = '3compartmentss'), overrides chem.name and chem.cas.

hourly.dose	Hourly dose rate mg/kg BW/h.
concentration	Desired concentration type, 'blood' or default 'plasma'.
suppress.messages	Whether or not the output message is suppressed.
recalc.blood2plasma	Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters. Use this if you have 'altered hematocrit, Funbound.plasma, or Krbc2pu.
tissue	Desired tissue conentration (defaults to whole body concentration.)
restrictive.clearance	If TRUE (default), then only the fraction of chemical not bound to protein is available for metabolism in the liver. If FALSE, then all chemical in the liver is metabolized (faster metabolism due to rapid off-binding).
bioactive.free.invivo	If FALSE (default), then the total concentration is treated as bioactive in vivo. If TRUE, the the unbound (free) plasma concentration is treated as bioactive in vivo. Only works with `tissue = NULL` in current implementation.
...	Additional parameters passed to parameterize function if parameters is NULL.

Value

Steady state concentration in uM units

Author(s)

Robert Pearce and John Wambaugh

`calc_analytic_css_3compss`

Calculate the analytic steady state concentration for the three compartment steady-state model

---

Description

This function calculates the analytic steady state plasma or venous blood concentrations as a result of infusion dosing.

Usage

```
calc_analytic_css_3compss(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  hourly.dose = 1/24,
  concentration = "plasma",
  suppress.messages = F,
  recalc.blood2plasma = F,
  tissue = NULL,
  restrictive.clearance = T,
```

```
  bioactive.free.invivo = FALSE,
  ...
)
```

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.
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_pbtk (for model = 'pbtk'), parameterize_3comp (for model = '3compartment), parmeterize_1comp(for model = '1compartment') or parameterize_steadystate (for model = '3compartmentss'), overrides chem.name and chem.cas.
hourly.dose	Hourly dose rate mg/kg BW/h.
concentration	Desired concentration type, 'blood' or default 'plasma'.
suppress.messages	Whether or not the output message is suppressed.
recalc.blood2plasma	Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters. Use this if you have 'altered hematocrit, Funbound.plasma, or Krbc2pu.
tissue	Desired tissue concentration (defaults to whole body concentration.)
restrictive.clearance	If TRUE (default), then only the fraction of chemical not bound to protein is available for metabolism in the liver. If FALSE, then all chemical in the liver is metabolized (faster metabolism due to rapid off-binding).
bioactive.free.invivo	If FALSE (default), then the total concentration is treated as bioactive in vivo. If TRUE, the the unbound (free) plasma concentration is treated as bioactive in vivo. Only works with tissue = NULL in current implementation.
...	Additional parameters passed to parameterize function if parameters is NULL.

Value

Steady state concentration in uM units

Author(s)

Robert Pearce and John Wambaugh

`calc_analytic_css_pbtk` *Calculate the analytic steady state concentration for model pbtk.*

Description

This function calculates the analytic steady state plasma or venous blood concentrations as a result of infusion dosing.

Usage

```
calc_analytic_css_pbtk(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  hourly.dose = 1/24,
  concentration = "plasma",
  suppress.messages = F,
  recalc.blood2plasma = F,
  tissue = NULL,
  restrictive.clearance = T,
  bioactive.free.invivo = FALSE,
  ...
)
```

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.
`dtxsid`	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
`parameters`	Chemical parameters from parameterize_pbtk (for model = 'pbtk'), parameterize_3comp (for model = '3compartment), parmeterize_1comp(for model = '1compartment') or parameterize_steadystate (for model = '3compartmentss'), overrides chem.name and chem.cas.
`hourly.dose`	Hourly dose rate mg/kg BW/h.
`concentration`	Desired concentration type, 'blood', 'tissue', or default 'plasma'.
`suppress.messages`	Whether or not the output message is suppressed.
`recalc.blood2plasma`	Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters. Use this if you have 'altered hematocrit, Funbound.plasma, or Krbc2pu.
`tissue`	Desired tissue conentration (defaults to whole body concentration.)
`restrictive.clearance`	If TRUE (default), then only the fraction of chemical not bound to protein is available for metabolism in the liver. If FALSE, then all chemical in the liver is metabolized (faster metabolism due to rapid off-binding).

bioactive.free.invivo
: If FALSE (default), then the total concentration is treated as bioactive in vivo. If TRUE, the the unbound (free) plasma concentration is treated as bioactive in vivo. Only works with tissue = NULL in current implementation.

...
: Additional parameters passed to parameterize function if parameters is NULL.

Value

Steady state concentration in uM units

Author(s)

Robert Pearce and John Wambaugh

---

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(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  species = "Human",
  f = 0.01,
  daily.dose = 1,
  doses.per.day = 3,
  days = 21,
  output.units = "uM",
  suppress.messages = F,
  tissue = "plasma",
  model = "pbtk",
  default.to.human = F,
  f.change = 1e-05,
  adjusted.Funbound.plasma = T,
  regression = T,
  well.stirred.correction = T,
  restrictive.clearance = T,
  dosing = NULL,
  ...
)
```

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.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_pbtk function, overrides chem.name and chem.cas.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
f	Fractional distance from the final steady state concentration that the average concentration must come within to be considered at steady state.
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.
suppress.messages	Whether or not to suppress messages.
tissue	Desired tissue concentration (defaults to whole body concentration.)
model	Model used in calculation, 'pbtk' for the multiple compartment model,'3compartment' for the three compartment model, and '1compartment' for the 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.
adjusted.Funbound.plasma	Uses adjusted Funbound.plasma when set to TRUE along with partition coefficients calculated with this value.
regression	Whether or not to use the regressions in calculating partition coefficients.
well.stirred.correction	Uses correction in calculation of hepatic clearance for well-stirred model if TRUE for model 1compartment elimination rate. This assumes clearance relative to amount unbound in whole blood instead of plasma, but converted to use with plasma concentration.
restrictive.clearance	Protein binding not taken into account (set to 1) in liver clearance if FALSE.
dosing	The dosing object for more complicated scenarios. Defaults to repeated daily.dose spread out over doses.per.day
...	Additional arguments passed to model solver (default of solve_pbtk).

Value

frac	Ratio of the mean concentration on the day steady state is reached (baed on doses.per.day) to the analytical Css (based on infusion dosing).
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, John Wambaugh

Examples

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

parms <- parameterize_3comp(chem.name='Bisphenol-A')
parms$Funbound.plasma <- .07
calc_css(parameters=parms,model='3compartment')

out <- solve_pbtk(chem.name = "Bisphenol A",
  days = 50,
  daily.dose=1,
  doses.per.day = 3)
plot.data <- as.data.frame(out)
css <- calc_analytic_css(chem.name = "Bisphenol A")
## Not run:
library("ggplot2")
c.vs.t <- ggplot(plot.data,aes(time, Cplasma)) + geom_line() +
geom_hline(yintercept = css) + ylab("Plasma Concentration (uM)") +
xlab("Day") + theme(axis.text = element_text(size = 16), axis.title =
element_text(size = 16), plot.title = element_text(size = 17)) +
ggtitle("Bisphenol A")

print(c.vs.t)

## End(Not run)

# Make a plot for all chemicals (takes a while):
## Not run:
days <- NULL
avg <- NULL
max <- NULL
for(this.cas in get_cheminfo(model="pbtk")){
  css.info <- calc_css(chem.cas = this.cas, doses.per.day = 1,suppress.messages=T)
  days[[this.cas]] <- css.info[["the.day"]]
  avg[[this.cas]] <- css.info[["avg"]]
  max[[this.cas]] <- css.info[["max"]]
}
days.data <- as.data.frame(days)
hist <- ggplot(days.data, aes(days)) +
geom_histogram(fill = "blue", binwidth = 1/6) + scale_x_log10() +
ylab("Number of Chemicals") + xlab("Days") + theme(axis.text =
element_text(size = 16), axis.title = element_text(size = 16))
print(hist)
avg.max.data <- as.data.frame(cbind(avg, max))
avg.vs.max <- ggplot(avg.max.data, aes(avg, max)) + geom_point() +
geom_abline() + scale_x_log10() + scale_y_log10() +
xlab("Average Concentration at Steady State (uM)") +
ylab("Max Concentration at Steady State (uM)") +
theme(axis.text = element_text(size = 16),
axis.title = element_text(size = 16))
print(avg.vs.max)
```

```
## End(Not run)
```

`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,
  dtxsid = NULL,
  parameters = NULL,
  species = "Human",
  suppress.messages = F,
  default.to.human = F,
  restrictive.clearance = T,
  adjusted.Funbound.plasma = T,
  regression = T,
  well.stirred.correction = T,
  clint.pvalue.threshold = 0.05,
  minimum.Funbound.plasma = 1e-04
)
```

Arguments

`chem.cas`	Either the cas number or the chemical name must be specified.
`chem.name`	Either the chemical name or the cas number must be specified.
`dtxsid`	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
`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.
`restrictive.clearance`	In calculating elimination rate, protein binding is not taken into account (set to 1) in liver clearance if FALSE.
`adjusted.Funbound.plasma`	Uses adjusted Funbound.plasma when set to TRUE along with partition coefficients calculated with this value.
`regression`	Whether or not to use the regressions in calculating partition coefficients.

well.stirred.correction
: Uses correction in calculation of hepatic clearance for -stirred model if TRUE. This assumes clearance relative to amount unbound in whole blood instead of plasma, but converted to use with plasma concentration.

clint.pvalue.threshold
: Hepatic clearance for chemicals where the in vitro clearance assay result has a p-values greater than the threshold are set to zero.

minimum.Funbound.plasma
: Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).

Details

Elimination rate calculated by dividing the total clearance (using the default -stirred hepatic model) by the volume of distribution. 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.cas="80-05-7")
```

---

calc_hepatic_clearance

Calculate the hepatic clearance (deprecated).

Description

This function is included for backward compatibility. It calls calc_hep_clearance which calculates the hepatic clearance in plasma for a well-stirred model or other type if specified. Based on Ito and Houston (2004)

Usage

```
calc_hepatic_clearance(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
```

```
  species = "Human",
  default.to.human = F,
  hepatic.model = "well-stirred",
  suppress.messages = F,
  well.stirred.correction = T,
  restrictive.clearance = T,
  adjusted.Funbound.plasma = T,
  ...
)
```

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.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_steadystate function, overrides chem.name and chem.cas.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
default.to.human	Substitutes missing animal values with human values if true.
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.
well.stirred.correction	Uses correction in calculation of hepatic clearance for well-stirred model if TRUE for hepatic.model well-stirred. This assumes clearance relative to amount unbound in whole blood instead of plasma, but converted to use with plasma concentration.
restrictive.clearance	Protein binding not taken into account (set to 1) in liver clearance if FALSE.
adjusted.Funbound.plasma	Uses adjusted Funbound.plasma when set to TRUE.
...	Additional parameters passed to parameterize_steadystate if parameters is NULL.

Value

Hepatic Clearance	Units of L/h/kg BW.

Author(s)

John Wambaugh and Robert Pearce

References

Ito, K., & Houston, J. B. (2004). "Comparison of the use of liver models for predicting drug clearance using in vitro kinetic data from hepatic microsomes and isolated hepatocytes." Pharmaceutical Tesearch, 21(5), 785-792.

Examples

```
calc_hep_clearance(chem.name="Ibuprofen",hepatic.model='unscaled')
calc_hep_clearance(chem.name="Ibuprofen",well.stirred.correction=FALSE)
```

`calc_hep_bioavailability`

Calculate first pass metabolism

Description

For models that don't described first pass blood flow from the gut, need to cacluate a hepatic bioavailability, that is, the fraction of chemical systemically available after metabolism during the first pass through the liver (Rowland, 1973).

Usage

```
calc_hep_bioavailability(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  restrictive.clearance = T,
  flow.34 = T
)
```

Arguments

`chem.cas`	Chemical Abstract Services Registry Number (CAS-RN) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
`chem.name`	Chemical name (spaces and capitalization ignored) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
`dtxsid`	EPA's 'DSSTox Structure ID (`https://comptox.epa.gov/dashboard`) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXSIDs
`parameters`	Parameters from the appropriate parameterization function for the model indicated by argument model
`restrictive.clearance`	Protein binding not taken into account (set to 1) in liver clearance if FALSE.
`flow.34`	A logical constraint

Value

A data.table whose columns are the parameters of the HTTK model specified in `model`.

Author(s)

John Wambaugh

References

Rowland, Malcolm, Leslie Z. Benet, and Garry G. Graham. "Clearance concepts in pharmacokinetics." Journal of pharmacokinetics and biopharmaceutics 1.2 (1973): 123-136.

`calc_hep_clearance` *Calculate the hepatic clearance.*

Description

This function calculates the hepatic clearance in plasma for a well-stirred model or other type if specified. Based on Ito and Houston (2004)

Usage

```
calc_hep_clearance(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  species = "Human",
  default.to.human = F,
  hepatic.model = "well-stirred",
  suppress.messages = F,
  well.stirred.correction = T,
  restrictive.clearance = T,
  adjusted.Funbound.plasma = T,
  ...
)
```

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.
`dtxsid`	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
`parameters`	Chemical parameters from parameterize_steadystate function, overrides chem.name and chem.cas.
`species`	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
`default.to.human`	Substitutes missing animal values with human values if true.
`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.
`well.stirred.correction`	Uses correction in calculation of hepatic clearance for well-stirred model if TRUE for hepatic.model well-stirred. This assumes clearance relative to amount unbound in whole blood instead of plasma, but converted to use with plasma concentration.

`restrictive.clearance`
: Protein binding not taken into account (set to 1) in liver clearance if FALSE.

`adjusted.Funbound.plasma`
: Uses adjusted Funbound.plasma when set to TRUE.

`...`
: Additional parameters passed to parameterize_steadystate if parameters is NULL.

Value

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

Author(s)

John Wambaugh and Robert Pearce

References

Ito, K., & Houston, J. B. (2004). "Comparison of the use of liver models for predicting drug clearance using in vitro kinetic data from hepatic microsomes and isolated hepatocytes." Pharmaceutical Tesearch, 21(5), 785-792.

Examples

```
calc_hep_clearance(chem.name="Ibuprofen",hepatic.model='unscaled')
calc_hep_clearance(chem.name="Ibuprofen",well.stirred.correction=FALSE)
```

---

calc_hep_fu *Calculate the free chemical in the hepaitic clearance assay*

Description

Method from Kilford et al. (2008) for fraction of unbound chemical in the hepatocyte intrinsic clearance assay

Usage

```
calc_hep_fu(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  Vr = 0.005,
  pH = 7.4
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Parameters from the appropriate parameterization function for the model indicated by argument model
Vr	Rratio of cell volume to incubation volume. Default is taken from
pH	pH of the incupation medium.

Value

A numeric fraction between zero and one

Author(s)

John Wambaugh and Robert Pearce

References

Kilford, Peter J., et al. "Hepatocellular binding of drugs: correction for unbound fraction in hepatocyte incubations using microsomal binding or drug lipophilicity data." Drug Metabolism and Disposition 36.7 (2008): 1194-1197.

Wetmore, Barbara A., et al. "Incorporating high-throughput exposure predictions with dosimetry-adjusted in vitro bioactivity to inform chemical toxicity testing." Toxicological Sciences 148.1 (2015): 121-136.

---

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,
  dtxsid = NULL,
  parameters = NULL,
  pH = NULL,
  pKa_Donor = NA,
  pKa_Accept = NA
)
```

Arguments

chem.cas	Either the chemical name or the CAS number must be specified.
chem.name	Either the chemical name or the CAS number must be specified.
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from a parameterize_MODEL function, overrides chem.name and chem.cas.
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 and John Wambaugh

References

Pearce, Robert G., et al. "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." Journal of pharmacokinetics and pharmacodynamics 44.6 (2017): 549-565.

Examples

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

`calc_krbc2pu` *Back-calculates the Red Blood Cell to Unbound Plasma Partition Coefficient*

Description

Given and observed ratio of chemial concentration in blood to plasma, this function calculates a Red Blood Cell to unbound plasma (Krbc2pu) partition coefficient that would be consistent with that observation.

Usage

```
calc_krbc2pu(
  Rb2p,
  Funbound.plasma,
  hematocrit = NULL,
  default.to.human = F,
  species = "Human",
  suppress.messages = T
)
```

Arguments

`Rb2p`	The chemical blood:plasma concentration ratop
`Funbound.plasma`	The free fraction of chemical in the presence of plasma protein Rblood2plasma.
`hematocrit`	Overwrites default hematocrit value in calculating Rblood2plasma.
`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`	Determine whether to display certain usage feedback.

Author(s)

John Wambaugh and Robert Pearce

References

Pearce, Robert G., et al. "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." Journal of pharmacokinetics and pharmacodynamics 44.6 (2017): 549-565.

Ruark, Christopher D., et al. "Predicting passive and active tissue: plasma partition coefficients: interindividual and interspecies variability." Journal of pharmaceutical sciences 103.7 (2014): 2189-2198.

calc_mc_css *Find the monte carlo steady state concentration.*

Description

This function finds the analytical steady state plasma concentration(from calc_analytic_css) using a monte carlo simulation (monte_carlo).

Usage

```
calc_mc_css(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  samples = 1000,
  which.quantile = 0.95,
  species = "Human",
  suppress.messages = F,
  model = "3compartmentss",
  httkpop = T,
  invitrouv = T,
  calcrb2p = T,
  censored.params = list(),
  vary.params = list(),
  return.samples = F,
  tissue = NULL,
  output.units = "mg/L",
  invitro.mc.arg.list = list(adjusted.Funbound.plasma = T, poormetab = T,
   fup.censored.dist = FALSE, fup.lod = 0.01, fup.meas.cv = 0.4, clint.meas.cv = 0.3,
    fup.pop.cv = 0.3, clint.pop.cv = 0.3),
 httkpop.generate.arg.list = list(method = "direct resampling", gendernum = NULL,
   agelim_years = NULL, agelim_months = NULL, weight_category = c("Underweight",
   "Normal", "Overweight", "Obese"), gfr_category = c("Normal", "Kidney Disease",
    "Kidney Failure"), reths = c("Mexican American", "Other Hispanic",
    "Non-Hispanic White", "Non-Hispanic Black", "Other")),
 convert.httkpop.arg.list = list(),
 parameterize.arg.list = list(default.to.human = F, clint.pvalue.threshold = 0.05,
    restrictive.clearance = T, regression = T),
 calc.analytic.css.arg.list = list(well.stirred.correction = T,
   adjusted.Funbound.plasma = T, regression = T, IVIVE = NULL, tissue = tissue,
    restrictive.clearance = T, bioactive.free.invivo = FALSE)
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD

dtxsid — EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXSIDs

parameters — Parameters from the appropriate parameterization function for the model indicated by argument model

samples — Number of samples generated in calculating quantiles.

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"). Species must be set to "Human" to run httkpop model.

suppress.messages — Whether or not to suppress output message.

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. This only applies when httkpop=TRUE and species="Human", otherwise '3compartmentss' is used.

httkpop — Whether or not to use population generator and sampler from httkpop. This is overwrites censored.params and vary.params and is only for human physiology. Species must also be set to 'Human'.

invitrouv — Logical to indicate whether to include in vitro parameters in uncertainty and variability analysis

calcrb2p — Logical determining whether or not to recalculate the chemical ratio of blood to plasma

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 parameter). This argument should be a list of sublists. 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. Not used with httkpop model.

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. Not used with httkpop model.

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

tissue — Desired steady state tissue concentration.

output.units — Plasma concentration units, either uM or default mg/L.

invitro.mc.arg.list — List of additional parameters passed to invitro_mc

httkpop.generate.arg.list — Additional parameters passed to httkpop_generate.

convert.httkpop.arg.list — Additional parameters passed to the convert_httkpop_* function for the model.

`parameterize.arg.list`
: Additional parameters passed to the parameterize_* function for the model.

`calc.analytic.css.arg.list`
: Additional parameters passed to `calc_analytic_css`.

Details

All arguments after httkpop only apply if httkpop is set to TRUE and species to "Human".

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

Tissue concentrations are calculated for the pbtk model with a default oral infusion dosing. All tissues other than gut, liver, and lung are the product of the steady state plasma concentration and the tissue to plasma partition coefficient.

The six sets of plausible *in vitro-in vivo* extrapolation (IVIVE) assumptions identified by Honda et al. (2019) are:

	in vivo Conc.	Metabolic Clearance	Bioactive Chemical Conc.	TK Statistic Used*
Honda1	Veinous (Plasma)	Restrictive	Free	Mean Conc.
Honda2	Veinous	Restrictive	Free	Max Conc.
Honda3	Veinous	Non-restrictive	Total	Mean Conc.
Honda4	Veinous	Non-restrictive	Total	Max Conc.
Honda5	Target Tissue	Non-restrictive	Total	Mean Conc.
Honda6	Target Tissue	Non-restrictive	Total	Max Conc.

*Assumption is currently ignored because analytical steady-state solutions are currently used by this function.

Author(s)

Caroline Ring, Robert Pearce, and John Wambaugh

References

Wambaugh, John F., et al. "Toxicokinetic triage for environmental chemicals." Toxicological Sciences 147.1 (2015): 55-67.

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment international 106 (2017): 105-118.

Honda, Gregory S., et al. "Using the Concordance of In Vitro and In Vivo Data to Evaluate Extrapolation Assumptions." 2019. PLoS ONE 14(5): e0217564.

Rowland, Malcolm, Leslie Z. Benet, and Garry G. Graham. "Clearance concepts in pharmacokinetics." Journal of pharmacokinetics and biopharmaceutics 1.2 (1973): 123-136.

Examples

