

Package ‘httk’

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

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R topics documented:

httk-package	4
add_chemtable	5
age_dist_smooth	6
age_draw_smooth	7
available_rblood2plasma	7
blood_mass_correct	8
blood_weight	9
bmiage	9
body_surface_area	10
bone_mass_age	11
brain_mass	12
calc_analytic_css	12
calc_css	14
calc_elimination_rate	16
calc_hepatic_clearance	17
calc_ionization	19
calc_mc_css	20
calc_mc_oral_equiv	23
calc_rblood2plasma	24
calc_stats	25
calc_total_clearance	27
calc_vdist	28
chem.invivo.PK.aggregate.data	29
chem.invivo.PK.data	30
chem.invivo.PK.summary.data	33
chem.lists	36
chem.physical_and_invitro.data	37
ckd_epi_eq	39
convert_httk	40
draw_fup_clint	41
estimate_gfr	42
estimate_gfr_ped	42
estimate_hematocrit	43
export_pbtj_jarnac	43
export_pbtj_sbml	44
gen_age_height_weight	45
gen_height_weight	46
get_cheminfo	47
get_gfr_category	48
get_httk_params	49
get_rblood2plasma	50
get_weight_class	51
get_wetmore_cheminfo	52
get_wetmore_css	53
get_wetmore_oral_equiv	54
hematocrit_infants	56

howgate	57
httkpop_bio	57
httkpop_direct_resample	58
httkpop_direct_resample_inner	59
httkpop_generate	60
httkpop_virtual_indiv	62
in.list	63
is_in_inclusive	65
johnson	65
kidney_mass_children	66
liver_mass_children	66
load_sipes2017	67
lump_tissues	68
lung_mass_children	69
mcnally_dt	69
monte_carlo	70
nhanes_mec_svy	73
Obach2008	74
onlyp	74
pancreas_mass_children	75
parameterize_1comp	75
parameterize_3comp	77
parameterize_pbtk	79
parameterize_schmitt	81
parameterize_steadystate	82
pc.data	84
physiology.data	85
predict_partitioning_schmitt	86
rfun	87
r_left_censored_norm	87
sipes.data	88
skeletal_muscle_mass	89
skeletal_muscle_mass_children	90
skin_mass_bosgra	90
solve_1comp	91
solve_3comp	93
solve_pbtk	95
spleen_mass_children	97
spline_heightweight	98
spline_hematocrit	98
spline_serumcreat	99
tc.dt	100
tissue.data	100
tissue_masses_flows	101
tissue_scale	102
Wetmore.data	102
Wetmore2012	103
wfl	104

httk-package	<i>High-Throughput Toxicokinetics httk: High-Throughput Toxicokinetics</i>
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Description

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

Author(s)

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See Also

Useful links:

https://cfpub.epa.gov/si/si_public_record_report.cfm?dirEntryId=311211

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

<https://doi.org/10.1093/toxsci/kfv171>

<https://doi.org/10.1093/toxsci/kfv118>

add_chemtable	<i>Add a table of chemical information for use in making http predictions.</i>
---------------	--

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

<code>new.table</code>	Object of class <code>data.frame</code> containing one row per chemical, with each chemical minimally by described by a CAS number.
<code>data.list</code>	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 <code>new.table</code> . 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'.
<code>current.table</code>	This is the table to which data are being added.
<code>reference</code>	This is the reference for the data in the new table. This may be omitted if a column in <code>data.list</code> gives the reference value for each chemical.
<code>species</code>	This is the species for the data in the new table. This may be omitted if a column in <code>data.list</code> gives the species value for each chemical or if the data are not species-specific (e.g., MW).
<code>overwrite</code>	If <code>overwrite=TRUE</code> then data in <code>current.table</code> will be replaced by any data in <code>new.table</code> that is for the same chemical and property. If <code>overwrite=FALSE</code> (DEFAULT) then new data for the same chemical and property are ignored. <code>Funbound.plasma</code> values of 0 (below limit of detection) are overwritten either way.

Value

<code>data.frame</code>	A new <code>data.frame</code> containing the data in <code>current.table</code> augmented by <code>new.table</code>
-------------------------	---

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::svsmooth()`, 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 `svsmooth` objects, each encoding a weighted smoothed distribution of ages.

References

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

age_draw_smooth	<i>Draws ages from a smoothed distribution for a given gender/race combination</i>
-----------------	--

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.

