Package 'httk'

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Title High-Throughput Toxicokinetics

Description Functions and data tables for simulation and statistical analysis of chemical toxicokinetics (``TK'') as in 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 (e.g., one compartment) ``TK'' models can be parameterized for several hundred chemicals and multiple species. These models are solved efficiently, often using compiled (C-based) code. A Monte Carlo sampler is included for simulating biological variability (Ring et al., 2017 <doi:10.1016/j.envint.2017.06.004>) and measurement limitations. 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 (e.g., Tox21, ToxCast) to real-world exposures via reverse dosimetry (also known as ``RTK'') (Wetmore et al., 2015 <doi:10.1093/toxsci/kfv171>).

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LazyData true

VignetteBuilder knitr, R.rsp

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

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

NeedsCompilation yes

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R topics documented:

`httk-package` *High-Throughput Toxicokinetics*

Description

Functions and data tables for simulation and statistical analysis of chemical toxicokinetics ("TK") as in 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 (e.g., one compartment) "TK" models can be parameterized for several hundred chemicals and multiple species. These models are solved efficiently, often using compiled (C-based) code. A Monte Carlo sampler is included for simulating biological variability (Ring et al., 2017 <doi:10.1016/j.envint.2017.06.004>) and measurement limitations. 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 (e.g., 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

EPA's ExpoCast (Exposure Forecasting) Project

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

Description

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

Usage

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

Arguments

new.table	Object of class data.frame containing one row per chemical, with each chemical minimally by described by a CAS number.
data.list	This list identifies which properties are to be read from the table. Each item in the list should point to a column in the table new.table. Valid names in the list are: 'Compound', 'CAS', 'DSSTox.GSID' 'SMILES.desalt', 'Reference', 'Species', 'MW', 'logP', 'pKa_Donor', 'pKa_Accept', 'logMA', 'Clint', 'Clint.pValue', 'Funbound.plasma', 'Fgutabs', 'Rblood2plasma'.
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.

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(200,200,200)))
my.new.data <- cbind(my.new.data,as.data.frame(c(2,3,4)))
my.new.data <- cbind(my.new.data,as.data.frame(c(0.01,0.02,0.3)))
my.new.data <- cbind(my.new.data,as.data.frame(c(0,10,100)))
colnames(my.new.data) <- c("Name","CASRN","MW","LogP","Fup","CLint")

chem.physical_and_invitro.data <- add_chemtable(my.new.data,
                                  current.table=chem.physical_and_invitro.data,
                                  data.list=list(
                                  Compound="Name",
                                  CAS="CASRN",
                                  MW="MW",
                                  logP="LogP",
                                  Funbound.plasma="Fup",
                                  Clint="CLint"),
                                  species="Human",
                                  reference="MyPaper 2015")
parameterize_steadystate(chem.name="C")
calc_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.

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

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.

Details

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

Author(s)

Caroline Ring

Caroline Ring

Caroline Ring

Caroline Ring

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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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

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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)

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

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

Details

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

Author(s)

Greg Honda

Greg Honda

Greg Honda

Greg Honda

Source

http://www.diamondse.info/

http://www.diamondse.info/

http://www.diamondse.info/

http://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.

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.

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.

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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.

`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,
  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.
`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

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.

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

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

http://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.

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.

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.

calc_analytic_css *Calculate the analytic steady state concentration.*

Description

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

Usage

```
calc_analytic_css(chem.name = NULL, chem.cas = NULL,
  parameters = NULL, daily.dose = 1, output.units = "uM",
  model = "pbtk", concentration = "plasma", suppress.messages = F,
  recalc.blood2plasma = F, tissue = NULL, restrictive.clearance = T,
  bioactive.free.invivo = F, IVIVE = 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.
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.
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.

`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.

`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.

`...` 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',
                default.to.human=TRUE,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,
  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.
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,
  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.

`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 oompartment 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,
  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.
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_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,
  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.

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

Arguments

`parameters`
: Chemical parameters from parameterize_pbtk function, overrides chem.name and chem.cas.

`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.

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.
concentration	Desired concentration type, 'blood' or default 'plasma'.
suppress.messages	Whether or not to suppress messages.
model	Model used in calculation, 'pbtk' for the multiple compartment model,'3compartment' for the three compartment model, 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.
...	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')
## Not run:
parms <- parameterize_3comp(chem.name='Bisphenol-A')
parms$Funbound.plasma <- .07
calc_css(parms,concentration='blood',model='3compartment')


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)

days <- NULL
avg <- NULL
max <- NULL
for(this.cas in get_cheminfo()){
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,
  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.
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.*

Description

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

Usage

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

Examples

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

---

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, 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.
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

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_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, parameters = NULL,
  daily.dose = 1, which.quantile = 0.95, species = "Human",
  output.units = "mg/L", suppress.messages = F,
  model = "3compartmentss", censored.params = list(Funbound.plasma =
  list(cv = 0.3, lod = 0.01)), vary.params = list(BW = 0.3, Vliverc =
  0.3, Qgfrc = 0.3, Qtotal.liverc = 0.3, million.cells.per.gliver = 0.3,
```

```
Clint = 0.3), fup.meas.cv = 0.4, clint.meas.cv = 0.3,
fup.pop.cv = 0.3, clint.pop.cv = 0.3, samples = 1000,
return.samples = F, default.to.human = F, tissue = NULL,
well.stirred.correction = T, adjusted.Funbound.plasma = T,
regression = T, clint.pvalue.threshold = 0.05,
restrictive.clearance = T, bioactive.free.invivo = FALSE,
concentration = "plasma", IVIVE = NULL, httkpop = T,
poormetab = T, fup.censored.dist = FALSE, fup.lod = 0.01,
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"), physiology.matrix = NULL,
parameter.matrix = NULL, ...)
```

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.
parameters	Parameters from parameterize_steadystate. Not used with httkpop model.
daily.dose	Total daily dose, mg/kg BW/day.
which.quantile	Which quantile from Monte Carlo simulation is requested. Can be a vector.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human"). Species must be set to "Human" to run httkpop model.
output.units	Plasma concentration units, either uM or default mg/L.
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.
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.
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.

samples Number of samples generated in calculating quantiles.