```
## Not run:
 set.seed(1234)
 calc_mc_css(chem.name='Bisphenol A',output.units='uM',
             samples=100,return.samples=TRUE)
```

```
set.seed(1234)
calc_mc_css(chem.name='2,4-d',which.quantile=.9,httkpop=FALSE,tissue='heart')

set.seed(1234)
calc_mc_css(chem.cas = "80-05-7", which.quantile = 0.5,
            output.units = "uM", samples = 2000,
            httkpop.generate.arg.list=list(method='vi', gendernum=NULL,
            agelim_years=NULL, agelim_months=NULL, weight_category =
            c("Underweight", "Normal", "Overweight", "Obese")))

params <- parameterize_pbtk(chem.cas="80-05-7")
set.seed(1234)
calc_mc_css(parameters=params,model="pbtk")

set.seed(1234)
# Standard HTTK Monte Carlo:
NSAMP = 500
calc_mc_css(chem.cas="90-43-7",model="pbtk",samples=NSAMP)
set.seed(1234)
calc_mc_css(chem.cas="90-43-7",
model="pbtk",
samples=NSAMP,
invitro.mc.arg.list = list(adjusted.Funbound.plasma = T,
  poormetab = T,
  fup.censored.dist = FALSE,
  fup.lod = 0.01,
  fup.meas.cv = 0.0,
  clint.meas.cv = 0.0,
  fup.pop.cv = 0.3,
  clint.pop.cv = 0.3))
set.seed(1234)
# HTTK Monte Carlo with no HTTK-Pop physiological variability):
calc_mc_css(chem.cas="90-43-7",model="pbtk",samples=NSAMP,httkpop=F)
set.seed(1234)
# HTTK Monte Carlo with no in vitro uncertainty and variability):
calc_mc_css(chem.cas="90-43-7",model="pbtk",samples=NSAMP,invitrouv=F)
set.seed(1234)
# HTTK Monte Carlo with no HTTK-Pop and no in vitro uncertainty and variability):
calc_mc_css(chem.cas="90-43-7",model="pbtk",samples=NSAMP,httkpop=F,invitrouv=F)
# Should be the same as the mean result:
calc_analytic_css(chem.cas="90-43-7",model="pbtk",output.units="mg/L")
set.seed(1234)
# HTTK Monte Carlo using basic Monte Carlo sampler:
calc_mc_css(chem.cas="90-43-7",
model="pbtk",
samples=NSAMP,
httkpop=F,
invitrouv=F,
vary.params=list(Pow=0.3))

## End(Not run)
```

`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,
  dtxsid = NULL,
  which.quantile = 0.95,
  species = "Human",
  input.units = "uM",
  output.units = "mgpkgpday",
  suppress.messages = F,
  return.samples = F,
  concentration = "plasma",
  restrictive.clearance = T,
  bioactive.free.invivo = F,
  tissue = NULL,
  IVIVE = NULL,
  ...
)
```

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.
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
which.quantile	Which quantile from Monte Carlo steady-state simulation (calc_mc_css) is requested. Can be a vector. Note that 95th concentration quantile is the same population as the 5th dose quantile.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
input.units	Units of given concentration, default of uM but can also be mg/L.
output.units	Units of dose, default of 'mgpkgpday' for mg/kg BW/ day or 'umolpkgpday' for umol/ kg BW/ day.
suppress.messages	Suppress text messages.
return.samples	Whether or not to return the vector containing the samples from the simulation instead of the selected quantile.
concentration	Desired concentration type, 'blood','tissue', or default 'plasma'.
restrictive.clearance	Protein binding not taken into account (set to 1) in liver clearance if FALSE.
bioactive.free.invivo	If FALSE (default), then the total concentration is treated as bioactive in vivo. If TRUE, the the unbound (free) plasma concentration is treated as bioactive in vivo. Only works with tissue = NULL in current implementation.

tissue	Desired steady state tissue conentration.
IVIVE	Honda et al. (2019) identified six plausible sets of assumptions for *in vitro-in vivo* extrapolation (IVIVE) assumptions. Argument may be set to "Honda1" through "Honda6". If used, this function overwrites the tissue, restrictive.clearance, and plasma.binding arguments. See Details below for more information.
...	Additional parameters passed to calc_mc_css for httkpop and variance of parameters.

Details

All arguments after httkpop only apply if httkpop is set to TRUE and species to "Human".

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

Tissue concentrations are calculated for the pbtk model with oral infusion dosing. All tissues other than gut, liver, and lung are the product of the steady state plasma concentration and the tissue to plasma partition coefficient.

The six sets of plausible *in vitro-in vivo* extrapolation (IVIVE) assumptions identified by Honda et al. (2019) are:

	in vivo Conc.	Metabolic Clearance	Bioactive Chemical Conc.	TK Statistic Used*
Honda1	Veinous (Plasma)	Restrictive	Free	Mean Conc.
Honda2	Veinous	Restrictive	Free	Max Conc.
Honda3	Veinous	Non-restrictive	Total	Mean Conc.
Honda4	Veinous	Non-restrictive	Total	Max Conc.
Honda5	Target Tissue	Non-restrictive	Total	Mean Conc.
Honda6	Target Tissue	Non-restrictive	Total	Max Conc.

*Assumption is currently ignored because analytical steady-state solutions are currently used by this function.

Value

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

Author(s)

John Wambaugh

References

Wetmore, Barbara A., et al. "Incorporating high-throughput exposure predictions with dosimetry-adjusted in vitro bioactivity to inform chemical toxicity testing." Toxicological Sciences 148.1 (2015): 121-136.

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment international 106 (2017): 105-118.

Honda, Gregory S., et al. "Using the Concordance of In Vitro and In Vivo Data to Evaluate Extrapolation Assumptions." 2019. PLoS ONE 14(5): e0217564.

Rowland, Malcolm, Leslie Z. Benet, and Garry G. Graham. "Clearance concepts in pharmacokinetics." Journal of pharmacokinetics and biopharmaceutics 1.2 (1973): 123-136.

Examples

```
## Not run:
calc_mc_oral_equiv(0.1,chem.cas="34256-82-1",which.quantile=c(0.05,0.5,0.95),
       tissue='brain')

## End(Not run)
```

`calc_mc_tk` *Conduct multiple TK simulations using Monte Carlo*

Description

This function finds the analytical steady state plasma concentration(from calc_analytic_css) using a monte carlo simulation (monte_carlo).

Usage

```
calc_mc_tk(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  samples = 1000,
  which.quantile = 0.95,
  species = "Human",
  suppress.messages = F,
  model = "pbtk",
  httkpop = T,
  invitrouv = T,
  calcrb2p = T,
  censored.params = list(),
  vary.params = list(),
  return.samples = F,
  tissue = NULL,
  output.units = "mg/L",
 solvemodel.arg.list = list(times = c(0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5)),
  invitro.mc.arg.list = list(adjusted.Funbound.plasma = T, poormetab = T,
   fup.censored.dist = FALSE, fup.lod = 0.01, fup.meas.cv = 0.4, clint.meas.cv = 0.3,
    fup.pop.cv = 0.3, clint.pop.cv = 0.3),
 httkpop.generate.arg.list = list(method = "direct resampling", gendernum = NULL,
   agelim_years = NULL, agelim_months = NULL, weight_category = c("Underweight",
  "Normal", "Overweight", "Obese"), gfr_category = c("Normal", "Kidney Disease",
    "Kidney Failure"), reths = c("Mexican American", "Other Hispanic",
    "Non-Hispanic White", "Non-Hispanic Black", "Other")),
  convert.httkpop.arg.list = list(),
 parameterize.arg.list = list(default.to.human = F, clint.pvalue.threshold = 0.05,
    restrictive.clearance = T, regression = T),
  return.all.sims = FALSE
)
```

Arguments

chem.cas	Either the CAS number, parameters, or the chemical name must be specified.
chem.name	Either the chemical parameters, name, or the CAS number must be specified.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Parameters from parameterize_steadystate. Not used with httkpop model.
samples	Number of samples generated in calculating quantiles.
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"). Species must be set to "Human" to run httkpop model.
suppress.messages	Whether or not to suppress output message.
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. This only applies when httkpop=TRUE and species="Human", otherwise '3compartmentss' is used.
httkpop	Whether or not to use population generator and sampler from httkpop. This is overwrites censored.params and vary.params and is only for human physiology. Species must also be set to 'Human'.
invitrouv	Logical to indicate whether to include in vitro parameters in uncertainty and variability analysis
calcrb2p	Logical determining whether or not to recalculate the chemical ratio of blood to plasma
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. Not used with httkpop model.
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. Not used with httkpop model.
return.samples	Whether or not to return the vector containing the samples from the simulation instead of the selected quantile.
tissue	Desired steady state tissue conentration.
output.units	Plasma concentration units, either uM or default mg/L.
solvemodel.arg.list	Additional arguments ultimately passed to solve_model
invitro.mc.arg.list	List of additional parameters passed to invitro_mc

`httkpop.generate.arg.list`
: Additional parameters passed to `httkpop_generate`.

`convert.httkpop.arg.list`
: Additional parameters passed to the convert_httkpop_* function for the model.

`parameterize.arg.list`
: Additional parameters passed to the parameterize_* function for the model.

`return.all.sims`
: Logical indicating whether to return the results of all simulations, in addition to the default toxicokinetic statistics

Details

All arguments after httkpop only apply if httkpop is set to TRUE and species to "Human".

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.

Tissue concentrations are calculated for the pbtk model with oral infusion dosing. All tissues other than gut, liver, and lung are the product of the steady state plasma concentration and the tissue to plasma partition coefficient.

The six sets of plausible *in vitro-in vivo* extrpolation (IVIVE) assumptions identified by Honda et al. (2019) are:

	in vivo Conc.	Metabolic Clearance	Bioactive Chemical Conc.	TK Statistic Used*
Honda1	Veinous (Plasma)	Restrictive	Free	Mean Conc.
Honda2	Veinous	Restrictive	Free	Max Conc.
Honda3	Veinous	Non-restrictive	Total	Mean Conc.
Honda4	Veinous	Non-restrictive	Total	Max Conc.
Honda5	Target Tissue	Non-restrictive	Total	Mean Conc.
Honda6	Target Tissue	Non-restrictive	Total	Max Conc.

*Assumption is currently ignored because analytical steady-state solutions are currently used by this function.

Author(s)

John Wambaugh

Examples

```
## Not run:
chemname="Abamectin"
times<- c(0,0.25,0.5,0.75,1,1.5,2,2.5,3,4,5)
age.ranges <- seq(6,80,by=10)
forward <- NULL
for (age.lower in age.ranges)
{
  label <- paste("Ages ",age.lower,"-",age.lower+4,sep="")
  set.seed(1234)
  forward[[label]] <- calc_mc_tk(
                        chem.name=chemname,
```

```
                        samples=NSAMP,
                        httkpop.generate.arg.list=list(
                          method="d",
                          agelim_years = c(age.lower, age.lower+9)),
                        solvemodel.arg.list = list(
                          times=times))
}


## End(Not run)
```

`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.

Usage

```
calc_rblood2plasma(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  hematocrit = NULL,
  Krbc2pu = NULL,
  Funbound.plasma = NULL,
  default.to.human = F,
  species = "Human",
  adjusted.Funbound.plasma = T,
  suppress.messages = T
)
```

Arguments

`chem.cas`	Either the CAS number or the chemical name must be specified.
`chem.name`	Either the chemical name or the CAS number must be specified.
`dtxsid`	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
`parameters`	Parameters from `parameterize_schmitt`
`hematocrit`	Overwrites default hematocrit value in calculating Rblood2plasma.
`Krbc2pu`	The red blood cell to unbound plasma chemical partition coefficient, typically from `predict_partitioning_schmitt`
`Funbound.plasma`	The fraction of chemical unbound (free) in the presence of plasma protein
`default.to.human`	Substitutes missing animal values with human values if true.
`species`	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").

`adjusted.Funbound.plasma`
: Whether or not to use Funbound.plasma adjustment.

`suppress.messages`
: Determine whether to display certain usage feedback.

Details

The red blood cell (RBC) parition coefficient as predicted by the Schmitt (2008) method is used in the calculation. The value is calculated with the equation: 1 - hematocrit + hematocrit * Krbc2pu * Funbound.plasma, summing the red blood cell to plasma and plasma:plasma (equal to 1) partition coefficients multiplied by their respective fractional volumes. When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data (hematocrit and temperature), but substitues human fraction unbound and tissue volumes.

Author(s)

John Wambaugh and Robert Pearce

References

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

Pearce, Robert G., et al. "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." Journal of pharmacokinetics and pharmacodynamics 44.6 (2017): 549-565.

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Examples

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

---

calc_stats *Calculate toxicokinetic summary statistics (deprecated).*

Description

#' This function is included for backward compatibility. It calls `calc_tkstats` which 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(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  route = "oral",
  stats = c("AUC", "peak", "mean"),
  species = "Human",
  days = 28,
  daily.dose = 1,
  dose = NULL,
  doses.per.day = 1,
  output.units = "uM",
  concentration = "plasma",
  tissue = "plasma",
  model = "pbtk",
  default.to.human = F,
  adjusted.Funbound.plasma = T,
  regression = T,
  restrictive.clearance = T,
  suppress.messages = F,
  ...
)
```

Arguments

chem.name	Name of desired chemical.
chem.cas	CAS number of desired chemical.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_pbtk function, overrides chem.name and chem.cas.
route	String specification of route of exposure for simulation: "oral", "iv", "inhalation", ...
stats	Desired values (either 'AUC', 'mean', 'peak', or a vector containing any combination).
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
days	Length of the simulation.
daily.dose	Total daily dose, mg/kg BW.
dose	Amount of a single dose at time zero, mg/kg BW.
doses.per.day	Number of doses per day.
output.units	Desired units (either "mg/L", "mg", "umol", or default "uM").
concentration	Desired concentration type, 'blood' or default 'plasma'.
tissue	Desired steady state tissue conentration.
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).

`adjusted.Funbound.plasma`
: Uses adjusted Funbound.plasma when set to TRUE along with partition coefficients calculated with this value.

`regression`
: Whether or not to use the regressions in calculating partition coefficients.

`restrictive.clearance`
: Protein binding not taken into account (set to 1) in liver clearance if FALSE.

`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.conc`
: The area under the curve divided by the number of days.

`peak.conc`
: The highest concentration.

Author(s)

Robert Pearce and John Wambaugh

Examples

```
calc_tkstats(chem.name='Bisphenol-A',days=100,stats='mean',model='3compartment')

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

## Not run:
# If you do not specify a chemical, calc_tkstats runs for all chemicals:
all.peak.conc.stats <- calc_tkstats(days=10, doses.per.day = 3, stats = "peak")

## End(Not run)

triclosan.stats <- calc_tkstats(days=10, chem.name = "triclosan")
```

`calc_tkstats` *Calculate toxicokinetic summary 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_tkstats(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  route = "oral",
  stats = c("AUC", "peak", "mean"),
  species = "Human",
  days = 28,
  daily.dose = 1,
  dose = NULL,
  doses.per.day = 1,
  output.units = "uM",
  concentration = "plasma",
  tissue = "plasma",
  model = "pbtk",
  default.to.human = F,
  adjusted.Funbound.plasma = T,
  regression = T,
  restrictive.clearance = T,
  suppress.messages = F,
  ...
)
```

Arguments

`chem.name`	Name of desired chemical.
`chem.cas`	CAS number of desired chemical.
`dtxsid`	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
`parameters`	Chemical parameters from parameterize_pbtk function, overrides chem.name and chem.cas.
`route`	String specification of route of exposure for simulation: "oral", "iv", "inhalation", ...
`stats`	Desired values (either 'AUC', 'mean', 'peak', or a vector containing any combination).
`species`	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
`days`	Length of the simulation.

daily.dose	Total daily dose, mg/kg BW.
dose	Amount of a single dose at time zero, mg/kg BW.
doses.per.day	Number of doses per day.
output.units	Desired units (either "mg/L", "mg", "umol", or default "uM").
concentration	Desired concentration type, 'blood' or default 'plasma'.
tissue	Desired steady state tissue conentration.
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).
adjusted.Funbound.plasma	Uses adjusted Funbound.plasma when set to TRUE along with partition coefficients calculated with this value.
regression	Whether or not to use the regressions in calculating partition coefficients.
restrictive.clearance	Protein binding not taken into account (set to 1) in liver clearance if FALSE.
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.conc	The area under the curve divided by the number of days.
peak.conc	The highest concentration.

Author(s)

Robert Pearce and John Wambaugh

Examples

```
calc_tkstats(chem.name='Bisphenol-A',days=100,stats='mean',model='3compartment')

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

## Not run:
# If you do not specify a chemical, calc_tkstats runs for all chemicals:
all.peak.conc.stats <- calc_tkstats(days=10, doses.per.day = 3, stats = "peak")
```

```
## End(Not run)

triclosan.stats <- calc_tkstats(days=10, chem.name = "triclosan")
```

`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,
  dtxsid = NULL,
  parameters = NULL,
  species = "Human",
  suppress.messages = F,
  default.to.human = F,
  well.stirred.correction = T,
  restrictive.clearance = T,
  adjusted.Funbound.plasma = T,
  ...
)
```

Arguments

`chem.cas`	Either the chemical name, CAS number, or the parameters must be specified.
`chem.name`	Either the chemical name, CAS number, or the parameters must be specified.
`dtxsid`	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
`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.
`well.stirred.correction`	Uses correction in calculation of hepatic clearance for well-stirred model if TRUE. This assumes clearance relative to amount unbound in whole blood instead of plasma, but converted to use with plasma concentration.
`restrictive.clearance`	Protein binding is not taken into account (set to 1) in liver clearance if FALSE.
`adjusted.Funbound.plasma`	Uses adjusted Funbound.plasma when set to TRUE.
`...`	Additional parameters passed to parameterize_steadystate if parameters is NULL.

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.

Usage

```
calc_vdist(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  default.to.human = F,
  species = "Human",
  suppress.messages = F,
  adjusted.Funbound.plasma = T,
  regression = T,
  minimum.Funbound.plasma = 1e-04
)
```

Arguments

`chem.cas`
: Either the CAS number or the chemical name must be specified when Funbound.plasma is not given in parameter list.

`chem.name`
: Either the chemical name or the CAS number must be specified when Funbound.plasma is not given in parameter list.

`dtxsid`
: EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs

`parameters`
: Parameters from parameterize_3comp, parameterize_pbtk or predict_partitioning_schmitt.

`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.

`adjusted.Funbound.plasma`
: Uses adjusted Funbound.plasma when set to TRUE along with parition coefficients calculated with this value.

`regression`
: Whether or not to use the regressions in calculating partition coefficients.

`minimum.Funbound.plasma`
: Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).

Details

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. 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 and Robert Pearce

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")
```

---

chem.invivo.PK.aggregate.data

Parameter Estimates from Wambaugh et al. (2018)

Description

This table includes 1 and 2 compartment fits of plasma concentration vs time data aggregated from chem.invivo.PK.data, performed in Wambaugh et al. 2018. Data includes volume of distribution (Vdist, L/kg), elimination rate (kelim, 1/h), gut absorption rate (kgutabs, 1/h), fraction absorbed (Fgutabs), and steady state concentration (Css, mg/L).