References

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

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)
```

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").
adjusted.Funbound.plasma	Whether or not to use Funbound.plasma adjustment if calculating Rblood2plasma.

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 unavailable 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.

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.

References

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

blood_weight	<i>Predict blood mass.</i>
--------------	----------------------------

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.

References

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

bmiage	<i>CDC BMI-for-age charts</i>
--------	-------------------------------

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 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

Source

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 cm².

References

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

bone_mass_age	<i>Predict bone mass.</i>
---------------	---------------------------

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.

References

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

brain_mass	<i>Predict brain mass.</i>
------------	----------------------------

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.

References

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

calc_analytic_css	<i>Calculate the analytic steady state concentration.</i>
-------------------	---

Description

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

Usage

```
calc_analytic_css(chem.name=NULL,chem.cas = NULL,parameters=NULL,daily.dose=1,  
  output.units='uM',model = 'pbtk',species='Human',  
  concentration='plasma',suppress.messages=F,  
  recalc.blood2plasma=F,default.to.human=F,tissue=NULL,  
  well.stirred.correction=T,adjusted.funbound.plasma=T,regression=T,  
  restrictive.clearance=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_pbtk (for model = 'pbtk'), parameterize_3comp (for model = '3compartment'), parameterize_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.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
suppress.messages	Whether or not the output message is suppressed.
concentration	Desired concentration type, 'blood' or default 'plasma'.
recalc.blood2plasma	Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters, calculated with hematocrit, Funbound.plasma, and Krbc2pu.
default.to.human	Substitutes missing rat values with human values if true.
tissue	Desired tissue concentration, overwrites concentration argument.
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 and 3compartmentss. 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 parameters passed to parameterize functions if parameters is NULL.

Details

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.

Value

Steady state concentration

Author(s)

Robert Pearce

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_css

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

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

Usage

```
calc_css(parameters=NULL,chem.name=NULL,chem.cas=NULL,species="Human", f = .01,
         daily.dose=1, doses.per.day=3,days = 10,output.units = "uM",
         concentration='plasma',suppress.messages=F,model='pbtk',default.to.human=F,
         f.change=0.00001,adjusted.funbound.plasma=T,regression=T,
         well.stirred.correction=T,restrictive.clearance=T,...)
```

Arguments

chem.name	Either the chemical name, CAS number, or parameters must be specified.
chem.cas	Either the chemical name, CAS number, or parameters must be specified.
f	Fractional distance from the final steady state concentration that the average concentration must come within to be considered at steady state.
parameters	Chemical parameters from parameterize_pbtk function, overrides chem.name and chem.cas.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
daily.dose	Total daily dose, mg/kg BW.
doses.per.day	Number of doses per day.
days	Initial number of days to run simulation that is multiplied on each iteration.
output.units	Units for returned concentrations, defaults to uM (specify units = "uM") but can also be mg/L.
concentration	Desired concentration type, 'blood' or default 'plasma'.
suppress.messages	Whether or not to suppress messages.

model	Model used in calculation, 'pbtk' for the multiple compartment model, '3compartment' for the three compartment model, 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	Fraction of the true steady state concentration reached on the day steady state is reached.
max	The maximum concentration of the simulation.
avg	The average concentration on the final day of the simulation.
the.day	The day the average concentration comes within 100 * p percent of the true steady state concentration.

Author(s)

Robert Pearce

Examples

```
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 metabolism 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)

```

Arguments

chem.name	Either the chemical name or the cas number must be specified.
chem.cas	Either the cas number or the chemical name must be specified.

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

Details

Elimination rate calculated by dividing the total clearance (using the default well-stirred hepatic model) by the volume of distribution.

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.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
default.to.human	Substitutes missing animal values with human values if true.
parameters	Chemical parameters from parameterize_steadystate function, overrides chem.name and chem.cas.
hepatic.model	Model used in calculating hepatic clearance, unscaled, parallel tube, dispersion, or default well-stirred.
suppress.messages	Whether or not to suppress the output message.
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

Examples

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

calc_ionization	<i>Calculate the ionization.</i>
-----------------	----------------------------------

Description

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

Usage

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

Arguments

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

$$zwitter/neutral = 1$$

$$for(iin1 : pkabove)negative = negative + 10^{i * pH - pKa1 - \dots - pKai}$$

$$for(iin1 : pkbelow)positive = positive + 10^{pKa1 + \dots + pKai - i * pH}$$

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

Value

fraction_neutral	fraction of compound neutral
fraction_charged	fraction of compound charged
fraction_negative	fraction of compound negative

fraction_positive
 fraction of compound positive

fraction_zwitter
 fraction of compound zwitterionic

Author(s)

Robert Pearce

Examples

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

calc_mc_css

Find the monte carlo steady state concentration.