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

default.to.human
Substitutes missing rat values with human values if true.

tissue Desired steady state tissue conentration.

well.stirred.correction
If TRUE (default) then the well-stirred correction (Rowland et al., 1973) is used in the calculation of hepatic clearance for the models that do not include flows for first-pass metabolism (currently, 1compartment and 3compartmentss). This assumes clearance relative to amount unbound in whole blood instead of plasma, but converted for use with plasma concentration.

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.

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.

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.

concentration Desired concentration type, 'blood','tissue', or default 'plasma'.

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.

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'.

poormetab TRUE (include poor metabolizers) or FALSE (exclude poor metabolizers)

fup.censored.dist
Logical. Whether to draw Funbound.plasma from a censored distribution or not.

fup.lod The average limit of detection for Funbound.plasma. if fup.censor == TRUE, the Funbound.plasma distribution will be censored below lod/2. Default value is 0.01.

method The population-generation method to use. Either "virtual individuals" or "direct resampling" (default). Short names may be used: "d" or "dr" for "direct resampling", and "v" or "vi" for "virtual individuals".

`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.

`physiology.matrix`
A data table generated by `httkpop_generate()`.

`parameter.matrix`
A data table generated by `get_httk_params()`.

`...` 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 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)

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:
 calc_mc_css(chem.name='Bisphenol A',output.units='uM',method='vi',
             samples=100,return.samples=TRUE)
 calc_mc_css(chem.name='2,4-d',which.quantile=.9,httkpop=FALSE,tissue='heart')

 calc_mc_css(chem.cas = "80-05-7", daily.dose = 1, which.quantile = 0.5,
             censored.params = list(Funbound.plasma = list(cv = 0.1,
                                                           lod = 0.005)),
             vary.params = list(BW = 0.15, Vliverc = 0.15, Qgfrc = 0.15,
                                Qtotal.liverc = 0.15,
                                million.cells.per.gliver = 0.15, Clint = 0.15),
             output.units = "uM", samples = 2000)

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

## 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,
  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.
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 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.

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),
                   method='vi',samples=100,tissue='brain')

## 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, params = NULL,
  hematocrit = NULL, default.to.human = F, 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.
params	Parameters from parameterize_schmitt.
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").
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. 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. than the description above ~~

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).

Examples

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

calc_stats *Calculate the statistics.*

Description

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

Usage

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

Arguments

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

Details

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

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

Value

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

Author(s)

John Wambaugh and Robert Pearce

Examples

```
calc_stats(chem.name='Bisphenol-A',days=100,stats='mean',model='3compartment')
calc_stats(chem.name='Bisphenol-A',days=100,stats=c('peak','mean'),species='Rat')
## Not run:
all.peak.stats <- calc_stats(days=10, doses.per.day = 3, stats = "peak")

## End(Not run)
triclosan.stats <- calc_stats(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,
  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.
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, 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.
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

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).

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).

Format

data.frame

Author(s)

John Wambaugh

John Wambaugh

Source

Wambaugh et al. 2018 Toxicological Sciences, in press

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.

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.

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.

Format

A data.frame containing 597 rows and 13 columns.

Author(s)

Sieto Bosgra

Sieto Bosgra

Sieto Bosgra

Source

Wambaugh et al. 2018 Toxicological Sciences, in press

Wambaugh et al. 2018 Toxicological Sciences, in press

Wambaugh et al. 2018 Toxicological Sciences, in press

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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

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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

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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.

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Format

A data.frame containing 100 rows and 25 columns.

Author(s)

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Source

Wambaugh et al. 2018 Toxicological Sciences, in press

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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.

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Format

A list containing ten lists.

Author(s)

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`chem.physical_and_invitro.data`

Physico-chemical properties and in vitro measurements for toxicokinetics

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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.

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Format

A data.frame containing 565 rows and 33 columns.

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Source

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Ito, K. and 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. Pharm Res 21(5), 785-92.

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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

convert_httk *Converts HTTK-Pop virtual population into parameters relevant to an HTTK model.*

Description

Converts HTTK-Pop virtual population into parameters relevant to an HTTK model.

Usage

```
convert_httk(indiv.model.bio, model, this.chem = NULL,
  parameters = NULL, adjusted.Funbound.plasma = T, regression = T,
  well.stirred.correction = T, restrictive.clearance = T,
  concentration = "plasma", clint.pvalue.threshold = 0.05)
```

Arguments

indiv.model.bio	A data.table containing the physiological parameters as expected by HTTK (from httkpop_bio) and Funbound.plasma and Clint values (from draw_fup_clint).
model	Which HTTK model to use. One of '1compartment', '3compartmentss', '3compartment', or 'pbtk'.
this.chem	CAS number for the chemical in the HTTK data set (see get_cheminfo) for which parameters are to be generated.
parameters	A list of chemical-specific model parameters containing at least Funbound.plasma, Clint, and Fhep.assay.correction.
adjusted.Funbound.plasma	Uses adjusted Funbound.plasma when set to TRUE.
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 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.
concentration	Blood, plasma, or tissue 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.

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

---

draw_fup_clint *Draw Funbound.plasma and Clint from censored or non-censored distributions.*

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

```
draw_fup_clint(this.chem = NULL, parameters = NULL, nsamp,
  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

this.chem	The CAS number of one of the HTTK chemicals (see get_cheminfo).
parameters	A list of chemical-specific model parameters containing at least Funbound.plasma, Clint, and Fhep.assay.correction.
nsamp	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).