Usage

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

Format

data.frame

Author(s)

John Wambaugh

Source

Wambaugh et al. 2018 Toxicological Sciences, in press

---

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 et al. 2018.

Usage

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

Format

A data.frame containing 597 rows and 13 columns.

Author(s)

Sieto Bosgra

Source

Wambaugh et al. 2018 Toxicological Sciences, in press

References

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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

Chan MP, Morisawa S, Nakayama A, Kawamoto Y, Sugimoto M, Yoneda M (2005). Toxicokinetics of 14C-endosulfan in male Sprague-Dawley rats following oral administration of single or repeated doses. Environ Toxicol. 20(5):533-41. PMID: 16161119

Cruz L, Castaneda-Hernandez G, Flores-Murrieta FJ, Garcia-Lopez P, Guizar-Sahagun G (2002). Alteration of phenacetin pharmacokinetics after experimental spinal cord injury. Proc West Pharmacol Soc. 45:4-5. PMID: 12434508

Della Paschoa OE, Mandema JW, Voskuyl RA, Danhof M (1998). Pharmacokinetic-pharmacodynamic modeling of the anticonvulsant and electroencephalogram effects of phenytoin in rats. J Pharmacol Exp Ther. 284(2):460-6. PMID: 9454785

Du B, Li X, Yu Q, A Y, Chen C (2010). Pharmacokinetic comparison of orally disintegrating, beta-cyclodextrin inclusion complex and conventional tablets of nicardipine in rats. Life Sci J. 7(2):80-4.

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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. 2018 Toxicological Sciences, in press

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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Cruz L, Castaneda-Hernandez G, Flores-Murrieta FJ, Garcia-Lopez P, Guizar-Sahagun G (2002). Alteration of phenacetin pharmacokinetics after experimental spinal cord injury. Proc West Pharmacol Soc. 45:4-5. PMID: 12434508

Della Paschoa OE, Mandema JW, Voskuyl RA, Danhof M (1998). Pharmacokinetic-pharmacodynamic modeling of the anticonvulsant and electroencephalogram effects of phenytoin in rats. J Pharmacol Exp Ther. 284(2):460-6. PMID: 9454785

Du B, Li X, Yu Q, A Y, Chen C (2010). Pharmacokinetic comparison of orally disintegrating, beta-cyclodextrin inclusion complex and conventional tablets of nicardipine in rats. Life Sci J. 7(2):80-4.

Farris FF, Dedrick RL, Allen PV, Smith JC (1993). Physiological model for the pharmacokinetics of methyl mercury in the growing rat. Toxicol Appl Pharmacol. 119(1):74-90. PMID: 8470126

Hays SM, Elswick BA, Blumenthal GM, Welsch F, Conolly RB, Gargas ML (2000). Development of a physiologically based pharmacokinetic model of 2-methoxyethanol and 2-methoxyacetic acid disposition in pregnant rats. Toxicol Appl Pharmacol. 163(1):67-74. PMID: 10662606

Igari Y, Sugiyama Y, Awazu S, Hanano M (1982). Comparative physiologically based pharmacokinetics of hexobarbital, phenobarbital and thiopental in the rat. J Pharmacokinet Biopharm. 10(1):53-75. PMID: 7069578

Ito K, Houston JB (2004). Comparison of the use of liver models for predicting drug clearance using in vitro kinetic data from hepatic microsomes and isolated hepatocytes. Pharm Res. 21(5):785-92. PMID: 15180335

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Wambaugh, John F., et al. "Toxicokinetic triage for environmental chemicals." Toxicological Sciences (2015): 228-237.

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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

References

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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 (g/mol), logP, logMA (membrane affinity), intrinsic clearance(uL/min/10^6 cells), and pKa. These data have been compiled from multiple sources, and can be used to parameterize a variety of toxicokinetic models. See variable EPA.ref for information on the reference EPA.

Usage

```
chem.physical_and_invitro.data
```

Format

A data.frame containing 565 rows and 33 columns.

Author(s)

John Wambaugh

Source

Wambaugh, John F., et al. "Toxicokinetic triage for environmental chemicals." Toxicological Sciences (2015): 228-237.

References

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

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

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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.

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Wetmore, B. A., Wambaugh, J. F., Ferguson, S. S., Li, L., Clewell, H. J., 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. (2013). Relative Impact of Incorporating Pharmacokinetics on

Predicting In Vivo Hazard and Mode of Action from High-Throughput In Vitro Toxicity Assays. Toxicological Sciences 132(2), 327-346, 10.1093/toxsci/kft012.

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`ckd_epi_eq` *CKD-EPI equation for GFR.*

Description

Predict GFR from serum creatinine, gender, race, and age.

Usage

```
ckd_epi_eq(scr, gender, reth, age_years)
```

Arguments

`scr`	Vector of serum creatinine values in mg/dL.
`gender`	Vector of genders (either 'Male' or 'Female').
`reth`	Vector of races/ethnicities.
`age_years`	Vector of ages in years.

Details

From Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150(9):604-612. doi:10.7326/0003-4819-150-9-200905050-00006

Value

Vector of GFR values in mL/min/1.73m^2.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

concentration_data_Linakis2020 *Concentration data involved in Linakis 2020 vignette analysis.*

Description

Concentration data involved in Linakis 2020 vignette analysis.

Usage

```
concentration_data_Linakis2020
```

Format

A data.frame containing x rows and y columns.

Author(s)

Matt Linakis

Source

Matt Linakis

References

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

convert_httkpop_1comp *Converts HTTK-Pop physiology into parameters relevant to the one compartment model*

Description

Converts HTTK-Pop physiology into parameters relevant to the one compartment model

Usage

```
convert_httkpop_1comp(parameters.dt, httkpop.dt, ...)
```

Arguments

parameters.dt	Data table returned by create_mc_samples
httkpop.dt	Data table returned by httkpop_generate
...	Additional arguments passed to propagate_invitrouv_1comp

Value

A data.table whose columns are the parameters of the HTTK model specified in model.

Author(s)

Caroline Ring, John Wambaugh, and Greg Honda

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

---

create_mc_samples *Create a data table of draws of parameter values for Monte Carlo*

Description

This function creates a data table of draws of parameter values for use with Monte Carlo methods

Usage

```
create_mc_samples(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  samples = 1000,
  species = "Human",
  suppress.messages = F,
  model = "3compartmentss",
  httkpop = T,
  invitrouv = T,
  calcrb2p = T,
  censored.params = list(),
  vary.params = list(),
  return.samples = F,
  tissue = NULL,
  httkpop.dt = NULL,
  invitro.mc.arg.list = list(adjusted.Funbound.plasma = T, poormetab = T,
   fup.censored.dist = FALSE, fup.lod = 0.01, fup.meas.cv = 0.4, clint.meas.cv = 0.3,
    fup.pop.cv = 0.3, clint.pop.cv = 0.3),
 httkpop.generate.arg.list = list(method = "direct resampling", gendernum = NULL,
   agelim_years = NULL, agelim_months = NULL, weight_category = c("Underweight",
   "Normal", "Overweight", "Obese"), gfr_category = c("Normal", "Kidney Disease",
    "Kidney Failure"), reths = c("Mexican American", "Other Hispanic",
    "Non-Hispanic White", "Non-Hispanic Black", "Other")),
  convert.httkpop.arg.list = list(),
  propagate.invitrouv.arg.list = list(),
  parameterize.arg.list = list(restrictive.clearance = T, default.to.human = F,
    clint.pvalue.threshold = 0.05, regression = T)
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Parameters from the appropriate parameterization function for the model indicated by argument model
samples	Number of samples generated in calculating quantiles.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human"). Species must be set to "Human" to run httkpop model.
suppress.messages	Whether or not to suppress output message.
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. This only applies when httkpop=TRUE and species="Human", otherwise '3compartmentss' is used.
httkpop	Whether or not to use the Ring et al. (2017) "httkpop" population generator. Species must be 'Human'.
invitrouv	Logical to indicate whether to include in vitro parameters such as intrinsic hepatic clearance rate and fraction unbound in plasma in uncertainty and variability analysis
calcrb2p	Logical determining whether or not to recalculate the chemical ratio of blood to plasma
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. Not used with httkpop model.
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. Not used with httkpop model.
return.samples	Whether or not to return the vector containing the samples from the simulation instead of the selected quantile.
tissue	Desired steady state tissue conentration.
httkpop.dt	A data table generated by httkpop_generate. This defaults to NULL, in which case httkpop_generate is called to generate this table.

`invitro.mc.arg.list`
: Additional parameters passed to `invitro_mc`.

`httkpop.generate.arg.list`
: Additional parameters passed to `httkpop_generate`.

`convert.httkpop.arg.list`
: Additional parameters passed to the convert_httkpop_* function for the model.

`propagate.invitrouv.arg.list`
: Additional parameters passed to model's associated in vitro uncertainty and variability propagation function

`parameterize.arg.list`
: Additional parameters passed to the parameterize_* function for the model.

Author(s)

Caroline Ring, Robert Pearce, and John Wambaugh

References

Wambaugh, John F., et al. "Toxicokinetic triage for environmental chemicals." Toxicological Sciences 147.1 (2015): 55-67.

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment international 106 (2017): 105-118.

Examples

```
## Not run:
sample_set = create_mc_samples(chem.name = 'bisphenol a')

## End(Not run)
```

EPA.ref *Reference for EPA Physico-Chemical Data*

Description

The physico-chemical data in the chem.phys_and_invitro.data table are obtained from EPA's Comptox Chemicals dashboard. This variable indicates the date the Dashboard was accessed.

Usage

```
EPA.ref
```

Format

An object of class `character` of length 1.

Author(s)

John Wambaugh

Source

https://comptox.epa.gov/dashboard

`estimate_gfr` *Predict GFR.*

Description

First predict serum creatinine using smoothing spline, then predict GFR using CKD-EPI equation.

Usage

```
estimate_gfr(gfrtmp.dt)
```

Arguments

`gfrtmp.dt`	A data.table with columns `gender`, `reth`, `age_years`, `age_months`, `BSA_adj`, `serum_creat`.

Value

The same data.table with a `gfr_est` column added, containing estimated GFR values.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

`estimate_gfr_ped` *Predict GFR in children.*

Description

BSA-based equation from Johnson et al. 2006, Clin Pharmacokinet 45(9) 931-56. Used in Wetmore et al. 2014.

Usage

```
estimate_gfr_ped(BSA)
```

Arguments

`BSA`	Vector of body surface areas in m^2.

Value

Vector of GFRs in mL/min/1.73m^2.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

`estimate_hematocrit` *Predict hematocrit using smoothing spline.*

Description

Using precalculated smoothing splines on NHANES log hematocrit vs. age in months (and KDE residuals) by gender and race/ethnicity, generate hematocrit values for individuals specified by age, gender, and race/ethnicity.

Usage

```
estimate_hematocrit(hcttmp_dt)
```

Arguments

`hcttmp_dt`	A data.table with columns `age_years`, `age_months`, `gender`, `reth`.

Value

The same data.table with a `hematocrit` column added.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

`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

```
## Not run:
export_pbtk_jarnac(chem.name='Nicotine',initial.amounts=list(Agutlumen=1),filename='PBTKmodel.jan')

## End(Not run)
```

`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

```
## Not run:
export_pbtk_sbml(chem.name='Nicotine',initial.amounts=list(Agutlumen=1),filename='PBTKmodel.xml')

## End(Not run)
```

Frank2018invivo — *Literature In Vivo Data on Doses Causing Neurological Effects*

Description

Studies were selected from Table 1 in Mundy et al., 2015, as the studies in that publication were cited as examples of compounds with evidence for developmental neurotoxicity. There were sufficient in vitro toxicokinetic data available for this package for only 6 of the 42 chemicals.

Usage

```
Frank2018invivo
```

Format

A data.frame containing 14 rows and 16 columns.

Author(s)

Timothy J. Shafer

References

Frank, Christopher L., et al. "Defining toxicological tipping points in neuronal network development." Toxicology and Applied Pharmacology 354 (2018): 81-93.

Mundy, William R., et al. "Expanding the test set: Chemicals with potential to disrupt mammalian brain development." Neurotoxicology and Teratology 52 (2015): 25-35.

gen_age_height_weight — *Generate ages, heights, and weights for a virtual population using the virtual-individuals method.*

Description

Generate ages, heights, and weights for a virtual population using the virtual-individuals method.

Usage

```
gen_age_height_weight(
  nsamp = NULL,
  gendernum = NULL,
  reths,
  weight_category,
  agelim_years,
  agelim_months
)
```

Arguments

nsamp	The desired number of individuals in the virtual population. nsamp need not be provided if gendernum is provided.
gendernum	Optional: A named list giving the numbers of male and female individuals to include in the population, e.g. list(Male=100,Female=100). Default is NULL, meaning both males and females are included, in their proportions in the NHANES data. If both nsamp and gendernum are provided, they must agree (i.e., nsamp must be the sum of gendernum).
reths	Optional: a character vector giving the races/ethnicities to include in the population. Default is c('Mexican American','Other Hispanic','Non-Hispanic White','Non-Hispanic Black','Other'), to include all races and ethnicities in their proportions in the NHANES data. User-supplied vector must contain one or more of these strings.
weight_category	Optional: The weight categories to include in the population. Default is c('Underweight','Normal' User-supplied vector must contain one or more of these strings.
agelim_years	Optional: A two-element numeric vector giving the minimum and maximum ages (in years) to include in the population. Default is c(0,79). If agelim_years is provided and agelim_months is not, agelim_years will override the default value of agelim_months.
agelim_months	Optional: A two-element numeric vector giving the minimum and maximum ages (in months) to include in the population. Default is c(0, 959), equivalent to the default agelim_years. If agelim_months is provided and agelim_years is not, agelim_months will override the default values of agelim_years.

Value

A data.table containing variables

gender Gender of each virtual individual

reth Race/ethnicity of each virtual individual

age_months Age in months of each virtual individual

age_years Age in years of each virtual individual

weight Body weight in kg of each virtual individual

height Height in cm of each virtual individual

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

importFrom survey svymean

gen_height_weight *Generate heights and weights for a virtual population.*

Description

Generate heights and weights for a virtual population.

Usage

```
gen_height_weight(hbw_dt)
```

Arguments

hbw_dt	A data.table describing the virtual population by race, gender, and age (in years and months). Must have variables gender, reth, age, and age.years.

Value

The same data.table with two new variables added: weight and height. Respectively, these give individual body weights in kg, and individual heights in cm.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

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 toxicokinetic model can be paramterized for a given species.

Usage

```
get_cheminfo(
  info = "CAS",
  species = "Human",
  fup.lod.default = 0.005,
  model = "3compartmentss",
  default.to.human = F
)
```

Arguments

info	A single character vector (or collection of character vectors) from "Compound", "CAS", "DTXSID, "logP", "pKa_Donor"," pKa_Accept", "MW", "Clint", "Clint.pValue", "Funbound.plasma","Structure_Formula", or "Substance_Type". info="all" gives all information for the model and species.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
fup.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 default.to.human is set to TRUE, and the species-specific data, Funbound.plasma and Clint, are missing from chem.physical_and_invitro.data, human values are given instead.

Value

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

Author(s)

John Wambaugh and Robert Pearce

Examples

```
## Not run:
# List all CAS numbers for which the 3compartmentss model can be run in humans:
get_cheminfo()

get_cheminfo(info=c('compound','funbound.plasma','logP'),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)

## End(Not run)
```

---

get_chem_id *Retrieve chemical identity from HTTK package*

Description

Given one of chem.name, chem.cas (Chemical Abstract Service Registry Number), or DTXSID (DSStox Substance Identifier https://comptox.epa.gov/dashboard) this function checks if the chemical is available and, if so, returns all three pieces of information.

Usage

```
get_chem_id(chem.cas = NULL, chem.name = NULL, dtxsid = NULL)
```

Arguments

chem.cas	CAS regstry number
chem.name	Chemical name
dtxsid	DSSTox Substance identifier

Author(s)

John Wambaugh and Robert Pearce

---

get_gfr_category *Categorize kidney function by GFR.*

Description

For adults: In general GFR > 60 is considered normal 15 < GFR < 60 is considered kidney disease GFR < 15 is considered kidney failure

Usage

```
get_gfr_category(age_years, age_months, gfr_est)
```

Arguments

age_years	Vector of ages in years.
age_months	Vector of ages in months.
gfr_est	Vector of estimated GFR values in mL/min/1.73m^2.

Details

These values can also be used for children 2 years old and greater (see PEDIATRICS IN REVIEW Vol. 29 No. 10 October 1, 2008 pp. 335-341 (doi: 10.1542/pir.29-10-335))

Value

Vector of GFR categories: 'Normal', 'Kidney Disease', 'Kidney Failure'.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

---

get_invitroPK_param *Retrieve data from chem.physical_and_invitro.data table*

Description

or fraction unbound in plasma) from the main HTTK data. This function looks for species-specific values.

Usage

```
get_invitroPK_param(
  param,
  species,
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL
)
```

Arguments

param	The in vitro pharmacokinetic parameter needed.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
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.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs

Value

The value of the parameter, if found

Author(s)

John Wambaugh and Robert Pearce

---

get_lit_cheminfo *Get literature 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 and other literature.

Usage

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

Arguments

info	A single character vector (or collection of character vectors) from "Compound","CAS","MW","Raw.E ,"r2","p.val","Concentration..uM.","Css_lower_5th_perc.mg.L.","Css_median_perc.mg.L.","Css_up 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

```
## Not run:
get_lit_cheminfo()
get_lit_cheminfo(info=c('CAS','MW'))

## End(Not run)
```

`get_lit_css` *Get literature 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 and other literature.

Usage

```
get_lit_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.cas	Either the cas number or the chemical name must be specified.
chem.name	Either the chemical name or the CAS number must be specified.
daily.dose	Total daily dose infused in units of mg/kg BW/day. Defaults to 1 mg/kg/day.
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.
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_lit_css(chem.cas="34256-82-1")


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

get_lit_css(chem.cas="80-05-7", daily.dose = 1,which.quantile = 0.5, output.units = "uM")
```

`get_lit_oral_equiv` *Get Literature 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 and other literature.

Usage

```
get_lit_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.
`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").
`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.
`clearance.assay.conc`	Concentration of chemical used in measureing intrinsic clearance data, 1 or 10 uM.
`...`	Additional parameters passed to get_lit_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_lit_cheminfo(),50)) table <- rbind(table,cbind(
as.data.frame(this.cas),as.data.frame(get_lit_oral_equiv(conc=1,chem.cas=this.cas))))
```

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

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

---

get_physchem_param *Get physico-chemical parameters from chem.physical_and_invitro.data*

Description

This function retrieves physico-chemical properties ("param") for the chemical specified by chem.name or chem.cas from the vLiver tables.

Usage

```
get_physchem_param(param, chem.name = NULL, chem.cas = NULL, dtxsid = NULL)
```

Arguments

param	The desired parameters, a vector or single value.
chem.name	The chemical names that you want parameters for, a vector or single value
chem.cas	The chemical CAS numbers that you want parameters for, a vector or single value
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs

Value

The parameters, either a single value, a named list for a single chemical, or a list of lists

Author(s)

John Wambaugh and Robert Pearce

Examples

```
get_physchem_param(param = 'logP', chem.cas = '80-05-7')
get_physchem_param(param = c('logP','MW'), chem.cas = c('80-05-7','81-81-2'))
```

---

get_rblood2plasma *Get ratio of the blood concentration to the plasma concentration.*

Description

This function attempts to retrieve a measured species- and chemical-specific blood:plasma concentration ratio.

Usage

```
get_rblood2plasma(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = 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 CAS number or the chemical name must be specified.
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
default.to.human	Substitutes missing animal values with human values if true.

Details

A value of NA is returned when the requested value is unavailable. Values are retrieved from chem.physical_and_invitro.data. details than the description above ~~

Author(s)

Robert Pearce

Examples

```
get_rblood2plasma(chem.name="Bisphenol A")
get_rblood2plasma(chem.name="Bisphenol A",species="Rat")
```

`get_weight_class` *Given vectors of age, BMI, recumbent length, weight, and gender, categorizes weight classes using CDC and WHO categories.*

Description

Given vectors of age, BMI, recumbent length, weight, and gender, categorizes weight classes using CDC and WHO categories.

Usage

```
get_weight_class(age_years, age_months, bmi, recumlen, weight, gender)
```

Arguments

`age_years`	A vector of ages in years.
`age_months`	A vector of ages in months.
`bmi`	A vector of BMIs.
`recumlen`	A vector of heights or recumbent lengths in cm.
`weight`	A vector of body weights in kg.
`gender`	A vector of genders (as 'Male' or 'Female').

Value

A character vector of weight classes. Each element will be one of 'Underweight', 'Normal', 'Overweight', or 'Obese'.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

hematocrit_infants *Predict hematocrit in infants under 1 year old.*

Description

For infants under 1 year, hematocrit was not measured in NHANES. Assume a log-normal distribution where plus/minus 1 standard deviation of the underlying normal distribution is given by the reference range. Draw hematocrit values from these distributions by age.

Usage

```
hematocrit_infants(age_months)
```

Arguments

age_months	Vector of ages in months; all must be <= 12.

Details

Age	Reference range
<1 month	31-49
1-6 months	29-42
7-12 months	33-38

Value

Vector of hematocrit percentages corresponding to the input vector of ages.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

honda.ivive *Return the assumptions used in Honda et al. 2019*

Description

This function returns four of the better performing sets of assumptions evaluated in Honda et al. 2019 (https://doi.org/10.1371/journal.pone.0217564).These include four different combinations of hepatic clearance assumption, in vivo bioactivity assumption, and relevant tissue assumption. Generally, this function is not called directly by the user, but instead called by setting the IVIVE option in calc_mc_oral_equiv, calc_mc_css, and calc_analytic functions. Currently, these IVIVE option is not implemented the solve_1comp etc. functions.

Usage

```
honda.ivive(method = "Honda1", tissue = "liver")
```

Arguments

method	This is set to one of "Honda1", "Honda2", "Honda3", or "Honda4".
tissue	This is only relevant to "Honda4" and indicates the relevant tissue compartment.

Details

"Honda1" - tissue = NULL, restrictive.clearance = TRUE, bioactive.free.invivo = TRUE This assumption assumes restrictive hepatic clearance, and treats the free concentration in plasma as the bioactive concentration in vivo. This option must be used in combination with the concentration in vitro predicted by armitage_eval(), otherwise the result will be the same as "Honda2". This option corresponds to the result in Figure 8 panel c) restrictive, mean free plasma conc., Armitage in Honda et al. 2019. "Honda2" - tissue = NULL, restrictive.clearance = TRUE, bioactive.free.invivo = TRUE This assumption assumes restrictive hepatic clearance, and treats the free concentration in plasma as the bioactive concentration in vivo. This option corresponds to the result in Figure 8 panel b) restrictive, mean free plasma conc. in Honda et al. 2019. "Honda3" - tissue = NULL, restrictive.clearance = TRUE, bioactive.free.invivo = TRUE This assumption assumes restrictive hepatic clearance, and treats the free concentration in plasma as the bioactive concentration in vivo. This option corresponds to the result in Figure 8 panel a) restrictive, mean total plasma conc. in Honda et al. 2019. "Honda4" - tissue = tissue, restrictive.clearance = FALSE, bioactive.free.invivo = TRUE This assumption assumes restrictive hepatic clearance, and treats the free concentration in plasma as the bioactive concentration in vivo. The input tissue should be relevant to the in vitro assay endpoint used as input or that the result is being compared to. This option corresponds to the result in Figure 8 panel d) nonrestrictive, mean tissue conc. in Honda et al. 2019.

Value

A list of tissue, bioactive.free.invivo, and restrictive.clearance assumptions.

Author(s)

Greg Honda and John Wambaugh

References

Honda, Gregory S., et al. "Using the Concordance of In Vitro and In Vivo Data to Evaluate Extrapolation Assumptions." 2019. PLoS ONE 14(5): e0217564.

Examples

```
honda.ivive(method = "Honda1", tissue = NULL)
```

howgate *Howgate 2006*

Description

This data set is only used in Vignette 5.

Usage

```
howgate
```

Format

A data.table containing 24 rows and 11 columns.

Author(s)

Caroline Ring

References

Howgate, E. M., et al. "Prediction of in vivo drug clearance from in vitro data. I: impact of inter-individual variability." Xenobiotica 36.6 (2006): 473-497.

httkpop *httkpop: Virtual population generator for HTTK.*

Description

The httkpop package generates virtual population physiologies for use in population TK.

Main function to generate a population

If you just want to generate a table of (chemical-independent) population physiology parameters, use `httkpop_generate`.

Using HTTK-Pop with HTTK

To generate a population and then run an HTTK model for that population, the workflow is as follows:

1. Generate a population using `httkpop_generate`.
2. For a given HTTK chemical and general model, convert the population data to corresponding sets of HTTK model parameters using `httkpop_mc`.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

httkpop_biotophys_default

Convert HTTK-Pop-generated parameters to HTTK physiological parameters

Description

Convert HTTK-Pop-generated parameters to HTTK physiological parameters

Usage

```
httkpop_biotophys_default(indiv_dt)
```

Arguments

indiv_dt	The data.table object returned by httkpop_generate()

Value

A data.table with the physiological parameters expected by any HTTK model, including body weight (BW), hematocrit, tissue volumes per kg body weight, tissue flows as fraction of CO, CO per (kg BW)^3/4, GFR per (kg BW)^3/4, portal vein flow per (kg BW)^3/4, and liver density.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

httkpop_direct_resample

Generate a virtual population by directly resampling the NHANES data.

Description

Generate a virtual population by directly resampling the NHANES data.

Usage

```
httkpop_direct_resample(
  nsamp = NULL,
  gendernum = NULL,
  agelim_years = NULL,
  agelim_months = NULL,
  weight_category = c("Underweight", "Normal", "Overweight", "Obese"),
  gfr_category = c("Normal", "Kidney Disease", "Kidney Failure"),
```

```
  reths = c("Mexican American", "Other Hispanic", "Non-Hispanic White",
    "Non-Hispanic Black", "Other")
)
```

Arguments

nsamp	The desired number of individuals in the virtual population. nsamp need not be provided if gendernum is provided.
gendernum	Optional: A named list giving the numbers of male and female individuals to include in the population, e.g. list(Male=100,Female=100). Default is NULL, meaning both males and females are included, in their proportions in the NHANES data. If both nsamp and gendernum are provided, they must agree (i.e., nsamp must be the sum of gendernum).
agelim_years	Optional: A two-element numeric vector giving the minimum and maximum ages (in years) to include in the population. Default is c(0,79). If agelim_years is provided and agelim_months is not, agelim_years will override the default value of agelim_months.
agelim_months	Optional: A two-element numeric vector giving the minimum and maximum ages (in months) to include in the population. Default is c(0, 959), equivalent to the default agelim_years. If agelim_months is provided and agelim_years is not, agelim_months will override the default values of agelim_years.
weight_category	Optional: The weight categories to include in the population. Default is c('Underweight','Normal' User-supplied vector must contain one or more of these strings.
gfr_category	The kidney function categories to include in the population. Default is c('Normal','Kidney Disease','Kidney Failure') to include all kidney function levels.
reths	Optional: a character vector giving the races/ethnicities to include in the population. Default is c('Mexican American','Other Hispanic','Non-Hispanic White','Non-Hispanic Black','Other'), to include all races and ethnicities in their proportions in the NHANES data. User-supplied vector must contain one or more of these strings.

Value

A data.table where each row represents an individual, and each column represents a demographic, anthropometric, or physiological parameter.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

`httkpop_direct_resample_inner` *Inner loop function called by* `httkpop_direct_resample`.

Description

Inner loop function called by `httkpop_direct_resample`.

Usage

```
httkpop_direct_resample_inner(
  nsamp,
  gendernum,
  agelim_months,
  agelim_years,
  reths,
  weight_category
)
```

Arguments

`nsamp`	The desired number of individuals in the virtual population. `nsamp` need not be provided if `gendernum` is provided.
`gendernum`	Optional: A named list giving the numbers of male and female individuals to include in the population, e.g. `list(Male=100,Female=100)`. Default is NULL, meaning both males and females are included, in their proportions in the NHANES data. If both `nsamp` and `gendernum` are provided, they must agree (i.e., `nsamp` must be the sum of `gendernum`).
`agelim_months`	Optional: A two-element numeric vector giving the minimum and maximum ages (in months) to include in the population. Default is c(0, 959), equivalent to the default `agelim_years`. If `agelim_months` is provided and `agelim_years` is not, agelim_months will override the default values of `agelim_years`.
`agelim_years`	Optional: A two-element numeric vector giving the minimum and maximum ages (in years) to include in the population. Default is c(0,79). If `agelim_years` is provided and `agelim_months` is not, `agelim_years` will override the default value of `agelim_months`.
`reths`	Optional: a character vector giving the races/ethnicities to include in the population. Default is `c('Mexican American','Other Hispanic','Non-Hispanic White','Non-Hispanic Black','Other')`, to include all races and ethnicities in their proportions in the NHANES data. User-supplied vector must contain one or more of these strings.
`weight_category`	Optional: The weight categories to include in the population. Default is `c('Underweight','Normal'` User-supplied vector must contain one or more of these strings.

Value

A data.table where each row represents an individual, and each column represents a demographic, anthropometric, or physiological parameter.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

`httkpop_generate` *Generate a virtual population*

Description

Generate a virtual population

Usage

```
httkpop_generate(
  method,
  nsamp = NULL,
  gendernum = NULL,
  agelim_years = NULL,
  agelim_months = NULL,
  weight_category = c("Underweight", "Normal", "Overweight", "Obese"),
  gfr_category = c("Normal", "Kidney Disease", "Kidney Failure"),
  reths = c("Mexican American", "Other Hispanic", "Non-Hispanic White",
    "Non-Hispanic Black", "Other")
)
```

Arguments

`method`	The population-generation method to use. Either "virtual individuals" or "direct resampling." Short names may be used: "d" or "dr" for "direct resampling", and "v" or "vi" for "virtual individuals".
`nsamp`	The desired number of individuals in the virtual population. `nsamp` need not be provided if `gendernum` is provided.
`gendernum`	Optional: A named list giving the numbers of male and female individuals to include in the population, e.g. `list(Male=100,Female=100)`. Default is NULL, meaning both males and females are included, in their proportions in the NHANES data. If both `nsamp` and `gendernum` are provided, they must agree (i.e., `nsamp` must be the sum of `gendernum`).
`agelim_years`	Optional: A two-element numeric vector giving the minimum and maximum ages (in years) to include in the population. Default is c(0,79). If only a single value is provided, both minimum and maximum ages will be set to that value; e.g. `agelim_years=3` is equivalent to `agelim_years=c(3,3)`. If `agelim_years` is provided and `agelim_months` is not, `agelim_years` will override the default value of `agelim_months`.

agelim_months Optional: A two-element numeric vector giving the minimum and maximum ages (in months) to include in the population. Default is c(0, 959), equivalent to the default agelim_years. If only a single value is provided, both minimum and maximum ages will be set to that value; e.g. agelim_months=36 is equivalent to agelim_months=c(36,36). If agelim_months is provided and agelim_years is not, agelim_months will override the default values of agelim_years.

weight_category Optional: The weight categories to include in the population. Default is c('Underweight','Normal' User-supplied vector must contain one or more of these strings.

gfr_category The kidney function categories to include in the population. Default is c('Normal','Kidney Disease','Kidney Failure') to include all kidney function levels.

reths Optional: a character vector giving the races/ethnicities to include in the population. Default is c('Mexican American','Other Hispanic','Non-Hispanic White','Non-Hispanic Black','Other'), to include all races and ethnicities in their proportions in the NHANES data. User-supplied vector must contain one or more of these strings.

Value

A data.table where each row represents an individual, and each column represents a demographic, anthropometric, or physiological parameter.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

Examples

```
## Not run:
#Simply generate a virtual population of 100 individuals,
 #using the direct-resampling method
 set.seed(42)
httkpop_generate(method='direct resampling', nsamp=100)
#Generate a population using the virtual-individuals method,
#including 80 females and 20 males,
#including only ages 20-65,
#including only Mexican American and
 #Non-Hispanic Black individuals,
 #including only non-obese individuals
httkpop_generate(method = 'virtual individuals',
gendernum=list(Female=80,
Male=20),
agelim_years=c(20,65),
reths=c('Mexican American',
'Non-Hispanic Black'),
weight_category=c('Underweight',
'Normal',
'Overweight'))
```

```
## End(Not run)
```

`httkpop_mc` *Converts the HTTK-Pop population data table to a table of the parameters needed by HTTK, for a specific chemical.*

Description

Takes the data table generated by `httkpop_generate`, and converts it to the corresponding table of HTTK model parameters for a specified chemical and HTTK model.

Usage

```
httkpop_mc(model, samples = 1000, httkpop.dt = NULL, ...)
```

Arguments

`model`	One of the HTTK models: "1compartment", "3compartmentss", "3compartment", or "pbtk".
`samples`	The number of Monte Carlo samples to use (can often think of these as separate individuals)
`httkpop.dt`	A data table generated by `httkpop_generate`. This defaults to NULL, in which case `httkpop_generate` is called to generate this table.
`...`	Additional arugments passed on to `httkpop_generate`.

Author(s)

Caroline Ring and John Wambaugh

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

Rowland, Malcolm, Leslie Z. Benet, and Garry G. Graham. "Clearance concepts in pharmacokinetics." Journal of Pharmacokinetics and Biopharmaceutics 1.2 (1973): 123-136.

Examples

```
set.seed(42)
indiv_examp <- httkpop_generate(method="d", nsamp=100)
httk_param <- httkpop_mc(httkpop.dt=indiv_examp,
model="1compartment")
```

`httkpop_virtual_indiv` *Generate a virtual population by the virtual individuals method.*

Description

Generate a virtual population by the virtual individuals method.

Usage

```
httkpop_virtual_indiv(
  nsamp = NULL,
  gendernum = NULL,
  agelim_years = NULL,
  agelim_months = NULL,
  weight_category = c("Underweight", "Normal", "Overweight", "Obese"),
  gfr_category = c("Normal", "Kidney Disease", "Kidney Failure"),
  reths = c("Mexican American", "Other Hispanic", "Non-Hispanic White",
    "Non-Hispanic Black", "Other")
)
```

Arguments

nsamp	The desired number of individuals in the virtual population. nsamp need not be provided if gendernum is provided.
gendernum	Optional: A named list giving the numbers of male and female individuals to include in the population, e.g. list(Male=100,Female=100). Default is NULL, meaning both males and females are included, in their proportions in the NHANES data. If both nsamp and gendernum are provided, they must agree (i.e., nsamp must be the sum of gendernum).
agelim_years	Optional: A two-element numeric vector giving the minimum and maximum ages (in years) to include in the population. Default is c(0,79). If agelim_years is provided and agelim_months is not, agelim_years will override the default value of agelim_months.
agelim_months	Optional: A two-element numeric vector giving the minimum and maximum ages (in months) to include in the population. Default is c(0, 959), equivalent to the default agelim_years. If agelim_months is provided and agelim_years is not, agelim_months will override the default values of agelim_years.
weight_category	Optional: The weight categories to include in the population. Default is c('Underweight','Normal' User-supplied vector must contain one or more of these strings.
gfr_category	The kidney function categories to include in the population. Default is c('Normal','Kidney Disease','Kidney Failure') to include all kidney function levels.
reths	Optional: a character vector giving the races/ethnicities to include in the population. Default is c('Mexican American','Other Hispanic','Non-Hispanic White','Non-Hispanic Black','Other'), to include all races and ethnicities in their proportions in the NHANES data. User-supplied vector must contain one or more of these strings.

Value

A data.table where each row represents an individual, and each column represents a demographic, anthropometric, or physiological parameter.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

---

in.list *Convenience Boolean (yes/no) functions to identify 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")
```

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.pare "NHANES.urine.parent","NHANES.urine.analyte"

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: https://www.cdc.gov/nchs/nhanes.htm.

See Also

is.httk for determining inclusion in httk project

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 ten
# chemicals. To build a table with all available chemicals use:
# for (this.cas in httk.table$CAS)
for (this.cas in httk.table$CAS[1:10])
{
  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"
}
```

`invitro_mc` *Draw in vitro TK parameters including uncertainty and variability.*

Description

Given a CAS in the HTTK data set, a virtual population from HTTK-Pop, some user specifications on the assumed distributions of Funbound.plasma and Clint, draw "individual" values of Funbound.plasma and Clint from those distributions.

Usage

```
invitro_mc(
  parameters.dt = NULL,
  samples,
  fup.meas.cv = 0.4,
  clint.meas.cv = 0.3,
  fup.pop.cv = 0.3,
  clint.pop.cv = 0.3,
  poormetab = TRUE,
  fup.lod = 0.01,
  fup.censored.dist = FALSE,
  adjusted.Funbound.plasma = T,
  clint.pvalue.threshold = 0.05,
  minimum.Funbound.plasma = 1e-04
)
```

Arguments

`parameters.dt`	A data table of physiological parameters
`samples`	The number of samples to draw.
`fup.meas.cv`	Coefficient of variation of distribution of measured `Funbound.plasma` values.
`clint.meas.cv`	Coefficient of variation of distribution of measured `Clint` values.
`fup.pop.cv`	Coefficient of variation of distribution of population `Funbound.plasma` values.
`clint.pop.cv`	Coefficient of variation of distribution of population `Clint` values.
`poormetab`	Logical. Whether to include poor metabolizers in the Clint distribution or not.
`fup.lod`	The average limit of detection for `Funbound.plasma`, below which distribution will be censored if fup.censored.dist is TRUE. Default 0.01.
`fup.censored.dist`	Logical. Whether to draw `Funbound.plasma` from a censored distribution or not.
`adjusted.Funbound.plasma`	Uses adjusted Funbound.plasma when set to TRUE.
`clint.pvalue.threshold`	Hepatic clearance for chemicals where the in vitro clearance assay result has a p-values greater than the threshold are set to zero.
`minimum.Funbound.plasma`	Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).
`parameters`	A list of chemical-specific model parameters containing at least Funbound.plasma, Clint, and Fhep.assay.correction.

Value

A data.table with three columns: `Funbound.plasma` and `Clint`, containing the sampled values, and `Fhep.assay.correction`, containing the value for fraction unbound in hepatocyte assay.

Author(s)

Caroline Ring and John Wambaugh

References

Wambaugh, John F., et al. "Assessing Toxicokinetic Uncertainty and Variability in Risk Prioritization." Toxicological Sciences (2019).

`is.httk` *Convenience Boolean (yes/no) function to identify chemical membership and treatment within the httk project.*

Description

Allows easy identification of whether or not a chemical CAS is included in various aspects of the httk research project (by model type and species of interest). While it is our intent to keep these lists up-to-date, the information here is only for convenience and should not be considered definitive.

Usage

```
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.
`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 included in the httk project with a given modeling scheme (PBTK) and a given species

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: https://www.cdc.gov/nchs/nhanes.htm.

See Also

`in.list` for determining chemical membership in several other key lists

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 ten
# chemicals. To build a table with all available chemicals use:
# for (this.cas in httk.table$CAS)
for (this.cas in httk.table$CAS[1:10])
{
  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"
}
```

is_in_inclusive *Checks whether a value, or all values in a vector, is within inclusive limits*

Description

Checks whether a value, or all values in a vector, is within inclusive limits

Usage

```
is_in_inclusive(x, lims)
```

Arguments

x	A numeric value, or vector of values.
lims	A two-element vector of (min, max) values for the inclusive limits. If x is a vector, lims may also be a two-column matrix with nrow=length(x) where the first column is lower limits and the second column is upper limits. If x is a vector and lims is a two-element vector, then each element of x will be checked against the same limits. If x is a vector and lims is a matrix, then each element of x will be checked against the limits given by the corresponding row of lims.

Value

A logical vector the same length as x, indicating whether each element of x is within the inclusive limits given by lims.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

johnson *Johnson 2006*

Description

This data set is only used in Vignette 5.

Usage

```
johnson
```

Format

A data.table containing 60 rows and 11 columns.

Author(s)

Caroline Ring

References

Johnson, Trevor N., Amin Rostami-Hodjegan, and Geoffrey T. Tucker. "Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children." Clinical pharmacokinetics 45.9 (2006): 931-956.

`kidney_mass_children` *Predict kidney mass for children*

Description

For individuals under age 18, predict kidney mass from weight, height, and gender. using equations from Ogiu et al. 1997

Usage

```
kidney_mass_children(weight, height, gender)
```

Arguments

`weight`	Vector of weights in kg.
`height`	Vector of heights in cm.
`gender`	Vector of genders (either 'Male' or 'Female').