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

---

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)
```

---

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

`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", exclude.fup.zero = NA,
  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", "logP", "pKa_Donor"," pKa_Accept", "MW", "Clint", "Clint.pValue", "Funbound.plasma", "DSSTox_Substance_Id","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").
exclude.fup.zero	Whether or not to exclude chemicals with a fraction of unbound plasma equal to zero or include them with a value of fup.lod.default. Defaults to FALSE for '3compartmentss' and TRUE for pk models and schmitt.
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_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_httk_params *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

```
get_httk_params(indiv_dt, chemcas = NULL, parameters = NULL, model,
  poormetab, fup.censored.dist = FALSE, fup.meas.cv = 0.4,
  clint.meas.cv = 0.3, fup.pop.cv = 0.1, clint.pop.cv = 0.1,
  fup.lod = 0.01, adjusted.Funbound.plasma = T, regression = T,
  well.stirred.correction = T, restrictive.clearance = T,
  concentration = "plasma", clint.pvalue.threshold = 0.05)
```

Arguments

indiv_dt	A data table generated by `httkpop_generate()`.
chemcas	The CAS number of one of the HTTK chemicals (see `get_cheminfo`). Defaults to NULL.
parameters	A list of chemical-specific model parameters containing at least Funbound.plasma, Clint, and Fhep.assay.correction, otherwise defaults to NULL.
model	One of the HTTK models: "1compartment", "3compartmentss", "3compartment", or "pbtk".

poormetab TRUE (include poor metabolizers) or FALSE (exclude poor metabolizers)

fup.censored.dist
: Logical. Whether to draw Funbound.plasma from a censored distribution or not.

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.

fup.lod The average limit of detection for Funbound.plasma. if fup.censor == TRUE, the Funbound.plasma distribution will be censored below lod/2. Default value is 0.01.

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

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

well.stirred.correction
: If TRUE (default) then the well-stirred correction (Rowland et al., 1973) is used in the calculation of hepatic clearance for the models that do not include flows for first-pass metabolism (currently, 1compartment and 3compartmentss). This assumes clearance relative to amount unbound in whole blood instead of plasma, but converted for use with plasma concentration.

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

concentration Blood, plasma, or tissue 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.

Value

A data.table whose columns correspond to the parameters of the HTTK model specified in model, and whose rows correspond to the individuals (rows) of indiv_dt.

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 <- get_httk_params(indiv_dt=indiv_examp,
```

```
chemcas="80-05-7",
model="1compartment",
poormetab=TRUE,
fup.censored.dist=TRUE)
```

`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 retrives 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)
```

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

Value

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

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 retrieves the in vivo ratio of the blood concentration to the plasma concentration.

Usage

```
get_rblood2plasma(chem.name = NULL, chem.cas = 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.
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.

This data set is only used in Vignette 5.

httkpop *httkpop: Virtual population generator for HTTK.*

Description

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

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Details

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`.

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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 `get_httk_params`.

Author(s)

Caroline Ring

Caroline Ring

Caroline Ring

Caroline Ring

References

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

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

`httkpop_bio` *Convert HTTK-Pop-generated parameters to HTTK physiological parameters*

Description

Convert HTTK-Pop-generated parameters to HTTK physiological parameters

Usage

```
httkpop_bio(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_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: http://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 fifty
# chemicals. To build a table with all available chemicals use:
# for (this.cas in httk.table$CAS)
for (this.cas in httk.table$CAS[1:50])
{
  this.index <- httk.table$CAS==this.cas
  if (is.nhanes(this.cas)) httk.table[this.index,"NHANES"] <- "Y"
  if (is.tox21(this.cas)) httk.table[this.index,"Tox21"] <- "Y"
  if (is.toxcast(this.cas)) httk.table[this.index,"ToxCast"] <- "Y"
  if (is.expocast(this.cas)) httk.table[this.index,"ExpoCast"] <- "Y"
  if (is.httk(this.cas,model="PBTK")) httk.table[this.index,"PBTK"] <- "Y"
  if (is.httk(this.cas,species="rat")) httk.table[this.index,"Rat"] <- "Y"
}
```

`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: http://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 fifty
# chemicals. To build a table with all available chemicals use:
# for (this.cas in httk.table$CAS)
for (this.cas in httk.table$CAS[1:50])
{
  this.index <- httk.table$CAS==this.cas
  if (is.nhanes(this.cas)) httk.table[this.index,"NHANES"] <- "Y"
  if (is.tox21(this.cas)) httk.table[this.index,"Tox21"] <- "Y"
  if (is.toxcast(this.cas)) httk.table[this.index,"ToxCast"] <- "Y"
  if (is.expocast(this.cas)) httk.table[this.index,"ExpoCast"] <- "Y"
  if (is.httk(this.cas,model="PBTK")) httk.table[this.index,"PBTK"] <- "Y"
  if (is.httk(this.cas,species="rat")) httk.table[this.index,"Rat"] <- "Y"
}
```

---

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.

This data set is only used in Vignette 5.

---

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.

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.

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.

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.

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(load.image = T, overwrite = F,
  target.env = .GlobalEnv)
```