Value

A vector of kidney masses in kg.

Author(s)

Caroline Ring

References

Ogiu, Nobuko, et al. "A statistical analysis of the internal organ weights of normal Japanese people." Health physics 72.3 (1997): 368-383.

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

liver_mass_children *Predict liver mass for children*

Description

For individuals under 18, predict the liver mass from height, weight, and gender, using equations from Ogiu et al. 1997

Usage

```
liver_mass_children(height, weight, gender)
```

Arguments

height	Vector of heights in cm.
weight	Vector of weights in kg.
gender	Vector of genders (either 'Male' or 'Female').

Value

A vector of liver masses in kg.

Author(s)

Caroline Ring

References

Ogiu, Nobuko, et al. "A statistical analysis of the internal organ weights of normal Japanese people." Health physics 72.3 (1997): 368-383.

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

load_sipes2017 *Load data from Sipes et al 2017.*

Description

This function returns an updated version of chem.physical_and_invitro.data that includes data predicted with Simulations Plus' ADMET predictor that was used in Sipes et al. 2017, included in admet.data.

Usage

```
load_sipes2017(overwrite = F, target.env = .GlobalEnv)
```

Arguments

overwrite	Only matters if load.image=FALSE. If overwrite=TRUE then existing data in chem.physical_and_invitro.data will be replaced by any data/predictions in Sipes et al. (2017) that is for the same chemical and property. If overwrite=FALSE (DEFAULT) then new data for the same chemical and property are ignored. Funbound.plasma values of 0 (below limit of detection) are overwritten either way.
target.env	The environment where the new chem.physical_and_invitro.data is loaded. Defaults to global environment.

Value

data.frame	An updated version of chem.physical_and_invitro.data.

Author(s)

Robert Pearce and John Wambaugh

References

Sipes, Nisha S., et al. "An intuitive approach for predicting potential human health risk with the Tox21 10k library." Environmental Science & Technology 51.18 (2017): 10786-10796.

Examples

```
## Not run:
chem.physical_and_invitro.data <- load_sipes2017()
chem.physical_and_invitro.data <- load_sipes2017(overwrite=T)

## End(Not run)
```

---

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,
  parameters = NULL,
  tissuelist = NULL,
  species = "Human",
  tissue.vols = NULL,
  tissue.flows = NULL
)
```

Arguments

Ktissue2pu.in	List of partition coefficients from predict_partitioning_schmitt.
parameters	A list of physiological parameters including flows and volumes for tissues in tissuelist
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").
tissue.vols	A list of volumes for tissues in tissuelist
tissue.flows	A list of flows for tissues in tissuelist

Details

This function returns the flows, volumes, and partition coefficients for the lumped tissues specified in tissue list Ktissue2plasma – tissue to free plasma concentration partition coefficients for every tissue specified by Schmitt (2008) (the tissue.data table) tissuelist – a list of character vectors, the name of each entry in the list is a lumped tissue, the words in the vector are the Schmitt (2008) tissues that are to be lumped, for example: tissuelist<-list(Rapid=c("Brain","Kidney")) species specifies the flow.col and vol.col in the tissuedata.table

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 and Robert Pearce

References

Pearce, Robert G., et al. "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." Journal of pharmacokinetics and pharmacodynamics 44.6 (2017): 549-565.

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)
```

lung_mass_children *Predict lung mass for children*

Description

For individuals under 18, predict the liver mass from height, weight, and gender, using equations from Ogiu et al. 1997

Usage

```
lung_mass_children(height, weight, gender)
```

Arguments

height	Vector of heights in cm.
weight	Vector of weights in kg.
gender	Vector of genders (either 'Male' or 'Female').

Value

A vector of lung masses in kg.

Author(s)

Caroline Ring

References

Ogiu, Nobuko, et al. "A statistical analysis of the internal organ weights of normal Japanese people." Health physics 72.3 (1997): 368-383.

Price, Paul S., et al. "Modeling interindividual variation in physiological factors used in PBPK models of humans." Critical reviews in toxicology 33.5 (2003): 469-503.

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

mcnally_dt *Reference tissue masses and flows from tables in McNally et al. 2014.*

Description

Reference tissue masses, flows, and marginal distributions from McNally et al. 2014.

Usage

```
mcnally_dt
```

Format

A data.table with variables:

`tissue` Body tissue

`gender` Gender: Male or Female

`mass_ref` Reference mass in kg, from Reference Man

`mass_cv` Coefficient of variation for mass

`mass_dist` Distribution for mass: Normal or Log-normal

`flow_ref` Reference flow in L/h, from Reference Man

`flow_cv` Coefficient of variation for flow (all normally distributed)

`height_ref` Reference heights (by gender)

`CO_ref` Reference cardiac output by gender

`flow_frac` Fraction of CO flowing to each tissue: `flow_ref`/`CO_ref`

Author(s)

Caroline Ring

Source

McNally K, Cotton R, Hogg A, Loizou G. "PopGen: A virtual human population generator." Toxicology 315, 70-85, 2004.

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

`metabolism_data_Linakis2020` *Metabolism data involved in Linakis 2020 vignette analysis.*

Description

Metabolism data involved in Linakis 2020 vignette analysis.

Usage

```
metabolism_data_Linakis2020
```

Format

A data.frame containing x rows and y columns.

Author(s)

Matt Linakis

Source

Matt Linakis

References

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

`monte_carlo` *Monte Carlo for pharmacokinetic models*

Description

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

Usage

```
monte_carlo(
  parameters,
  cv.params = NULL,
  censored.params = NULL,
  samples = 1000
)
```

Arguments

`parameters`	These parameters that are also listed in either cv.params or censored.params are sampled using Monte Carlo.
`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 "parameters". New values are sampled with mean equal to the value in "parameters" 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 parameter). 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.

Author(s)

John Wambaugh

References

Wambaugh, John F., et al. "Toxicokinetic triage for environmental chemicals." Toxicological Sciences 147.1 (2015): 55-67.

Pearce, Robert G., et al. "Httk: R package for high-throughput toxicokinetics." Journal of statistical software 79.4 (2017): 1.

Examples

```
#Example from Pearce et al. (2017):
## Not run:
library(ggplot2)
library(scales)
vary.params <- NULL
parameters <- parameterize_pbtk(chem.name = "Zoxamide")
for(this.param in names(subset(parameters,
names(parameters) != "Funbound.plasma"))) vary.parameters[this.param] <- .2
censored.params <- list(Funbound.plasma = list(cv = 0.2, lod = 0.01))
set.seed(1)
out <- monte_carlo(parameters, cv.params = vary.params,
censored.params = censored.params, model = "pbtk", suppress.messages = T)
zoxamide <- ggplot(as.data.frame(out), aes(out)) +
geom_histogram(fill="blue", binwidth=1/6) + scale_x_log10() +
ylab("Number of Samples") + xlab("Steady State Concentration (uM)") +
theme(axis.text = element_text(size = 16),
axis.title = element_text(size = 16))
print(zoxamide)


# Fig 1 in Wambaugh et al. (2015) SimCYP vs. our predictions:

vary.params <- list(BW=0.3)
vary.parameters[["Vliverc"]]<-0.3
vary.parameters[["Qgfrc"]]<-0.3
vary.parameters[["Qtotal.liverc"]]<-0.3
vary.parameters[["million.cells.per.gliver"]]<-0.3
vary.parameters[["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.parameters[["Funbound.plasma"]] == 0.0)
    {
      these.parameters[["Funbound.plasma"]] <- 0.005
    }
    these.parameters[["Fhep.assay.correction"]] <- 1
    vLiver.human.values <- monte_carlo(these.params,
                                       cv.params=vary.params,
```

```
                                        censored.params=censored.params,
                                        output.units="mg/L",
                                        model='3compartmentss',
                                        suppress.messages=T,
                                        well.stirred.correction=F,
                                        Funbound.plasma.correction=F)
    percentiles <- c("5","50","95")
    for (this.index in 1:3)
    {
      this.row <- as.data.frame(get_wetmore_css(chem.cas=this.CAS))
      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)
```

---

nhanes_mec_svy *Pre-processed NHANES data.*

Description

NHANES data on demographics, anthropometrics, and some laboratory measures, cleaned and combined into a single data set.

Usage

```
nhanes_mec_svy
```

Format

A survey.design2 object, including masked cluster and strata. Variables are available as a data.table by `nhanes_mec_svy$variables`. Variables are as described in NHANES Demographics and Examination documentation, with the exception of:

`wtmec6yr` 6-year sample weights for combining 3 cycles, computed by dividing 2-year sample weights by 3.

`bmxhtlenavg` Average of height and recumbent length if both were measured; if only one was measured, takes value of the one that was measured.

`logbmxwt` Natural log of measured body weight.

`logbmxhtlenavg` Natural log of `bmxhtlenavg`.

`weight_class` One of Underweight, Normal, Overweight, or Obese. Assigned using methods in `get_weight_class`.

Author(s)

Caroline Ring

Source

https://wwwn.cdc.gov/nchs/nhanes/Default.aspx

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

Obach2008 *Published Pharmacokinetic Parameters from Obach et al. 2008*

Description

This data set is used in Vignette 4 for steady state concentration.

Usage

```
Obach2008
```

Format

A data.frame containing 670 rows and 8 columns.

References

Obach, R. Scott, Franco Lombardo, and Nigel J. Waters. "Trend analysis of a database of intravenous pharmacokinetic parameters in humans for 670 drug compounds." Drug Metabolism and Disposition 36.7 (2008): 1385-1405.

`onlyp` *NHANES Exposure Data*

Description

This data set is only used in Vignette 6.

Usage

```
onlyp
```

Format

A data.table containing 1060 rows and 5 columns.

Author(s)

Caroline Ring

References

Wambaugh, John F., et al. "High throughput heuristics for prioritizing human exposure to environmental chemicals." Environmental science & technology 48.21 (2014): 12760-12767.

`pancreas_mass_children` *Predict pancreas mass for children*

Description

For individuals under 18, predict the pancreas mass from height, weight, and gender, using equations from Ogiu et al.

Usage

```
pancreas_mass_children(height, weight, gender)
```

Arguments

`height`	Vector of heights in cm.
`weight`	Vector of weights in kg.
`gender`	Vector of genders (either 'Male' or 'Female').

Value

A vector of pancreas masses in kg.

Author(s)

Caroline Ring

References

Ogiu, Nobuko, et al. "A statistical analysis of the internal organ weights of normal Japanese people." Health physics 72.3 (1997): 368-383.

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

`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,
  dtxsid = NULL,
  species = "Human",
  default.to.human = F,
  adjusted.Funbound.plasma = T,
  regression = T,
  restrictive.clearance = T,
  well.stirred.correction = T,
  suppress.messages = F,
  clint.pvalue.threshold = 0.05,
  minimum.Funbound.plasma = 1e-04
)
```

Arguments

`chem.cas`	Chemical Abstract Services Registry Number (CAS-RN) – the chemical must be identified by either CAS, name, or DTXISD
`chem.name`	Chemical name (spaces and capitalization ignored) – the chemical must be identified by either CAS, name, or DTXISD
`dtxsid`	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) – the chemical must be identified by either CAS, name, or DTXSIDs
`species`	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
`default.to.human`	Substitutes missing rat values with human values if true.

adjusted.Funbound.plasma
: Uses adjusted Funbound.plasma when set to TRUE along with volume of distribution calculated with this value.

regression
: Whether or not to use the regressions in calculating partition coefficients in volume of distribution calculation.

restrictive.clearance
: In calculating elimination rate and hepatic bioavailability, protein binding is not taken into account (set to 1) in liver clearance if FALSE.

well.stirred.correction
: Uses correction in calculation of hepatic clearance for well-stirred model if TRUE. This assumes clearance relative to amount unbound in whole blood instead of plasma, but converted to use with plasma concentration.

suppress.messages
: Whether or not to suppress messages.

clint.pvalue.threshold
: Hepatic clearance for chemicals where the in vitro clearance assay result has a p-value greater than the threshold are set to zero.

minimum.Funbound.plasma
: Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).

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.

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

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. Not used in calculations but included for the conversion of plasma outputs.

hepatic.bioavailability
: Fraction of dose remaining after first pass clearance, calculated from the corrected well-stirred model.

BW
: Body Weight, kg.

Author(s)

John Wambaugh and Robert Pearce

References

Pearce, Robert G., et al. "Httk: R package for high-throughput toxicokinetics." Journal of statistical software 79.4 (2017): 1.

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_1comp(chem.name='Bisphenol-A',species='Rat')
parameters <- parameterize_1comp(chem.cas='80-05-7',
                                 restrictive.clearance=FALSE,
                                 species='rabbit',
                                 default.to.human=TRUE)
out <- solve_1comp(parameters=parameters)
```

`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,
  dtxsid = NULL,
  species = "Human",
  default.to.human = F,
  force.human.clint.fup = F,
  clint.pvalue.threshold = 0.05,
  adjusted.Funbound.plasma = T,
  regression = T,
  suppress.messages = F,
  restrictive.clearance = T,
  minimum.Funbound.plasma = 1e-04
)
```

Arguments

`chem.cas`	Chemical Abstract Services Registry Number (CAS-RN) – the chemical must be identified by either CAS, name, or DTXISD
`chem.name`	Chemical name (spaces and capitalization ignored) – the chemical must be identified by either CAS, name, or DTXISD
`dtxsid`	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) – the chemical must be identified by either CAS, name, or DTXSIDs

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.fup
: 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.

adjusted.Funbound.plasma
: Returns adjusted Funbound.plasma when set to TRUE along with parition coefficients calculated with this value.

regression Whether or not to use the regressions in calculating partition coefficients.

suppress.messages
: Whether or not the output message is suppressed.

restrictive.clearance
: In calculating hepatic.bioavailability, protein binding is not taken into account (set to 1) in liver clearance if FALSE.

minimum.Funbound.plasma
: Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).

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

Pearce, Robert G., et al. "Httk: R package for high-throughput toxicokinetics." Journal of statistical software 79.4 (2017): 1.

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',
                                 species='rabbit',default.to.human=TRUE)
out <- solve_3comp(parameters=parameters,plots=TRUE)
```

---

parameterize_gas_pbtk *Parameterize_gas_pbtk*

Description

This function initializes the parameters needed in the function solve_gas_pbtk

Usage

```
parameterize_gas_pbtk(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
  default.to.human = F,
 tissuelist = list(liver = c("liver"), kidney = c("kidney"), lung = c("lung"), gut =
    c("gut")),
  force.human.clint.fup = F,
  clint.pvalue.threshold = 0.05,
  adjusted.Funbound.plasma = T,
  regression = T,
```

```
  vmax = 0,
  km = 1,
  exercise = F,
  fR = 12,
  VT = 0.75,
  VD = 0.15,
  suppress.messages = F,
  minimum.Funbound.plasma = 1e-04,
  ...
)
```

Arguments

chem.cas	Either the chemical name or the CAS number must be specified.
chem.name	Either the chemical name or the CAS number must be specified.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
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.fup	Forces use of human values for hepatic intrinsic clearance and fraction of unbound plasma if true.
clint.pvalue.threshold	Hepatic clearance for chemicals where the in vitro clearance assay result has a p-values greater than the threshold are set to zero.
adjusted.Funbound.plasma	Returns adjusted Funbound.plasma when set to TRUE along with parition coefficients calculated with this value.
regression	Whether or not to use the regressions in calculating partition coefficients.
vmax	Michaelis-Menten vmax value in reactions/min
km	Michaelis-Menten concentration of half-maximal reaction velocity in desired output concentration units.
exercise	Logical indicator of whether to simulate an exercise-induced heightened respiration rate
fR	Respiratory frequency (breaths/minute), used especially to adjust breathing rate in the case of exercise. This parameter, along with VT and VD (below) gives another option for calculating Qalv (Alveolar ventilation) in case pulmonary ventilation rate is not known
VT	Tidal volume (L), to be modulated especially as part of simulating the state of exercise
VD	Anatomical dead space (L), to be modulated especially as part of simulating the state of exercise
suppress.messages	Whether or not the output message is suppressed.

`minimum.Funbound.plasma`
: Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).

`...`
: Other parameters

Value

`BW`
: Body Weight, kg.

`Clint`
: Hepatic intrinsic clearance, uL/min/10^6 cells

`Clint.dist`
: Distribution of hepatic intrinsic clearance values (median, lower 95th, upper 95th, p value)

`Clmetabolismc`
: Hepatic Clearance, L/h/kg BW.

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

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

`Funbound.plasma`
: Fraction of chemical unbound to plasma.

`Funbound.plasma.adjustment`
: Fraction unbound to plasma adjusted as described in Pearce et al. 2017

`Funbound.plasma.dist`
: Distribution of fraction unbound to plasma (median, lower 95th, upper 95th)

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

`Kblood2air`
: Ratio of concentration of chemical in blood to air

`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.

`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.

`km`
: Michaelis-Menten concentration of half-maximal activity

`Kmuc2air`
: Mucus to air partition coefficient

`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.

`kUrtc`
: Unscaled upper respiratory tract uptake parameter (L/h/kg^0.75)

`liver.density`
: Density of liver in g/mL

`MA`
: phospholipid:water distribution coefficient, membrane affinity

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

`MW`
: Molecular Weight, g/mol.

pKa_Accept	compound H association equilibrium constant(s)
pKa_Donor	compound H dissociation equilibirum constant(s)
Pow	octanol:water partition coefficient (not log transformed)
Qalvc	Unscaled alveolar ventilation rate (L/h/kg^0.75)
Qcardiacc	Cardiac Output, L/h/kg BW^3/4.
Qgfrc	Glomerular Filtration Rate, L/h/kg BW^0.75, 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.
Qlungf	Fraction of cardiac output flowing to lung tissue.
Qrestf	Fraction of blood flow to rest of body
Rblood2plasma	The ratio of the concentration of the chemical in the blood to the concentration in the plasma from available_rblood2plasma.
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.
vmax	Michaelis-Menten maximum reaction velocity (1/min)
Vmucc	Unscaled mucosal volume (L/kg BW^0.75
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)

Matt Linakis, Robert Pearce, John Wambaugh

References

Linakis, Matthew W., et al. "Development and Evaluation of a High Throughput Inhalation Model for Organic Chemicals", submitted

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_gas_pbtk(chem.cas='129-00-0')

parameters <- parameterize_gas_pbtk(chem.name='pyrene',species='Rat')

parameterize_gas_pbtk(chem.cas = '56-23-5')

parameters <- parameterize_gas_pbtk(chem.name='Carbon tetrachloride',species='Rat')

# Change the tissue lumping:
```

```
compartments <- list(liver=c("liver"),fast=c("heart","brain","muscle","kidney"),
                     lung=c("lung"),gut=c("gut"),slow=c("bone"))
parameterize_gas_pbtk(chem.name="Bisphenol a",species="Rat",default.to.human=TRUE,
                  tissuelist=compartments)
```

`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,
  dtxsid = NULL,
  species = "Human",
  default.to.human = F,
 tissuelist = list(liver = c("liver"), kidney = c("kidney"), lung = c("lung"), gut =
   c("gut")),
  force.human.clint.fup = F,
  clint.pvalue.threshold = 0.05,
  adjusted.Funbound.plasma = T,
  regression = T,
  suppress.messages = F,
  restrictive.clearance = T,
  minimum.Funbound.plasma = 1e-04
)
```

Arguments

`chem.cas`	Chemical Abstract Services Registry Number (CAS-RN) – the chemical must be identified by either CAS, name, or DTXISD
`chem.name`	Chemical name (spaces and capitalization ignored) – the chemical must be identified by either CAS, name, or DTXISD
`dtxsid`	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) – the chemical must be identified by either CAS, name, or DTXSIDs
`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.fup`	Forces use of human values for hepatic intrinsic clearance and fraction of unbound plasma if true.

clint.pvalue.threshold
: Hepatic clearance for chemicals where the in vitro clearance assay result has a p-values greater than the threshold are set to zero.

adjusted.Funbound.plasma
: Returns adjusted Funbound.plasma when set to TRUE along with parition coefficients calculated with this value.

regression
: Whether or not to use the regressions in calculating partition coefficients.

suppress.messages
: Whether or not the output message is suppressed.

restrictive.clearance
: In calculating hepatic.bioavailability, protein binding is not taken into account (set to 1) in liver clearance if FALSE.

minimum.Funbound.plasma
: Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).