Arguments

load.image	If overwrite=TRUE (DEFAULT)) then the default HTTK chemical data plus the any new data/predictions from Sipes et al. (2017) will be quickly loaded. This is the same as load.image=F, but much faster, however any other data added by the user will be deleted.
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, tissuelist = NULL, species = "Human")
```

Arguments

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

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

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.

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.

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.

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

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`

Details

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

Author(s)

Caroline Ring

Caroline Ring

Caroline Ring

Caroline Ring

Source

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

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

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

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

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

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

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

`monte_carlo` *Monte Carlo for pharmacokinetic models*

Description

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

Usage

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

Arguments

`params`	All parameters needed by the function indicated by the argument "name.model". These paramters that are also listed in either cv.params or censored.params are sampled using Monte Carlo.
`which.quantile`	This argument specifies which quantiles are to be calculated. It can be a vector or a single value. It defaults to the 0.95 quantile (95%).
`cv.params`	The parameters listed in cv.params are sampled from a normal distribution that is truncated at zero. This argument should be a list of coefficients of variation (cv) for the normal distribution. Each entry in the list is named for a parameter in "params". New values are sampled with mean equal to the value in "params" and standard deviation equal to the mean times the cv.
`censored.params`	The parameters listed in censored.params are sampled from a normal distribution that is censored for values less than the limit of detection (specified separately for each paramter). This argument should be a list of sub-lists. Each sublist is named for a parameter in "params" and contains two elements: "cv" (coefficient of variation) and "LOD" (limit of detection), below which parameter values are censored. New values are sampled with mean equal to the value in "params" and standard deviation equal to the mean times the cv.Censored values are sampled on a uniform distribution between 0 and the limit of detection.
`samples`	This argument is the number of samples to be generated for calculating quantiles.
`name.model`	This argument is a character vector giving the name of the model to be sampled. Defaults to 'calc_analytic_css'.

`output.col.model`
: If the evaluation of the function indicated by "model" returns a list, then model.output.col is the element from that list that is sampled and is used for calculating quantiles. Defaults to NA (i.e., the function returns a single value).

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

`...`
: Additional arguments passed to name.model.

Author(s)

John Wambaugh

Examples

```
#Example from httk jss paper:
## Not run:
library(ggplot2)
library(scales)
vary.params <- NULL
params <- parameterize_pbtk(chem.name = "Zoxamide")
for(this.param in names(subset(params,
names(params) != "Funbound.plasma"))) vary.params[this.param] <- .2
censored.params <- list(Funbound.plasma = list(cv = 0.2, lod = 0.01))
set.seed(1)
out <- monte_carlo(params, cv.params = vary.params,
censored.params = censored.params, return.samples = T,
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.params[["Vliverc"]]<-0.3
vary.params[["Qgfrc"]]<-0.3
vary.params[["Qtotal.liverc"]]<-0.3
vary.params[["million.cells.per.gliver"]]<-0.3
vary.params[["Clint"]]<-0.3
censored.params<-list(Funbound.plasma=list(cv=0.3,lod=0.01))

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



Wetmore.table <- NULL
for (this.CAS in get_cheminfo(model="3compartmentss")){
  if (this.CAS %in% get_wetmore_cheminfo()){
    print(this.CAS)
    these.params <- parameterize_steadystate(chem.cas=this.CAS)
```

```
    if (these.params[["Funbound.plasma"]] == 0.0)
    {
      these.params[["Funbound.plasma"]] <- 0.005
    }
    these.params[["Fhep.assay.correction"]] <- 1
    vLiver.human.values <- monte_carlo(these.params,
                                       cv.params=vary.params,
                                       censored.params=censored.params,
                                       which.quantile=c(0.05,0.5,0.95),
                                       output.units="mg/L",
                                       model='3compartmentss',
                                       suppress.messages=T,
                                       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,
                                which.quantile=as.numeric(percentiles[this.index])/100))
      this.row <- cbind(this.row, as.data.frame(vLiver.human.values[this.index]))
      this.row <- cbind(this.row, as.data.frame(percentiles[this.index]))
      this.row <- cbind(this.row, as.data.frame("Human"))
      this.row <- cbind(this.row, as.data.frame(this.CAS))
      this.row <- cbind(this.row, as.data.frame(pValues[pValues$CAS==this.CAS,
                                                        "Human.Clint.pValue"]<0.05))
      colnames(this.row) <- c("Wetmore", "Predicted", "Percentile", "Species",
                              "CAS", "Systematic")
      if (is.na(this.row["Systematic"])) this.row["Systematic"] <- F
      Wetmore.table <- Wetmore.table <- rbind(Wetmore.table,this.row)
    }
  }
}

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


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

print(Fig1)

Fig1a.fit <- lm(log(Wetmore) ~ log(Predicted)*Percentile, Wetmore.table)
```

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

## End(Not run)
```

`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

http://www.cdc.gov/nhanes/nhanes_questionnaires.htm

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.

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

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.

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.

This data set is only used in Vignette 6.

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.

`parameterize_1comp` *Parameterize_1comp*

Description

This function initializes the parameters needed in the function solve_1comp.