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.

kgutabs
: Rate that chemical enters the gut from gutlumen, 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 from available_rblood2plasma.
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

Pearce, Robert G., et al. "Httk: R package for high-throughput toxicokinetics." Journal of statistical software 79.4 (2017): 1.

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 *Get the Parameters for Schmitt's Tissue Partition Coefficient 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,
  dtxsid = NULL,
  parameters = NULL,
  species = "Human",
  default.to.human = F,
  force.human.fup = F,
  suppress.messages = F,
  minimum.Funbound.plasma = 1e-04
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemcial and physiological description parameters needed to run the Schmitt et al. (2008) model
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.
force.human.fup	Returns human fraction of unbound plasma in calculation for rats if true. When species is specified as rabbit, dog, or mouse, the human unbound fraction is substituted.
suppress.messages	Whether or not the output message is suppressed.
minimum.Funbound.plasma	Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).

Value

Funbound.plasma	corrected unbound fraction in plasma
unadjusted.Funbound.plasma	measured unbound fraction in plasma (0.005 if below limit of detection)
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
plasma.pH	pH of the plasma

Author(s)

Robert Pearce and John Wambaugh

References

Schmitt, Walter. "General approach for the calculation of tissue to plasma partition coefficients." Toxicology in Vitro 22.2 (2008): 457-467.

Schmitt, Walter. "Corrigendum to: General approach for the calculation of tissue to plasma partition coefficients" Toxicology in Vitro 22.6 (2008): 1666.

Peyret, Thomas, Patrick Poulin, and Kannan Krishnan. "A unified algorithm for predicting partition coefficients for PBPK modeling of drugs and environmental chemicals." Toxicology and applied pharmacology 249.3 (2010): 197-207.

Pearce, Robert G., et al. "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." Journal of pharmacokinetics and pharmacodynamics 44.6 (2017): 549-565.

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,
  dtxsid = NULL,
  species = "Human",
  clint.pvalue.threshold = 0.05,
  default.to.human = F,
  human.clint.fup = F,
  adjusted.Funbound.plasma = T,
  restrictive.clearance = T,
  fup.lod.default = 0.005,
  suppress.messages = F,
  minimum.Funbound.plasma = 1e-04
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) – the chemical must be identified by either CAS, name, or DTXSIDs
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.fup	Uses human hepatic intrinsic clearance and fraction of unbound plasma in calculation of partition coefficients for rats if true.
adjusted.Funbound.plasma	Returns adjusted Funbound.plasma when set to TRUE.
restrictive.clearance	In calculating hepatic.bioavailability, protein binding is not taken into account (set to 1) in liver clearance if FALSE.
fup.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.
suppress.messages	Whether or not the output message is suppressed.
minimum.Funbound.plasma	Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).

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	Glomerular 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)

`hepatic.bioavailability`
: Fraction of dose remaining after first pass clearance, calculated from the corrected well-stirred model.

Author(s)

John Wambaugh

References

Pearce, Robert G., et al. "Httk: R package for high-throughput toxicokinetics." Journal of statistical software 79.4 (2017): 1.

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

---

pc.data *Partition Coefficient Data*

Description

Measured rat in vivo partition coefficients and data for predicting them.

Usage

```
pc.data
```

Format

A data.frame.

Author(s)

Jimena Davis and Robert Pearce

References

Schmitt, W., General approach for the calculation of tissue to plasma partition coefficients. Toxicology in Vitro, 2008. 22(2): p. 457-467.

Schmitt, W., Corrigendum to:"General approach for the calculation of tissue to plasma partition coefficients"[Toxicology in Vitro 22 (2008) 457-467]. Toxicology in Vitro, 2008. 22(6): p. 1666.

Poulin, P. and F.P. Theil, A priori prediction of tissue: plasma partition coefficients of drugs to facilitate the use of physiologically based pharmacokinetic models in drug discovery. Journal of pharmaceutical sciences, 2000. 89(1): p. 16-35.

Rodgers, T. and M. Rowland, Physiologically based pharmacokinetic modelling 2: predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions. Journal of pharmaceutical sciences, 2006. 95(6): p. 1238-1257.

Rodgers, T., D. Leahy, and M. Rowland, Physiologically based pharmacokinetic modeling 1: predicting the tissue distribution of moderate-to-strong bases. Journal of pharmaceutical sciences, 2005. 94(6): p. 1259-1276.

Rodgers, T., D. Leahy, and M. Rowland, Tissue distribution of basic drugs: Accounting for enantiomeric, compound and regional differences amongst beta-blocking drugs in rat. Journal of pharmaceutical sciences, 2005. 94(6): p. 1237-1248.

Gueorguieva, I., et al., Development of a whole body physiologically based model to characterise the pharmacokinetics of benzodiazepines. 1: Estimation of rat tissue-plasma partition ratios. Journal of pharmacokinetics and pharmacodynamics, 2004. 31(4): p. 269-298.

Poulin, P., K. Schoenlein, and F.P. Theil, Prediction of adipose tissue: plasma partition coefficients for structurally unrelated drugs. Journal of pharmaceutical sciences, 2001. 90(4): p. 436-447.

Bjorkman, S., Prediction of the volume of distribution of a drug: which tissue-plasma partition coefficients are needed? Journal of pharmacy and pharmacology, 2002. 54(9): p. 1237-1245.

Yun, Y. and A. Edginton, Correlation-based prediction of tissue-to-plasma partition coefficients using readily available input parameters. Xenobiotica, 2013. 43(10): p. 839-852.

Uchimura, T., et al., Prediction of human blood-to-plasma drug concentration ratio. Biopharmaceutics & drug disposition, 2010. 31(5-6): p. 286-297.

`pharma` *DRUGS\NORMAN: Pharmaceutical List with EU, Swiss, US Consumption Data*

Description

SWISSPHARMA is a list of pharmaceuticals with consumption data from Switzerland, France, Germany and the USA, used for a suspect screening/exposure modelling approach described in Singer et al 2016, DOI: 10.1021/acs.est.5b03332. The original data is available on the NORMAN Suspect List Exchange.

Usage

```
pharma
```

Format

An object of class `data.frame` with 954 rows and 14 columns.

Source

https://comptox.epa.gov/dashboard/chemical_lists/swisspharma

References

Wambaugh et al. (2019) "Assessing Toxicokinetic Uncertainty and Variability in Risk Prioritization", Toxicological Sciences, 172(2), 235-251.

---

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, John F., et al. "Toxicokinetic triage for environmental chemicals." Toxicological Sciences (2015): 228-237.

References

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

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 for the tissues contained in the tissue.data table.

Usage

```
predict_partitioning_schmitt(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  species = "Human",
  default.to.human = F,
  parameters = NULL,
  alpha = 0.001,
  adjusted.Funbound.plasma = T,
  regression = T,
 regression.list = c("brain", "adipose", "gut", "heart", "kidney", "liver", "lung",
    "muscle", "skin", "spleen", "bone"),
  tissues = NULL,
  minimum.Funbound.plasma = 1e-04,
  suppress.messages = 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.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
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 parameterize_schmitt overrides chem.name, dtxsid, and chem.cas.
alpha	Ratio of Distribution coefficient D of totally charged species and that of the neutral form
adjusted.Funbound.plasma	Whether or not to use Funbound.plasma adjustment.
regression	Whether or not to use the regressions. Regressions are used by default.
regression.list	Tissues to use regressions on.
tissues	Vector of desired partition coefficients. Returns all by default.

`minimum.Funbound.plasma`
: Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).

`suppress.messages`
: Whether or not the output message is suppressed.

Details

A separate regression is used when adjusted.Funbound.plasma is FALSE.

A regression is used for membrane affinity when not provided. The regressions for correcting each tissue are performed on tissue plasma partition coefficients (Ktissue2pu * Funbound.plasma) calculated with the corrected Funbound.plasma value and divided by this value to get Ktissue2pu. Thus the regressions should be used with the corrected Funbound.plasma.

The red blood cell regression can be used but is not by default because of the span of the data used, reducing confidence in the regression for higher and lower predicted values.

Human tissue volumes are used for species other than Rat.

Value

Returns tissue to unbound plasma partition coefficients for each tissue.

Author(s)

Robert Pearce

References

Schmitt, Walter. "General approach for the calculation of tissue to plasma partition coefficients." Toxicology in Vitro 22.2 (2008): 457-467.

Birnbaum, L., et al. "Physiological parameter values for PBPK models." International Life Sciences Institute, Risk Science Institute, Washington, DC (1994).

Pearce, Robert G., et al. "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." Journal of pharmacokinetics and pharmacodynamics 44.6 (2017): 549-565.

Yun, Y. E., and A. N. Edginton. "Correlation-based prediction of tissue-to-plasma partition coefficients using readily available input parameters." Xenobiotica 43.10 (2013): 839-852.

Examples

```
predict_partitioning_schmitt(chem.name='ibuprofen',regression=FALSE)
```

propagate_invitrouv_1comp

Propagates uncertainty and variability in in vitro HTTK data into one compartment model parameters

Description

Propagates uncertainty and variability in in vitro HTTK data into one compartment model parameters

Usage

```
propagate_invitrouv_1comp(parameters.dt, ...)
```

Arguments

parameters.dt	The data table of parameters being used by the Monte Carlo sampler
...	Additional arguments passed to calc_elimination_rate

Value

A data.table whose columns are the parameters of the HTTK model specified in model.

Author(s)

John Wambaugh

propagate_invitrouv_3comp

Propagates uncertainty and variability in in vitro HTTK data into three compartment model parameters

Description

Propagates uncertainty and variability in in vitro HTTK data into three compartment model parameters

Usage

```
propagate_invitrouv_3comp(parameters.dt, ...)
```

Arguments

parameters.dt	The data table of parameters being used by the Monte Carlo sampler
...	Additional arguments passed to calc_hep_clearance

Value

A data.table whose columns are the parameters of the HTTK model specified in model.

Author(s)

John Wambaugh

`propagate_invitrouv_pbtk` *Propagates uncertainty and variability in in vitro HTTK data into PBPK model parameters*

Description

Propagates uncertainty and variability in in vitro HTTK data into PBPK model parameters

Usage

```
propagate_invitrouv_pbtk(parameters.dt, ...)
```

Arguments

`parameters.dt`	The data table of parameters being used by the Monte Carlo sampler
`...`	Additional arguments passed to `calc_hep_clearance`

Value

A data.table whose columns are the parameters of the HTTK model specified in `model`.

Author(s)

John Wambaugh

`reset_httk` *Reset HTTK to Default Data Tables*

Description

This function returns an updated version of chem.physical_and_invitro.data that includes data predicted with Simulations Plus' ADMET predictor that was used in Sipes et al. 2017, included in admet.data.

Usage

```
reset_httk(target.env = .GlobalEnv)
```

Arguments

`target.env`	The environment where the new chem.physical_and_invitro.data is loaded. Defaults to global environment.

Value

`data.frame`	The package default version of chem.physical_and_invitro.data.

Author(s)

John Wambaugh

Examples

```
## Not run:
chem.physical_and_invitro.data <- load_sipes2017()
reset_httk()

## End(Not run)
```

`rfun` *Randomly draws from a one-dimensional KDE*

Description

Randomly draws from a one-dimensional KDE

Usage

```
rfun(n, fhat)
```

Arguments

`n`	Number of samples to draw
`fhat`	A list with elements x, w, and h (h is the KDE bandwidth).

Value

A vector of n samples from the KDE fhat

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

r_left_censored_norm *Returns draws from a normal distribution with a lower censoring limit of lod (limit of detection)*

Description

Returns draws from a normal distribution with a lower censoring limit of lod (limit of detection)

Usage

```
r_left_censored_norm(n, mean = 0, sd = 1, lod = 0.005, lower = 0, upper = 1)
```

Arguments

n	Number of samples to take
mean	Mean of censored distribution. Default 0.
sd	Standard deviation of censored distribution. Default 1.
lod	Bound below which to censor. Default 0.005.
lower	Lower bound on censored distribution. Default 0.
upper	Upper bound on censored distribution. Default 1.

Value

A vector of samples from the specified censored distribution.

scale_dosing *Scale mg/kg body weight doses according to body weight and units*

Description

This function transforms the dose (in mg/kg) into the appropriate units. It handles single doses, matrices of doses, or daily repeated doses at varying intervals. Gut absorption is also factored in through the parameter Fgutabs, and scaling is currently avoided in the inhalation exposure case with a scale factor of 1

Usage

```
scale_dosing(dosing, parameters, route, output.units = "uM")
```

Arguments

dosing	List of dosing metrics used in simulation, which must include the general entries with names "initial.dose", "doses.per.day", "daily.dose", and "dosing.matrix". The "dosing.matrix" is used for more precise dose regimen specification, and is a matrix consisting of two columns or rows named "time" and "dose" containing the time and amount, in mg/kg BW, of each dose. The minimal usage case involves all entries but "initial.dose" set to NULL in value.

parameters	Chemical parameters from parameterize_pbtk function, overrides chem.name and chem.cas.
route	String specification of route of exposure for simulation: "oral", "iv", "inhalation", ...
output.units	Desired units (either "mg/L", "mg", "umol", or default "uM").

Author(s)

John Wambaugh

`set_httk_precision` *set_httk_precision*

Description

Although the ODE solver and other functions return very precise numbers, we cannot (or at least do not spend enough computing time to) be sure of the precioion to an arbitrary level. This function both limits the number of signficant figures reported and truncates the numerical precision.

Usage

```
set_httk_precision(in.num, sig.fig = 4, num.prec = 9)
```

Arguments

in.num	The numeric variable (or assembly of numerics) to be processed.
sig.fig	The number of significant figures reported. Defaults to 4.
num.prec	The precision maintained, digits below 10^num.prec are dropped. Defaults to 9.

Value

numeric values

Author(s)

John Wambaugh

sipes2017 *Sipes et al. 2017 data*

Description

This table includes in silico predicted chemical-specifc plasma protein unbound fraction (fup) and intrinsic hepatic clearance values for the entire Tox21 library (see https://www.epa.gov/chemical-research/toxicology-testing-21st-century-tox21). Predictions were made with Simulations Plus ADMET predictor, as reported in Sipes et al. (2017).

Usage

```
sipes2017
```

Format

data.frame

Author(s)

Nisha Sipes

Source

ADMET, Simulations Plus

References

Sipes, Nisha S., et al. "An Intuitive Approach for Predicting Potential Human Health Risk with the Tox21 10k Library." Environmental Science & Technology 51.18 (2017): 10786-10796.

skeletal_muscle_mass *Predict skeletal muscle mass*

Description

Predict skeletal muscle mass from age, height, and gender.

Usage

```
skeletal_muscle_mass(smm, age_years, height, gender)
```

Arguments

smm	Vector of allometrically-scaled skeletal muscle masses.
age_years	Vector of ages in years.
height	Vector of heights in cm.
gender	Vector of genders, either 'Male' or 'Female.'

Details

For individuals over age 18, use allometrically-scaled muscle mass with an age-based scaling factor, to account for loss of muscle mass with age (Janssen et al. 2000). For individuals under age 18, use skeletal_muscle_mass_children.

Value

Vector of skeletal muscle masses in kg.

Author(s)

Caroline Ring

References

Janssen, Ian, et al. "Skeletal muscle mass and distribution in 468 men and women aged 18-88 yer." Journal of Applied Physiology 89.1 (2000): 81-88

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

See Also

skeletal_muscle_mass_children

---

skeletal_muscle_mass_children

Predict skeletal muscle mass for children

Description

For individuals under age 18, predict skeletal muscle mass from gender and age, using a nonlinear equation from Webber and Barr (2012)

Usage

```
skeletal_muscle_mass_children(gender, age_years)
```

Arguments

gender	Vector of genders (either 'Male' or 'Female').
age_years	Vector of ages in years.

Value

Vector of skeletal muscle masses in kg.

Author(s)

Caroline Ring

References

Webber, Colin E., and Ronald D. Barr. "Age-and gender-dependent values of skeletal muscle mass in healthy children and adolescents." Journal of cachexia, sarcopenia and muscle 3.1 (2012): 25-29.

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

`skin_mass_bosgra` *Predict skin mass*

Description

Using equation from Bosgra et al. 2012, predict skin mass from body surface area.

Usage

```
skin_mass_bosgra(BSA)
```

Arguments

`BSA`	Vector of body surface areas in cm^2.

Value

Vector of skin masses in kg.

Author(s)

Caroline Ring

References

Bosgra, Sieto, et al. "An improved model to predict physiologically based model parameters and their inter-individual variability from anthropometry." Critical reviews in toxicology 42.9 (2012): 751-767.

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

solve_1comp *Solve one compartment TK model*

Description

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

Usage

```
solve_1comp(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  times = NULL,
  parameters = NULL,
  days = 10,
  tsteps = 4,
  daily.dose = NULL,
  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-08,
  atol = 1e-12,
  default.to.human = F,
  recalc.blood2plasma = F,
  recalc.clearance = F,
  dosing.matrix = NULL,
  adjusted.Funbound.plasma = T,
  regression = T,
  restrictive.clearance = T,
  minimum.Funbound.plasma = 1e-04,
  monitor.vars = 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.
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
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.
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", 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 rat values with human values if true.
recalc.blood2plasma	Whether or not to recalculate the blood:plasma chemical concentrationr ratio
recalc.clearance	Whether or not to recalculate the elimination rate.
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.
adjusted.Funbound.plasma	Uses adjusted Funbound.plasma when set to TRUE along with volume of distribution calculated with this value.
regression	Whether or not to use the regressions in calculating partition coefficients in volume of distribution calculation.
restrictive.clearance	In calculating elimination rate, protein binding is not taken into account (set to 1) in liver clearance if FALSE.
minimum.Funbound.plasma	Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).
monitor.vars	Which variables are returned as a function of time. Defaults value of NULL provides "Agutlumen", "Ccompartment", "Ametabolized", "AUC"
...	Additional arguments passed to the integrator.

Details

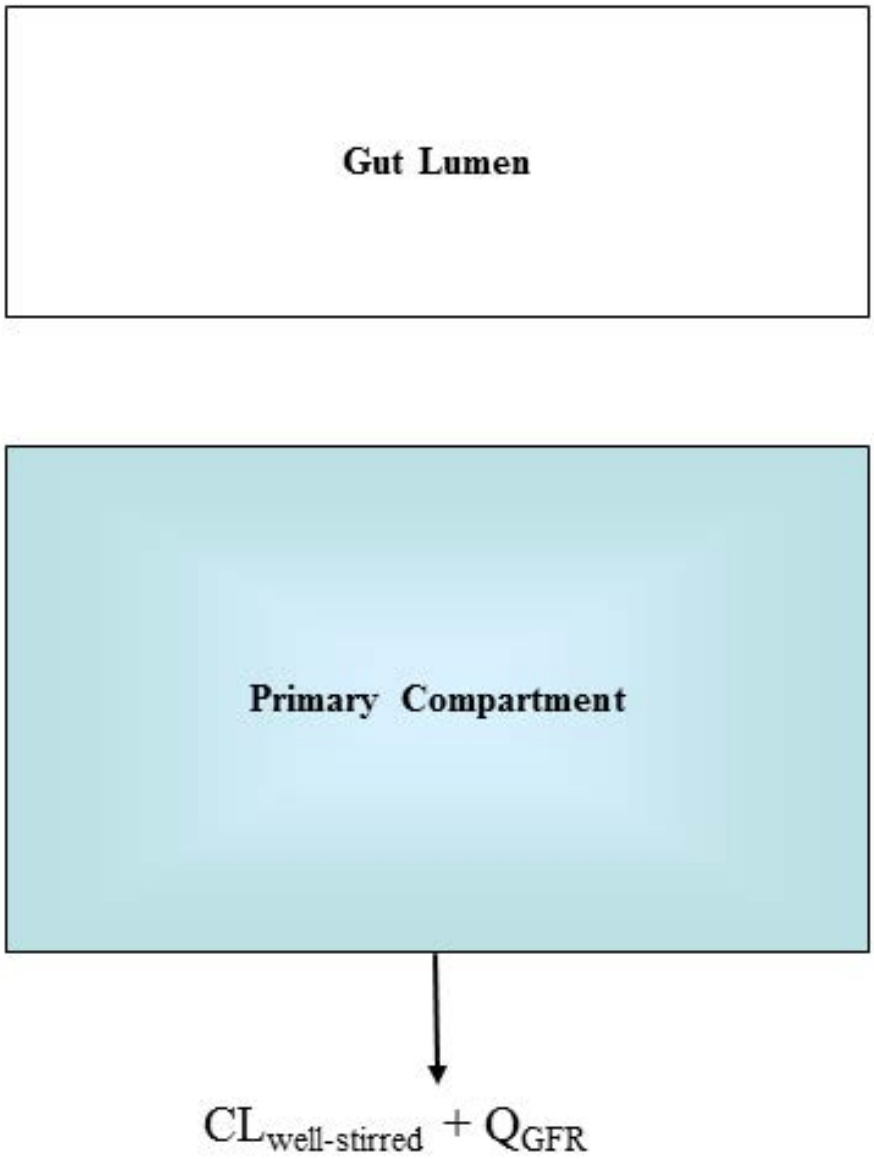
Note that the model parameters have units of hours while the model output is in days.

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.

Model Figure



altalt

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

References

Pearce, Robert G., et al. "Httk: R package for high-throughput toxicokinetics." Journal of statistical software 79.4 (2017): 1.

Examples

```
solve_1comp(chem.name='Bisphenol-A',days=1)
params <- parameterize_1comp(chem.cas="80-05-7")
solve_1comp(parameters=params)
```

`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,
  dtxsid = NULL,
  times = NULL,
  parameters = NULL,
  days = 10,
  tsteps = 4,
  daily.dose = NULL,
  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-08,
  atol = 1e-12,
  default.to.human = F,
  recalc.blood2plasma = F,
  recalc.clearance = F,
  dosing.matrix = NULL,
```

```
  adjusted.Funbound.plasma = T,
  regression = T,
  restrictive.clearance = T,
  minimum.Funbound.plasma = 1e-04,
  monitor.vars = 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.
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
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.
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.

`adjusted.Funbound.plasma`
: Uses adjusted Funbound.plasma when set to TRUE along with partition coefficients calculated with this value.

`regression`
: Whether or not to use the regressions in calculating partition coefficients.

`restrictive.clearance`
: Protein binding not taken into account (set to 1) in liver clearance if FALSE.

`minimum.Funbound.plasma`
: Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).

`monitor.vars`
: Which variables are returned as a function of time. Defaults value of NULL provides "Cliver", "Csyscomp", "Atubules", "Ametabolized", "AUC"

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

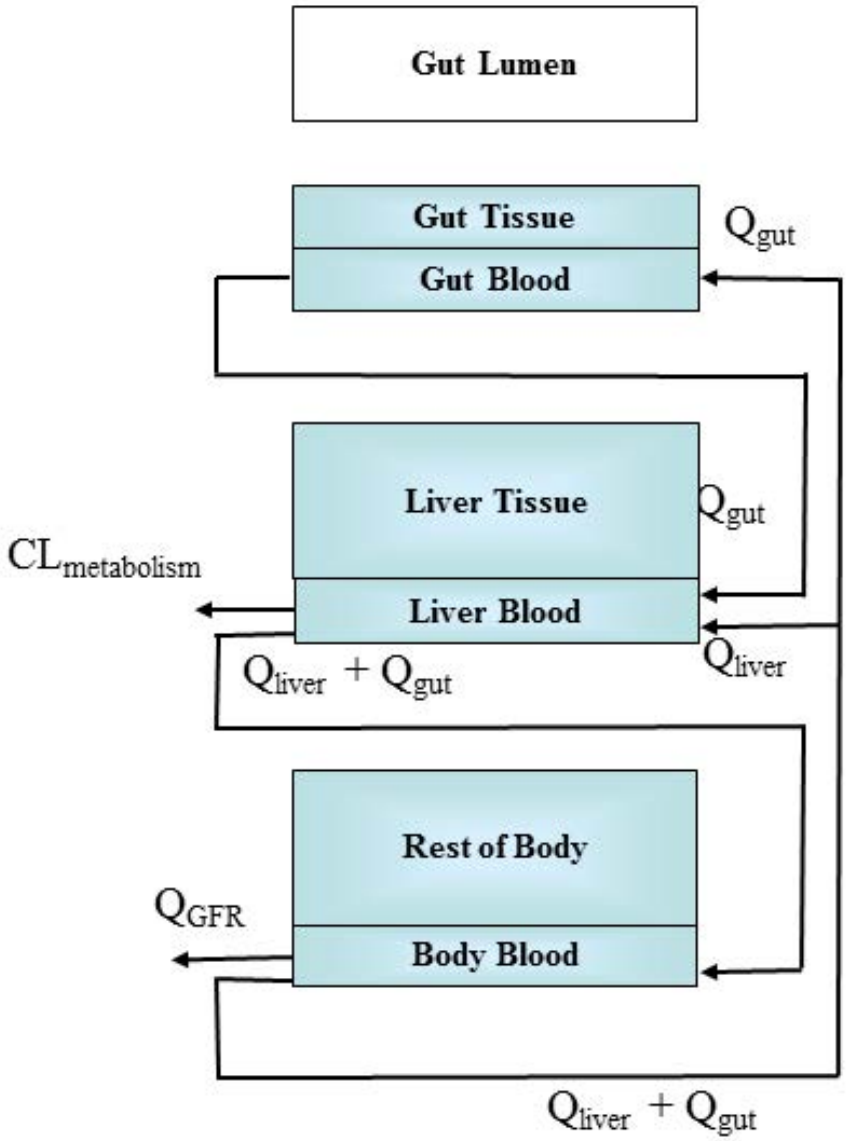
Details

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 gutlumen, gut, liver, and rest-of-body, with the plasma equivalent to the liver plasma.

Model Figure



altalt

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

References

Pearce, Robert G., et al. "Httk: R package for high-throughput toxicokinetics." Journal of statistical software 79.4 (2017): 1.

Examples

```
solve_3comp(chem.name='Bisphenol-A',doses.per.day=2,daily.dose=.5,days=1,tsteps=2)

params <-parameterize_3comp(chem.cas="80-05-7")
solve_3comp(parameters=params)
```

---

solve_gas_pbtk *solve_gas_pbtk*

Description

This function solves for the amounts or concentrations of a chemical in different tissues as functions of time as a result of inhalation exposure.

Usage

```
solve_gas_pbtk(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  times = NULL,
  days = 10,
  tsteps = 4,
  daily.dose = NULL,
  doses.per.day = NULL,
  dose = NULL,
  dosing.matrix = NULL,
  forcings = NULL,
  exp.start.time = 0,
  exp.conc = 1,
  period = 24,
  exp.duration = 12,
  fcontrol = list(method = "constant", rule = 2, f = 0),
  initial.values = NULL,
  plots = F,
  suppress.messages = F,
  species = "Human",
  output.units = "uM",
  method = "lsoda",
  rtol = 1e-08,
  atol = 1e-12,
  default.to.human = F,
  recalc.blood2plasma = F,
```

```
  recalc.clearance = F,
  adjusted.Funbound.plasma = T,
  regression = T,
  restrictive.clearance = T,
  minimum.Funbound.plasma = 1e-04,
  monitor.vars = NULL,
  vmax = 0,
  km = 1,
  exercise = F,
  fR = 12,
  VT = 0.75,
  VD = 0.15,
  ...
)
```

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.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_gas_pbtk (or other bespoke) function, overrides chem.name and chem.cas.
times	Optional time sequence for specified number of days. Dosing sequence begins at the beginning of times.
days	Length of the simulation.
tsteps	The number of time steps per hour.
daily.dose	Total daily dose, mg/kg BW.
doses.per.day	Number of doses per day.
dose	Amount of a single dose, mg/kg BW.
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. With the gas pbtk model, dosing.matrix is set to specify forcing concentrations to the integrator, either in combination with eventdata or on its own.
forcings	Manual input of "forcings" data series argument for ode integrator, defaults to NULL
exp.start.time	Start time in specifying forcing exposure series, default 0.
exp.conc	Specified inhalation exposure concentration for use in assembling "forcings" data series argument for integrator. Defaults to uM, in line with output.units
period	For use in assembling forcing function data series "forcings" argument, specified in hours
exp.duration	For use in assembling forcing function data series 'forcings' argument, specified in hours
fcontrol	List of arguments for finetuning inhalation forcing function in conjunction with existing ode integrator methods
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").
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 hepatic clearance (Clmetabolism) with new million.cells.per.gliver parameter.
adjusted.Funbound.plasma	Uses adjusted Funbound.plasma when set to TRUE along with partition coefficients calculated with this value.
regression	Whether or not to use the regressions in calculating partition coefficients.
restrictive.clearance	Protein binding not taken into account (set to 1) in liver clearance if FALSE.
minimum.Funbound.plasma	Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).
monitor.vars	Which variables are returned as a function of time. Defaults value of NULL provides "Cgut", "Cliver", "Cven", "Clung", "Cart", "Crest", "Ckidney", "Cplasma", "Calv", "Cendexh", "Cmixexh", "Cmuc", "Atubules", "Ametabolized", "AUC"
vmax	Michaelis-Menten vmax value in reactions/min
km	Michaelis-Menten concentration of half-maximal reaction velocity in desired output concentration units.
exercise	Logical indicator of whether to simulate an exercise-induced heightened respiration rate
fR	Respiratory frequency (breaths/minute), used especially to adjust breathing rate in the case of exercise. This parameter, along with VT and VD (below) gives another option for calculating Qalv (Alveolar ventilation) in case pulmonary ventilation rate is not known
VT	Tidal volume (L), to be modulated especially as part of simulating the state of exercise
VD	Anatomical dead space (L), to be modulated especially as part of simulating the state of exercise
...	Additional arguments passed to the integrator.

Details

The default dosing scheme involves specifying the start time of exposure, the concentration of gas inhaled, the period of a given assumed cycle of exposure, and the duration of the exposure during that period. Together, these arguments determine the forcings passed to the ODE integrator. The "forcings" can also be specified manually, or effectively turned off by setting exposure concentration to zero, if the user prefers to simulate dosing by other means.

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.

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 gut lumen, 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.

Model parameters are named according to the following convention:

prefix	suffic	Meaning	units
K		Partition coefficient for tissue to free plasma \ tab unitless	
V		Volume	L
Q		Flow	L/h
k		Rate	1/h
	c	Parameter is proportional to body weight	1 / kg for volumes and 1/kg^(3/4) for flows

When species is specified but chemical-specific in vitro data are not available, the function uses the appropriate physiological data (volumes and flows) but default.to.human = TRUE must be used to substitute 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)

Matt Linakis, John Wambaugh, and Mark Sfeir

References

Linakis, Matthew W., et al. "Development and Evaluation of a High Throughput Inhalation Model for Organic Chemicals", submitted

Pearce, Robert G., et al. "Httk: R package for high-throughput toxicokinetics." Journal of statistical software 79.4 (2017): 1.

Examples

```
solve_gas_pbtk(chem.name='Pyrene',dose=.5,days = 3,tsteps=2)
```

```
out <- solve_gas_pbtk(chem.name='pyrene',exp.conc = 0, doses.per.day = 2,
daily.dose = 3, plots=TRUE,initial.values=c(Aven=20))

out <- solve_gas_pbtk(chem.name = 'pyrene',exp.conc = 3, period = 24,
exp.duration = 6, exercise = TRUE)

params <- parameterize_gas_pbtk(chem.cas="80-05-7")
solve_gas_pbtk(parameters=params)
```

`solve_model` *Solve_model*

Description

solve_model's arguments prepare an ode system for numerical solution over time of the amounts or concentrations (uM) of chemical in the different bodily compartments of a given available species (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").

Usage

```
solve_model(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  times = NULL,
  parameters = NULL,
  model = NULL,
  route = "oral",
  dosing = NULL,
  days = 10,
  tsteps = 4,
  initial.values = NULL,
  plots = F,
  monitor.vars = NULL,
  suppress.messages = F,
  species = "Human",
  output.units = "uM",
  method = "lsoda",
  rtol = 1e-08,
  atol = 1e-12,
  recalc.blood2plasma = F,
  recalc.clearance = F,
  adjusted.Funbound.plasma = T,
  minimum.Funbound.plasma = 1e-04,
 parameterize.arg.list = list(default.to.human = F, clint.pvalue.threshold = 0.05,
    restrictive.clearance = T, regression = T),
  ...
)
```

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.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
times	Optional time sequence for specified number of days. Dosing sequence begins at the beginning of times.
parameters	List of chemical parameters, as output by parameterize_pbtk function. Overrides chem.name and chem.cas.
model	Specified model to use in simulation: "pbtk", "3compartment", "3compartmentss", "1compartment", "schmitt", ...
route	String specification of route of exposure for simulation: "oral", "iv", "inhalation", ...
dosing	List of dosing metrics passed to solver for a given model, which must at least include entries with names "initial.dose", "doses.per.day", "daily.dose", and "dosing.matrix". The "dosing.matrix" can be used for more precise dose regimen specification, and is a matrix consisting of two columns or rows named "time" and "dose" which contain the time and amount, in mg/kg BW, of each dose. If none of the namesake entries of the dosing list is set to a non-NULL value, solve_model uses a default dose of 1 mg/kg BW along with the dose type (add/multiply) specified for a given route (e.g. add the dose to gut lumen for oral route)
days	Simulated period. Default 10 days.
tsteps	The number of time steps per hour. Default of 4.
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.
monitor.vars	Which variables are returned as a function of time. Default values of NULL looks up variables specified in modelinfo_MODEL.R
suppress.messages	Whether or not the output message is suppressed.
species	Species desired (models have been designed to be parameterized for some subset of the following species: "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
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).
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.
adjusted.Funbound.plasma	Uses adjusted Funbound.plasma when set to TRUE along with partition coefficients calculated with this value.

`minimum.Funbound.plasma`
: Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset)

`parameterize.arg.list`
: Additional parameterized passed to the model parameterization function.

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

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

`regression`
: Whether or not to use the regressions in calculating partition coefficients.

`restrictive.clearance`
: Protein binding not taken into account (set to 1) in liver clearance if FALSE.

Details

The minimal usage case requires input that includes a chemical identifier (whether name, CAS number, or other chemical parameterization) and a model system of interest ("pbtk", "3compartment", "3compartmentss", "1compartment", "schmitt", ...).

The 'dosing' argument includes all parameters needed to describe exposure in terms of route of administration, frequency, and quantity short of scenarios that require use of a more precise forcing function. If the dosing argument's namesake entries are left NULL, solve_model defaults to a single-time dose of 1 mg/kg BW according to the given dosing route and associated type (either add/multiply, e.g. typically adds dose to gut lumen when oral route is specified).

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

Model parameters are named according to the following convention:

prefix	suffix	Meaning	units
K		Partition coefficient for tissue to free plasma \ tab unitless	
V		Volume	L
Q		Flow	L/h
k		Rate	1/h
	c	Parameter is proportional to body weight	1 / kg for volumes and 1/kg^(3/4) for flows

When species is specified but chemical-specific in vitro data are not available, the function uses the appropriate physiological data (volumes and flows) but default.to.human = TRUE must be used to substitute 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

References

Pearce, Robert G., et al. "Httk: R package for high-throughput toxicokinetics." Journal of statistical software 79.4 (2017): 1.

`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,
  dtxsid = NULL,
  times = NULL,
  parameters = NULL,
  days = 10,
  tsteps = 4,
  daily.dose = NULL,
  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-08,
  atol = 1e-12,
  default.to.human = F,
  recalc.blood2plasma = F,
  recalc.clearance = F,
  dosing.matrix = NULL,
  adjusted.Funbound.plasma = T,
  regression = T,
  restrictive.clearance = T,
  minimum.Funbound.plasma = 1e-04,
  monitor.vars = 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.
`dtxsid`	EPA's DSSTox Structure ID (`https://comptox.epa.gov/dashboard`) the chemical must be identified by either CAS, name, or DTXSIDs
`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 of time steps per hour.
daily.dose	Total daily dose, mg/kg BW.
dose	Amount of a single dose, mg/kg BW.
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.
adjusted.Funbound.plasma	Uses adjusted Funbound.plasma when set to TRUE along with partition coefficients calculated with this value.
regression	Whether or not to use the regressions in calculating partition coefficients.
restrictive.clearance	Protein binding not taken into account (set to 1) in liver clearance if FALSE.
minimum.Funbound.plasma	Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).
monitor.vars	Which variables are returned as a function of time. The default value of NULL provides "Cgut", "Cliver", "Cven", "Clung", "Cart", "Crest", "Ckidney", "Cplasma", "Atubules", "Ametabolized", and "AUC"
...	Additional arguments passed to the integrator.

Details

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

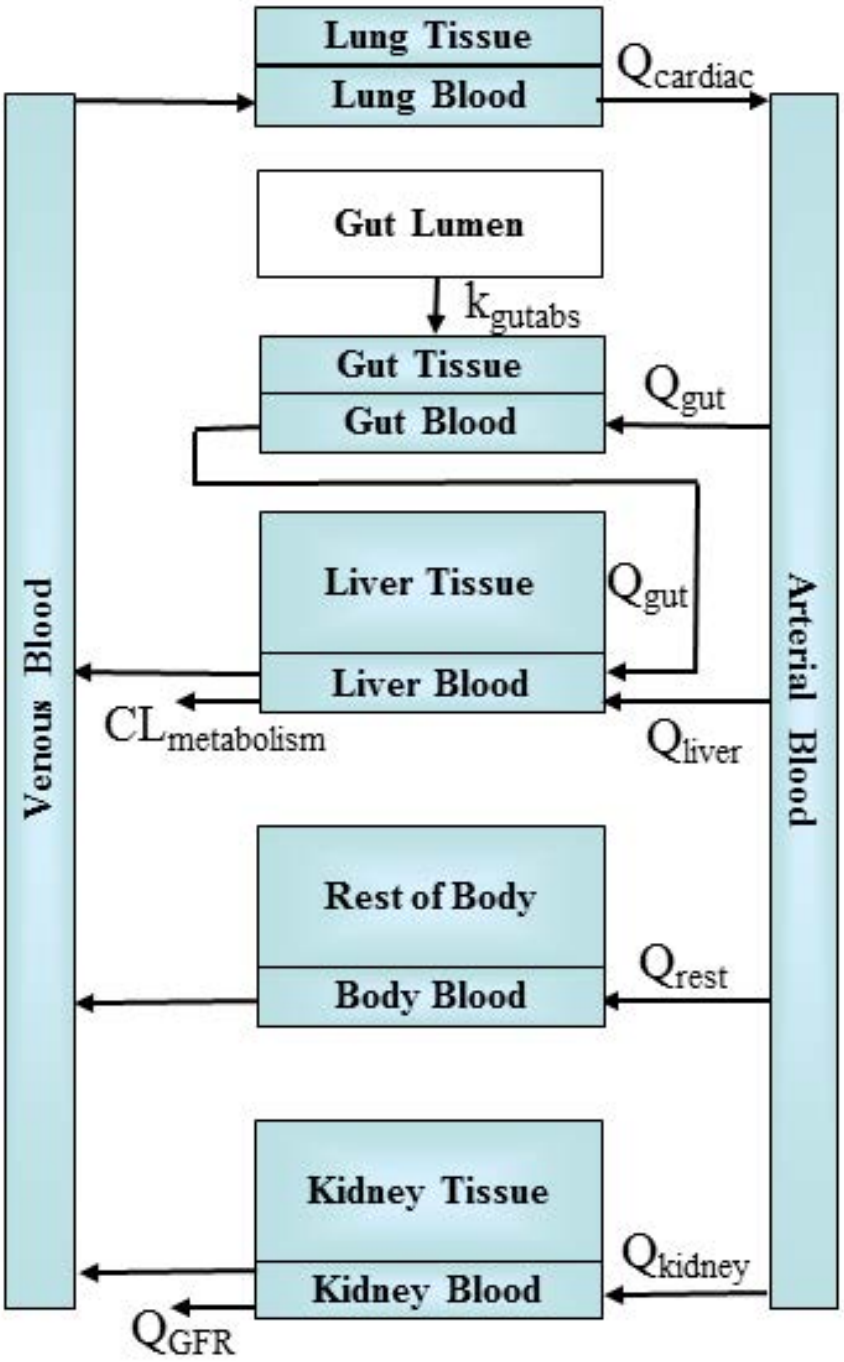
Default NULL value for doses.per.day solves for a single dose.

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.

Model Figure



altalt

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

References

Pearce, Robert G., et al. "Httk: R package for high-throughput toxicokinetics." Journal of statistical software 79.4 (2017): 1.