Usage

```
parameterize_1comp(chem.cas = NULL, chem.name = NULL,
  species = "Human", default.to.human = F,
  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`	Either the chemical name or the CAS number must be specified.
`chem.name`	Either the chemical name or the CAS number must be specified.
`species`	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
`default.to.human`	Substitutes missing rat values with human values if true.
`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-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).

Value

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

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,
  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,
  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.
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.
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

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_pbtk *Parameterize_PBTK*

Description

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

Usage

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

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

Examples

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

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

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

parameterize_schmitt *Parameterize Schmitt's method.*

Description

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

Usage

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

Details

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

force.human.fup calculates Funbound.plasma.corrected with the human lipid fractional volume in plasma.

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

Examples

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

`parameterize_steadystate` *Parameterize_SteadyState*

Description

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

Usage

```
parameterize_steadystate(chem.cas = NULL, chem.name = NULL,
  species = "Human", clint.pvalue.threshold = 0.05,
  default.to.human = F, human.clint.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`	Either the chemical name or the CAS number must be specified.
`chem.name`	Either the chemical name or the CAS number must be specified.
`species`	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
`clint.pvalue.threshold`	Hepatic clearances with clearance assays having p-values greater than the threshold are set to zero.
`default.to.human`	Substitutes missing rat values with human values if true.
`human.clint.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

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.

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

Format

A data.frame.

Author(s)

Jimena Davis and Robert Pearce

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.

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. "Assessing Toxicokinetic Uncertainty and Variability in Risk Prioritization ", submitted.

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).

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).

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).

Format

A data.frame containing 11 rows and 7 columns.

Author(s)

John Wambaugh and Nisha Sipes

John Wambaugh and Nisha Sipes

John Wambaugh and Nisha Sipes

Source

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

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

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

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

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,
  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)
```

Arguments

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

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

Examples

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

---

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.

sipes2017 *Sipes et al. 2017 data*

Description

This table includes data predicted with Simulations Plus' ADMET predictor, used in load_sipes2017,
that was used in Sipes et al. 2017. The column names are equivalent to those of chem.physical_and_invitro.data.

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.

`sipes2017.table` *Physico-chemical properties and toxicokinetics, measured values and Sipes et al. (2017)*

Description

This is an image of the chem.phys_and_invitro.data table that has had the Sipes et al. (2017) ADMET predictions adfdded to it. The 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.

Usage