Examples

```
solve_pbtk(chem.name='Bisphenol-A',daily.dose=.5,days=1,doses.per.day=2,tsteps=2)

out <- solve_pbtk(chem.name='bisphenola',dose=0,output.units="mg/L",
                  initial.values=c(Agut=200))

params <- parameterize_pbtk(chem.cas="80-05-7")
solve_pbtk(parameters=params)

## Not run:
parameters <- parameterize_pbtk(chem.name = "triclosan", species = "rat")
parameters["Funbound.plasma"] <- 0.1
out <- solve_pbtk(parameters=parameters)

library("ggplot2")
out <- solve_pbtk(chem.name = "Bisphenol A", days = 50, doses.per.day = 3)
plot.data <- as.data.frame(out)
css <- calc_analytic_css(chem.name = "Bisphenol A")
c.vs.t <- ggplot(plot.data,aes(time, Cplasma)) + geom_line() +
geom_hline(yintercept = css) + ylab("Plasma Concentration (uM)") +
xlab("Day") + theme(axis.text = element_text(size = 16), axis.title =
element_text(size = 16), plot.title = element_text(size = 17)) +
ggtitle("Bisphenol A")
print(c.vs.t)

## End(Not run)
```

---

spleen_mass_children *Predict spleen mass for children*

Description

For individuals under 18, predict the spleen mass from height, weight, and gender, using equations from Ogiu et al. (1997)

Usage

```
spleen_mass_children(height, weight, gender)
```

Arguments

height	Vector of heights in cm.
weight	Vector of weights in kg.
gender	Vector of genders (either 'Male' or 'Female').

Value

A vector of spleen masses in kg.

Author(s)

Caroline Ring

References

Ogiu, Nobuko, et al. "A statistical analysis of the internal organ weights of normal Japanese people." Health physics 72.3 (1997): 368-383.

Price, Paul S., et al. "Modeling interindividual variation in physiological factors used in PBPK models of humans." Critical reviews in toxicology 33.5 (2003): 469-503.

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

---

spline_heightweight *Smoothing splines for log height vs. age and log body weight vs. age, along with 2-D KDE residuals, by race and gender.*

Description

#'Smoothing splines and KDE fits to joint distribution of height and weight residuals pre-calculated from NHANES height, weight, and age data by race/ethnicity and gender.

Usage

```
spline_heightweight
```

Format

A data.table with 6 variables:

- g Gender: Male or Female
- r Race/ethnicity: Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other
- height_spline A list of smooth.spline objects, each giving a smoothed relationship between log height in cm and age in months
- weight_spline A list of smooth.spline objects, each giving a smoothed relationship between log body weight in kg and age in months
- hw_kde A list of kde objects; each is a 2-D KDE of the distribution of log height and log body weight residuals about the smoothing splines.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

`spline_hematocrit` *Smoothing splines for log hematocrit vs. age in months, and KDE residuals, by race and gender.*

Description

Smoothing splines and KDE residuals pre-calculated from NHANES hematocrit and age data by race/ethnicity and gender.

Usage

```
spline_hematocrit
```

Format

A data.table with 6 variables:

`gender` Gender: Male or Female

`reth` Race/ethnicity: Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other

`hct_spline` A list of smooth.spline objects, each giving a smoothed relationship between log hematocrit and age in months

`hct_kde` A list of kde objects; each is a KDE of the distribution of residuals about the smoothing spline.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

spline_serumcreat *Smoothing splines for log serum creatinine vs. age in months, along with KDE residuals, by race and gender.*

Description

#'Smoothing splines and KDE residuals pre-calculated from NHANES serum creatinine and age data by race/ethnicity and gender.

Usage

```
spline_serumcreat
```

Format

A data.table with 6 variables:

`gender` Gender: Male or Female

`reth` Race/ethnicity: Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other

`sc_spline` A list of smooth.spline objects, each giving a smoothed relationship between log serum creatinine and age in months

`sc_kde` A list of kde objects; each is a KDE of the distribution of residuals about the smoothing spline.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

supptab1_Linakis2020 *Supplementary output from Linakis 2020 vignette analysis.*

Description

Supplementary output from Linakis 2020 vignette analysis.

Usage

```
supptab1_Linakis2020
```

Format

A data.frame containing x rows and y columns.

Author(s)

Matt Linakis

Source

Matt Linakis

References

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

`supptab2_Linakis2020` *More supplementary output from Linakis 2020 vignette analysis.*

Description

More supplementary output from Linakis 2020 vignette analysis.

Usage

```
supptab2_Linakis2020
```

Format

A data.frame containing x rows and y columns.

Author(s)

Matt Linakis

Source

Matt Linakis

References

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

Tables.Rdata.stamp *A timestamp of table creation*

Description

The Tables.RData file is separately created as part of building a new release of HTTK. This time stamp indicates the script used to build the file and when it was run.

Usage

```
Tables.Rdata.stamp
```

Format

An object of class `character` of length 1.

Author(s)

John Wambaugh

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

Description

This data set contains values from Schmitt (2008) and Ruark et al. (2014) 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. Tissue volumes were calculated by converting the fractional mass of each tissue with its density (both from ICRP), lumping the remaining tissues into the rest-of-body, excluding the mass of the gastrointestinal contents

Usage

```
tissue.data
```

Format

A data.frame containing 13 rows and 20 columns.

Author(s)

John Wambaugh, Robert Pearce, and Nisha Sipes

Source

Pearce et al. (2017), in preparation,

Wambaugh, John F., et al. "Toxicokinetic triage for environmental chemicals." Toxicological Sciences (2015): 228-237.

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

Ruark, Christopher D., et al. "Predicting passive and active tissue: plasma partition coefficients: Interindividual and interspecies variability." Journal of pharmaceutical sciences 103.7 (2014): 2189-2198.

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.

ICRP. Report of the Task Group on Reference Man. ICRP Publication 23 1975

`tissue_masses_flows` *Given a data.table describing a virtual population by the NHANES quantities, generates HTTK physiological parameters for each individual.*

Description

Given a data.table describing a virtual population by the NHANES quantities, generates HTTK physiological parameters for each individual.

Usage

```
tissue_masses_flows(tmf_dt)
```

Arguments

`tmf_dt`	A data.table generated by `gen_age_height_weight()`, containing variables `gender`, `reth`, `age_months`, `age_years`, `weight`, and `height`.

Value

The same data.table, with aditional variables describing tissue masses and flows.

Author(s)

Caroline Ring

References

Barter, Zoe E., et al. "Scaling factors for the extrapolation of in vivo metabolic drug clearance from in vitro data: reaching a consensus on values of human micro-somal protein and hepatocellularity per gram of liver." Current Drug Metabolism 8.1 (2007): 33-45.

Birnbaum, L., et al. "Physiological parameter values for PBPK models." International Life Sciences Institute, Risk Science Institute, Washington, DC (1994).

Geigy Pharmaceuticals, "Scientific Tables", 7th Edition, John Wiley and Sons (1970)

McNally, Kevin, et al. "PopGen: a virtual human population generator." Toxicology 315 (2014): 70-85.

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

tissue_scale *Allometric scaling.*

Description

Allometrically scale a tissue mass or flow based on height^3/4.

Usage

```
tissue_scale(height_ref, height_indiv, tissue_mean_ref)
```

Arguments

height_ref	Reference height in cm.
height_indiv	Individual height in cm.
tissue_mean_ref	Reference tissue mass or flow.

Value

Allometrically scaled tissue mass or flow, in the same units as tissue_mean_ref.

Author(s)

Caroline Ring

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

wambaugh2019 *in vitro Toxicokinetic Data from Wambaugh et al. (2019)*

Description

These data are the new HTTK in vitro data for chemicals reported in Wambaugh et al. (2019) They are the processed values used to make the figures in that manuscript. These data summarize the results of Bayesian analysis of the in vitro toxicokinetic experiments conducted by Cyprotex to characterize fraction unbound in the presence of pooled human plasma protein and the intrnsic hepatic clearance of the chemical by pooled human hepatocytes.

Usage

```
wambaugh2019
```

Format

A data frame with 496 rows and 17 variables:

Compound The name of the chemical

CAS The Chemical Abstracts Service Registry Number

Human.Clint Median of Bayesian credible interval for intrinsic hepatic clearance (uL/min/million hepatocytes)]

Human.Clint.pValue Probability that there is no clearance

Human.Funbound.plasma Median of Bayesian credibl interval for fraction of chemical free in the presence of plasma

pKa_Accept pH(s) at which hydrogen acceptor sites (if any) are at equilibrium

pKa_Donor pH(s) at which hydrogne donor sites (if any) are at equilibrium

DSSTox_Substance_Id Identifier for CompTox Chemical Dashboard

SMILES Simplified Molecular-Input Line-Entry System structure description

Human.Clint.Low95 Lower 95th percentile of Bayesian credible interval for intrinsic hepatic clearance (uL/min/million hepatocytes)

Human.Clint.High95 Uppper 95th percentile of Bayesian credible interval for intrinsic hepatic clearance (uL/min/million hepatocytes)

Human.Clint.Point Point estimate of intrinsic hepatic clearance (uL/min/million hepatocytes)

Human.Funbound.plasma.Low95 Lower 95th percentile of Bayesian credible interval for fraction of chemical free in the presence of plasma

Human.Funbound.plasma.High95 Upper 95th percentile of Bayesian credible interval for fraction of chemical free in the presence of plasma

Human.Funbound.plasma.Point Point estimate of the fraction of chemical free in the presence of plasma

MW Molecular weight (Daltons)

logP log base ten of octanol:water partiion coefficient

Author(s)

John Wambaugh

Source

Wambaugh et al. (2019)

References

Wambaugh et al. (2019) "Assessing Toxicokinetic Uncertainty and Variability in Risk Prioritization", Toxicological Sciences, 172(2), 235-251.

wambaugh2019.nhanes *NHANES Chemical Intake Rates for chemicals in Wambaugh et al. (2019)*

Description

These data are a subset of the Bayesian inferrences reported by Ring et al. (2017) from the U.S. Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES). They reflect the populaton median intake rate (mg/kg body weight/day), with uncertainty.

Usage

```
wambaugh2019.nhanes
```

Format

A data frame with 20 rows and 4 variables:

lP The median of the Bayesian credible interval for median population intake rate (mg/kg bodyweight/day)

lP.min The lower 95th percentile of the Bayesian credible interval for median population intake rate (mg/kg bodyweight/day)

lP.max The upper 95th percentile of the Bayesian credible interval for median population intake rate (mg/kg bodyweight/day)

CASRN The Chemical Abstracts Service Registry Number

Author(s)

John Wambaugh

Source

Wambaugh et al. (2019)

References

Ring, Caroline L., et al. "Identifying populations sensitive to evironmental chemicals by simulating toxicokinetic variability." Environment international 106 (2017): 105-118

Wambaugh et al. (2019) "Assessing Toxicokinetic Uncertainty and Variability in Risk Prioritization", Toxicological Sciences, 172(2), 235-251.

wambaugh2019.raw *Raw Bayesian in vitro Toxicokinetic Data Analysis from Wambaugh et al. (2019)*

Description

These data are the new HTTK in vitro data for chemicals reported in Wambaugh et al. (2019) They are the output of different Bayesian models evaluated to compare using a single protein concentration vs. the new three concentration titration protocol. These data summarize the results of Bayesian analysis of the in vitro toxicokinetic experiments conducted by Cyprotex to characterize fraction unbound in the presence of pooled human plasma protein and the intrnsic hepatic clearance of the chemical by pooled human hepatocytes. This file includes replicates (diferent CompoundName id's but same chemical')

Usage

```
wambaugh2019.raw
```

Format

A data frame with 530 rows and 28 variables:

DTXSID Identifier for CompTox Chemical Dashboard

Name The name of the chemical

CAS The Chemical Abstracts Service Registry Number

CompoundName Sample name provided by EPA to Cyprotex

Fup.point Point estimate of the fraction of chemical free in the presence of plasma

Base.Fup.Med Median of Bayesian credible interval for fraction of chemical free in the presence of plasma for analysis of 100 physiological plasma protein data only (base model)

Base.Fup.Low Lower 95th percentile of Bayesian credible interval for fraction of chemical free in the presence of plasma for analysis of 100 physiological plasma protein data only (base model)

Base.Fup.High Upper 95th percentile of Bayesian credible interval for fraction of chemical free in the presence of plasma for analysis of 100 physiological plasma protein data only (base model)

Affinity.Fup.Med Median of Bayesian credible interval for fraction of chemical free in the presence of plasma for analysis of protein titration protocol data (affinity model)

Affinity.Fup.Low Lower 95th percentile of Bayesian credible interval for fraction of chemical free in the presence of plasma for analysis of protein titration protocol data (affinity model)

Affinity.Fup.High Upper 95th percentile of Bayesian credible interval for fraction of chemical free in the presence of plasma for analysis of protein titration protocol data (affinity model)

Affinity.Kd.Med Median of Bayesian credible interval for protein binding affinity from analysis of protein titration protocol data (affinity model)

Affinity.Kd.Low Lower 95th percentile of Bayesian credible interval for protein binding affinity from analysis of protein titration protocol data (affinity model)

Affinity.Kd.High Upper 95th percentile of Bayesian credible interval for protein binding affinity from analysis of protein titration protocol data (affinity model)

Decreases.Prob Probability that the chemical concentration decreased systematiclally during hepatic clearance assay.

Saturates.Prob Probability that the rate of chemical concentration decrease varied between the 1 and 10 uM hepatic clearance experiments.

Slope.1uM.Median Estimated slope for chemcial concentration decrease in the 1 uM hepatic clearance assay.

Slope.10uM.Median Estimated slope for chemcial concentration decrease in the 10 uM hepatic clearance assay.

CLint.1uM.Median Median of Bayesian credible interval for intrinsic hepatic clearance at 1 uM inititial chemical concentration (uL/min/million hepatocytes)]

CLint.1uM.Low95th Lower 95th percentile of Bayesian credible interval for intrinsic hepatic clearance at 1 uM inititial chemical concentration (uL/min/million hepatocytes)

CLint.1uM.High95th Uppper 95th percentile of Bayesian credible interval for intrinsic hepatic clearance at 1 uM inititial chemical concentration(uL/min/million hepatocytes)

CLint.10uM.Median Median of Bayesian credible interval for intrinsic hepatic clearance at 10 uM inititial chemical concentration (uL/min/million hepatocytes)]

CLint.10uM.Low95th Lower 95th percentile of Bayesian credible interval for intrinsic hepatic clearance at 10 uM inititial chemical concentration (uL/min/million hepatocytes)

CLint.10uM.High95th Uppper 95th percentile of Bayesian credible interval for intrinsic hepatic clearance at 10 uM inititial chemical concentration(uL/min/million hepatocytes)

CLint.1uM.Point Point estimate of intrinsic hepatic clearance (uL/min/million hepatocytes) for 1 uM initial chemical concentration

CLint.10uM.Point Point estimate of intrinsic hepatic clearance (uL/min/million hepatocytes) for 10 uM initial chemical concentration

Fit Classification of clearance observed

SMILES Simplified Molecular-Input Line-Entry System structure description

Author(s)

John Wambaugh

Source

Wambaugh et al. (2019)

References

Wambaugh et al. (2019) "Assessing Toxicokinetic Uncertainty and Variability in Risk Prioritization", Toxicological Sciences, 172(2), 235-251.

wambaugh2019.seem3 *ExpoCast SEEM3 Consensus Exposure Model Predictions for Chemical Intake Rates*

Description

These data are a subset of the Bayesian inferrences reported by Ring et al. (2019) for a consensus model of twelve exposue predictors. The predictors were calibrated based upon their ability to predict intake rates inferred National Health and Nutrition Examination Survey (NHANES). They reflect the populaton median intake rate (mg/kg body weight/day), with uncertainty.

Usage

```
wambaugh2019.seem3
```

Format

A data frame with 385 rows and 38 variables:

Author(s)

John Wambaugh

Source

Wambaugh et al. (2019)

References

Ring, Caroline L., et al. "Consensus modeling of median chemical intake for the US population based on predictions of exposure pathways." Environmental science & technology 53.2 (2018): 719-732.

Wambaugh et al. (2019) "Assessing Toxicokinetic Uncertainty and Variability in Risk Prioritization", Toxicological Sciences, 172(2), 235-251.

wambaugh2019.tox21 *Tox21 2015 Active Hit Calls (EPA)*

Description

The ToxCast and Tox21 research programs employ batteries of high throughput assays to assess chemical bioactivity in vitro. Not every chemical is tested through every assay. Most assays are conducted in concentration response, and each corresponding assay endpoint is analyzed statistically to determine if there is a concentration-dependent response or "hit" using the ToxCast Pipeline. Most assay endpoint-chemical combinations are non-responsive. Here, only the hits are treated as potential indicators of bioactivity. This bioactivity does not have a direct toxicological interpretation. The October 2015 release (invitrodb_v2) of the ToxCast and Tox21 data were used for this analysis. This object contains just the chemicals in Wambaugh et al. (2019) and only the quantiles across all assays for the ACC.

Usage

```
wambaugh2019.tox21
```

Format

A data.table with 401 rows and 6 columns

Author(s)

John Wambaugh

Source

ftp://newftp.epa.gov/COMPTOX/High_Throughput_Screening_Data/Previous_Data/ToxCast_Data_Release_Oct_2015/

References

Kavlock, Robert, et al. "Update on EPA's ToxCast program: providing high throughput decision support tools for chemical risk management." Chemical research in toxicology 25.7 (2012): 1287-1302.

Tice, Raymond R., et al. "Improving the human hazard characterization of chemicals: a Tox21 update." Environmental health perspectives 121.7 (2013): 756-765.

Richard, Ann M., et al. "ToxCast chemical landscape: paving the road to 21st century toxicology." Chemical research in toxicology 29.8 (2016): 1225-1251.

Filer, Dayne L., et al. "tcpl: the ToxCast pipeline for high-throughput screening data." Bioinformatics 33.4 (2016): 618-620.

Wambaugh, John F., et al. "Assessing Toxicokinetic Uncertainty and Variability in Risk Prioritization." Toxicological Sciences 172.2 (2019): 235-251.

---

well_param *Microtiter Plate Well Descriptions for Armitage et al. (2014) Model*

Description

Microtiter Plate Well Descriptions for Armitage et al. (2014) model from Honda et al. (2019)

Usage

```
well_param
```

Format

A data frame / data table with 11 rows and 8 variables:

sysID Identifier for each multi-well plate system

well_desc Well description

well_number Number of wells on plate

area_bottom Area of well bottom in mm^2

cell_yield Number of cells

diam Diameter of well in mm

v_total Total volume of well in uL or mm^3)

v_working Working volume of well in uL or mm^3

Author(s)

Greg Honda

Source

https://www.corning.com/catalog/cls/documents/application-notes/CLS-AN-209.pdf

References

Armitage, J. M.; Wania, F.; Arnot, J. A. Environ. Sci. Technol. 2014, 48, 9770-9779. dx.doi.org/10.1021/es501955g

Honda, Gregory S., et al. "Using the Concordance of In Vitro and In Vivo Data to Evaluate Extrapolation Assumptions", PloS ONE 14.5 (2019): e0217564.

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, John F., et al. "Toxicokinetic triage for environmental chemicals." Toxicological Sciences (2015): 228-237.

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.

`Wetmore2012` *Published toxicokinetic predictions based on in vitro data from Wetmore et al. 2012.*

Description

This data set overlaps with Wetmore.data and is used only in Vignette 4 for steady state concentration.

Usage

```
Wetmore2012
```

Format

A data.frame containing 13 rows and 15 columns.

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)

`wfl` *WHO weight-for-length charts*

Description

Charts giving weight-for-length percentiles for boys and girls under age 2.

Usage

```
wfl
```

Format

A data.table object with variables

`Sex` 'Male' or 'Female'

`Length` length in cm

`L`, `M`, `S` LMS parameters; see https://www.cdc.gov/growthcharts/percentile_data_files.htm

`P2.3`, `P5`, `P10`, `P25`, `P50`, `P75`, `P90`, `P95`, **and** `P97.7` weight percentiles

Details

For infants under age 2, weight class depends on weight for length percentile. #'

Underweight <2.3rd percentile

Normal weight 2.3rd-97.7th percentile

Obese >=97.7th percentile

Author(s)

Caroline Ring

Source

https://www.cdc.gov/growthcharts/who/girls_weight_head_circumference.htm and https://www.cdc.gov/growthcharts/who/boys_weight_head_circumference.htm

References

Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

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