```
sipes2017.table
```

Format

A data.frame containing 9211 rows and 47 columns.

Author(s)

John Wambaugh

Source

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

References

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

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

Hilal, S., Karickhoff, S. and Carreira, L. (1995). A rigorous test for SPARC's chemical reactivity models: Estimation of more than 4300 ionization pKas. Quantitative Structure-Activity Relationships 14(4), 348-355.

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Lau, Y. Y., Sapidou, E., Cui, X., White, R. E. and Cheng, K. C. (2002). Development of a novel in vitro model to predict hepatic clearance using fresh, cryopreserved, and sandwich-cultured hepatocytes. Drug Metabolism and Disposition 30(12), 1446-54.

McGinnity, D. F., Soars, M. G., Urbanowicz, R. A. and Riley, R. J. (2004). Evaluation of fresh and cryopreserved hepatocytes as in vitro drug metabolism tools for the prediction of metabolic clearance. Drug Metabolism and Disposition 32(11), 1247-53, 10.1124/dmd.104.000026.

Naritomi, Y., Terashita, S., Kagayama, A. and Sugiyama, Y. (2003). Utility of Hepatocytes in Predicting Drug Metabolism: Comparison of Hepatic Intrinsic Clearance in Rats and Humans in Vivo and in Vitro. Drug Metabolism and Disposition 31(5), 580-588, 10.1124/dmd.31.5.580.

Obach, R. S. (1999). Prediction of human clearance of twenty-nine drugs from hepatic microsomal intrinsic clearance data: An examination of in vitro half-life approach and nonspecific binding to microsomes. Drug Metabolism and Disposition 27(11), 1350-9.

Obach, R. S., Lombardo, F. and Waters, N. J. (2008). Trend analysis of a database of intravenous pharmacokinetic parameters in humans for 670 drug compounds. Drug Metabolism and Disposition 36(7), 1385-405, 10.1124/dmd.108.020479.

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Pirovano, Alessandra, et al. "QSARs for estimating intrinsic hepatic clearance of organic chemicals in humans." Environmental toxicology and pharmacology 42 (2016): 190-197.

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Shibata, Y., Takahashi, H., Chiba, M. and Ishii, Y. (2002). Prediction of Hepatic Clearance and Availability by Cryopreserved Human Hepatocytes: An Application of Serum Incubation Method. Drug Metabolism and Disposition 30(8), 892-896, 10.1124/dmd.30.8.892.

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.

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Uchimura, Takahide, et al. "Prediction of human blood-to-plasma drug concentration ratio." Biopharmaceutics & drug disposition 31.5-6 (2010): 286-297.

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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.

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.

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.

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 J Cachexia Sarcopenia Muscle 2012 3:25-29.

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.

`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.

`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, times = NULL,
  parameters = NULL, daily.dose = 1, dose = NULL,
  doses.per.day = NULL, days = 10, tsteps = 4,
  suppress.messages = F, species = "Human", output.units = "uM",
  plots = F, initial.values = NULL, iv.dose = F, method = "lsoda",
  rtol = 1e-08, atol = 1e-12, default.to.human = F,
  dosing.matrix = NULL, recalc.elimination = F,
  adjusted.Funbound.plasma = T, regression = T,
  restrictive.clearance = T, well.stirred.correction = 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.
times	Optional time sequence for specified number of days.
parameters	Chemical parameters from parameterize_1comp function, overrides chem.name and chem.cas.
daily.dose	Total daily dose, mg/kg BW.
dose	Amount of a single dose, mg/kg BW. Overwrites daily.dose.
doses.per.day	Number of doses per day.
days	Length of the simulation.
tsteps	The number time steps per hour.
suppress.messages	Whether or not the output message is suppressed.
species	Species desired (either "Rat", "Rabbit", "Dog", or default "Human").
output.units	Desired units (either "mg/L", "mg", "umol", or default "uM").
plots	Plots all outputs if true.
initial.values	Vector containing the initial concentrations or amounts of the chemical in specified tissues with units corresponding to output.units. Defaults are zero.
iv.dose	Simulates a single i.v. dose if true.
method	Method used by integrator (deSolve).
rtol	Argument passed to integrator (deSolve).
atol	Argument passed to integrator (deSolve).
default.to.human	Substitutes missing rat values with human values if true.
dosing.matrix	Vector of dosing times or a matrix consisting of two columns or rows named "dose" and "time" containing the time and amount, in mg/kg BW, of each dose.
recalc.elimination	Whether or not to recalculate the elimination rate.
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.
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.
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).
...	Additional arguments passed to the integrator.

Details

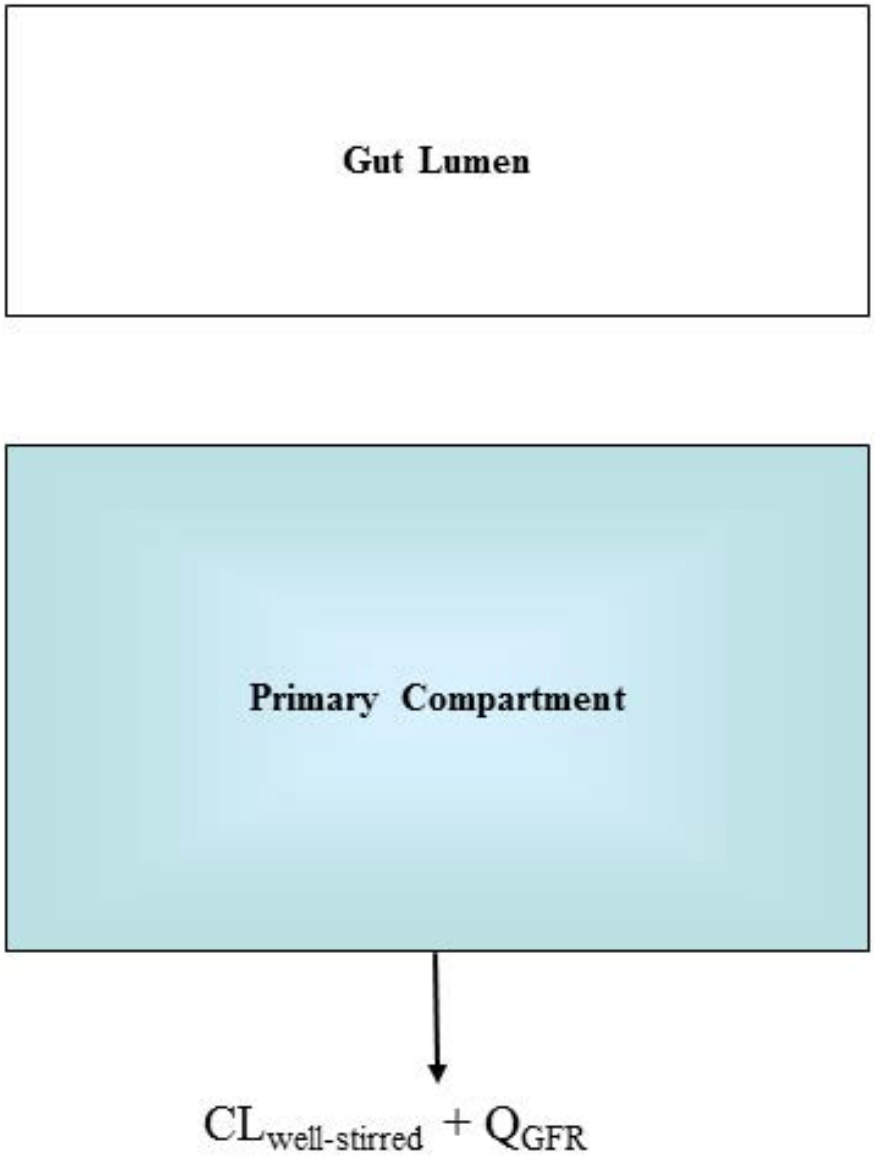
Note that the model parameters have units of hours while the model output is in days.

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. function does. ~~

Usage

```
solve_3comp(chem.name = NULL, chem.cas = NULL, times = NULL,
  parameters = NULL, days = 10, tsteps = 4, daily.dose = 1,
  dose = NULL, doses.per.day = NULL, initial.values = NULL,
  plots = F, suppress.messages = F, species = "Human", iv.dose = F,
  output.units = "uM", method = "lsoda", rtol = 1e-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, ...)
```

Arguments

`chem.name`	Either the chemical name, CAS number, or the parameters must be specified.
`chem.cas`	Either the chemical name, CAS number, or the parameters must be specified.
`times`	Optional time sequence for specified number of days. The dosing sequence begins at the beginning of times.
`parameters`	Chemical parameters from parameterize_3comp function, overrides chem.name and chem.cas.
`days`	Length of the simulation.

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

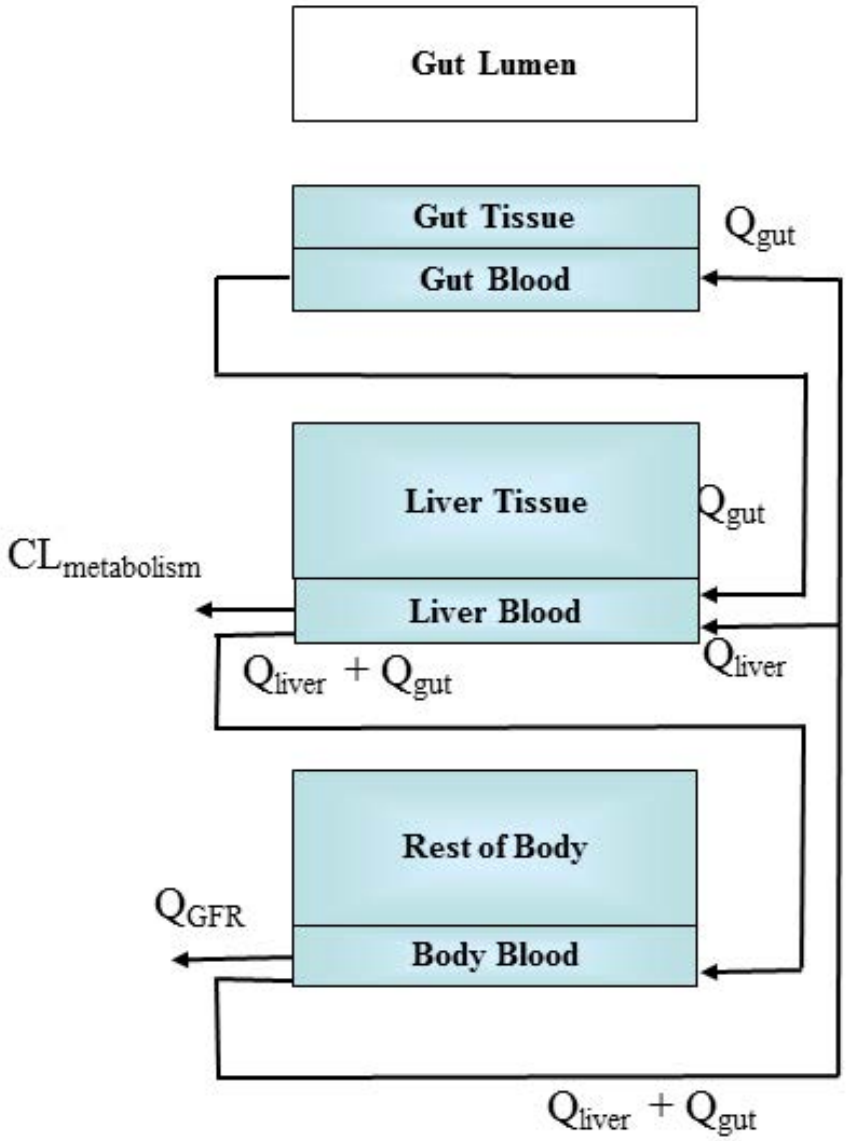
Details

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,dose=.5,days=1,tsteps=2)
params <-parameterize_3comp(chem.cas="80-05-7")
solve_3comp(parameters=params)
```

`solve_pbtk` *Solve_PBTK*

Description

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

Usage

```
solve_pbtk(chem.name = NULL, chem.cas = NULL, times = NULL,
  parameters = NULL, days = 10, tsteps = 4, daily.dose = 1,
  dose = NULL, doses.per.day = NULL, initial.values = NULL,
  plots = F, suppress.messages = F, species = "Human", iv.dose = F,
  output.units = "uM", method = "lsoda", rtol = 1e-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, ...)
```

Arguments

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

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

`species`
: Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").

`iv.dose`
: Simulates a single i.v. dose if true.

`output.units`
: Desired units (either "mg/L", "mg", "umol", or default "uM").

`method`
: Method used by integrator (deSolve).

`rtol`
: Argument passed to integrator (deSolve).

`atol`
: Argument passed to integrator (deSolve).

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

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

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

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

`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).

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

Details

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

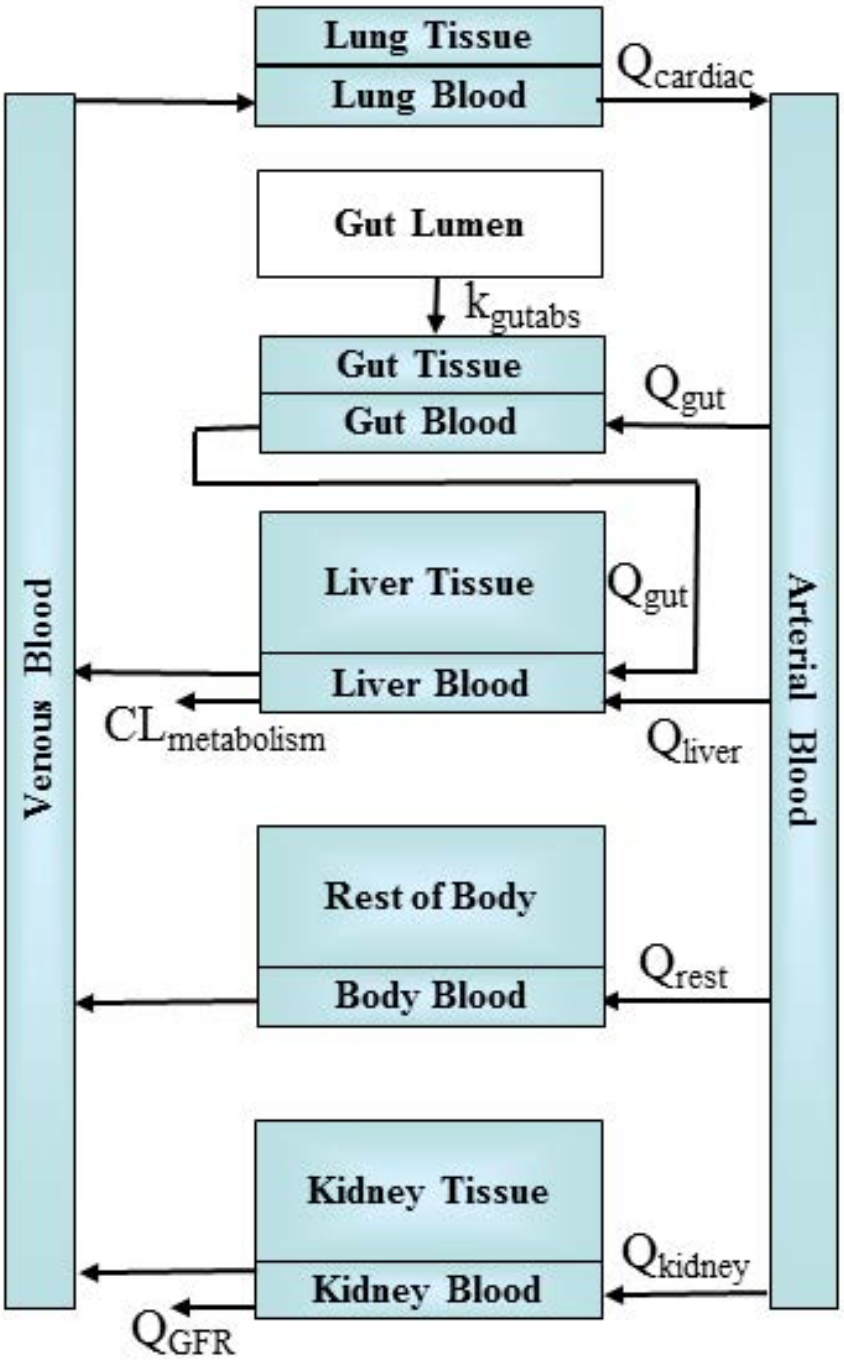
Default NULL value for doses.per.day solves for a single dose.

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',dose=.5,days=1,doses.per.day=2,tsteps=2)
out <- solve_pbtk(chem.name='bisphenola',dose=0,output.units='mg',
                  plots=TRUE,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.

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.

`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.

#'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

Caroline Ring

References

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

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.

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

Caroline Ring

References

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

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.

#'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

Caroline Ring

References

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

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

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

Description

A timestamp of table creation

Usage

```
Tables.Rdata.stamp
```

Format

An object of class `character` of length 1.

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

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

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

ToxCast2015subset *ToxCast and 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.

Usage

```
ToxCast2015subset
```

Format

A data.table with 62412 rows and 5 columns

Author(s)

Caroline Ring

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.

---

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

Description

These data are the new HTTK in vitro data for chemicals reported in Wambaugh et al. (submitted) 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. (submitted)

References

Wambaugh et al. "Assessing Toxicokinetic Uncertainty and Variability in Risk Prioritization", submitted.

`wambaugh2019.nhanes` *NHANES Chemical Intake Rates for chemicals in Wambaugh et al. (submitted))*

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. (submitted)

References

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

---

wambaugh2019.raw *Raw Bayesian in vitro Toxicokinetic Data Analysis from Wambaugh et al. (submitted)*

Description

These data are the new HTTK in vitro data for chemicals reported in Wambaugh et al. (submitted) 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 initital chemical concentration (uL/min/million hepatocytes)]

CLint.1uM.Low95th Lower 95th percentile of Bayesian credible interval for intrinsic hepatic clearance at 1 uM initital chemical concentration (uL/min/million hepatocytes)

CLint.1uM.High95th Uppper 95th percentile of Bayesian credible interval for intrinsic hepatic clearance at 1 uM initital chemical concentration(uL/min/million hepatocytes)

CLint.10uM.Median Median of Bayesian credible interval for intrinsic hepatic clearance at 10 uM initital chemical concentration (uL/min/million hepatocytes)]

CLint.10uM.Low95th Lower 95th percentile of Bayesian credible interval for intrinsic hepatic clearance at 10 uM initital chemical concentration (uL/min/million hepatocytes)

CLint.10uM.High95th Uppper 95th percentile of Bayesian credible interval for intrinsic hepatic clearance at 10 uM initital 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. (submitted)

References

Wambaugh et al. "Assessing Toxicokinetic Uncertainty and Variability in Risk Prioritization", submitted.

`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. (submitted)

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.

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)

Microtiter Plate Well Descriptions for Armitage et al. (2014) model from Honda et al. (2019)

Usage

```
well_param
```

Format

A data frame with 53940 rows and 10 variables:

area_bottom

cell_yield

diam

sysID

v_total

v_working

well_desc

well_number

Author(s)

Greg Honda

Greg Honda

Source

http://www.diamondse.info/

http://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.

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.

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.

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.

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 http://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

For infants under age 2, weight class depends on weight for length percentile. #'

Underweight <2.3rd percentile

Normal 2.3rd-97.7th percentile

weight 2.3rd-97.7th percentile

Obese >=97.7th percentile

Author(s)

Caroline Ring

Caroline Ring

Source

http://www.cdc.gov/growthcharts/who/girls_weight_head_circumference.htm and http://www.cdc.gov/growthcharts/who/boys_weight_head_circumference.htm

http://www.cdc.gov/growthcharts/who/girls_weight_head_circumference.htm and http://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

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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