Description

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

Usage

```
calc_mc_css(chem.cas=NULL,chem.name=NULL,parameters=NULL,daily.dose=1,
  which.quantile=0.95,species="Human",output.units="mg/L",suppress.messages=F,
  censored.params=list(Funbound.plasma=list(cv=0.3,lod=0.01)),
  vary.params=list(BW=0.3,Vliverc=0.3,Qgfr=0.3,Qtotal.liverc=0.3,
  million.cells.per.gliver=0.3,Clint=0.3),samples=1000,
  return.samples=F,default.to.human=F,tissue=NULL,well.stirred.correction=T,
  adjusted.Funbound.plasma=T,regression=T,restrictive.clearance=T,httkpop=T,
  model='3compartmentss',poormetab=T,fup.censor=T,Clint.vary=T,
  sigma.factor=0.3,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.name	Either the chemical parameters, name, or the CAS number must be specified.
chem.cas	Either the CAS number, parameters, or the chemical name must be specified.
parameters	Parameters from parameterize_steadystate. 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.
censored.params	The parameters listed in censored.params are sampled from a normal distribution that is censored for values less than the limit of detection (specified separately for each parameter). This argument should be a list of sub-lists. Each sublist is named for a parameter in "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.
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 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.
well.stirred.correction	Uses correction in calculation of hepatic clearance for well-stirred model if TRUE for model 1compartment and 3compartmentss. 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.
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'.
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.

poormetab	TRUE (include poor metabolizers) or FALSE (exclude poor metabolizers)
fup.censor	TRUE (draw Funbound.plasma from a censored distribution) or FALSE (draw Funbound.plasma from a non-censored distribution)
sigma.factor	The coefficient of variation to use for Clint and Funbound.plasma distributions. Default value is 0.3.
Clint.vary	TRUE (sample Clint values) or FALSE (hold Clint fixed). Default TRUE. If Clint.vary is FALSE, then poormetab will have no effect.
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', 'Overweight'). 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', 'End Stage Renal Disease'). User-supplied vector must contain one or more of these strings.
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'). 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().

Details

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

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.

Author(s)

John Wambaugh

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, Qgfr = 0.15,
  Qtotal.liverc = 0.15, million.cells.per.gliver = 0.15, Clint = 0.15),
  output.units = "uM", samples = 2000)

## End(Not run)
```

calc_mc_oral_equiv *Calculate Monte Carlo Oral Equivalent Dose*

Description

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

Usage

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

Arguments

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

Value

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

Author(s)

John Wambaugh

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	<i>Calculate the constant ratio of the blood concentration to the plasma concentration.</i>
--------------------	---

Description

This function calculates the constant ratio of the blood concentration to the plasma concentration.

Usage

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


Arguments

chem.name	Either the chemical name or the CAS number must be specified.
chem.cas	Either the CAS number or the chemical name must be specified.
default.to.human	Substitutes missing animal values with human values if true.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
adjusted.funbound.plasma	Whether or not to use Funbound.plasma adjustment.

Details

The red blood cell (RBC) partition coefficient as predicted by the Schmitt (2008) method is used in the calculation. The value is calculated with the equation: $1 - \text{hematocrit} + \text{hematocrit} * K_{\text{rbc2pu}} * \text{Funbound.plasma}$, summing the red blood cell to plasma and plasma:plasma (equal to 1) partition coefficients multiplied by their respective fractional volumes.

Author(s)

John Wambaugh

References

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

Examples

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

calc_stats	<i>Calculate the statistics.</i>
------------	----------------------------------

Description

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

Usage

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

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

Arguments

chem.name	Either the chemical name or the CAS number must be specified when Funbound.plasma is not given in parameter list.
chem.cas	Either the CAS number or the chemical name 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 partition coefficients calculated with this value.
regression	Whether or not to use the regressions in calculating partition coefficients.

Details

The effective volume of distribution is calculated by summing each tissues volume times it's partition coefficient relative to plasma. Plasma, and the partitioning 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.

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).

Usage

chem.invivo.PK.aggregate.data

Format

data.frame

Author(s)

John Wambaugh

Source

Wambaugh et al. 2018 Toxicological Sciences, in press

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

Description

This data set includes time and dose specific measurements of chemical concentration in tissues taken from animals administered control doses of the chemicals either orally or intravenously. This plasma concentration-time data is from rat experiments reported in public sources. Toxicokinetic data were retrieved from those studies by the Netherlands Organisation for Applied Scientific Research (TNO) using curve stripping (TechDig v2). This data is provided for statistical analysis as in Wambaugh et al. 2018.

Usage

chem.invivo.PK.data

Format

A data.frame containing 597 rows and 13 columns.

Author(s)

Sieto Bosgra

Source

Wambaugh et al. 2018 Toxicological Sciences, in press

References

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Yeung PK, Alcos A, Tang J (2009). Pharmacokinetics and Hemodynamic Effects of Diltiazem in Rats Following Single vs Multiple Doses In Vivo. *Open Drug Metab J.* 3:56-62.

chem.invivo.PK.summary.data

Summary of published toxicokinetic time course experiments

Description

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

Usage

chem.invivo.PK.summary.data

Format

A data.frame containing 100 rows and 25 columns.

Author(s)

John Wambaugh

Source

Wambaugh et al. 2018 *Toxicological Sciences*, in press

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chem.lists

Chemical membership in different research projects

Description

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

Usage

chem.lists

Format

A list containing ten lists.

Author(s)

John Wambaugh

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chem.physical_and_invitro.data

Physico-chemical properties and in vitro measurements for toxicokinetics

Description

This data set contains the necessary information to make basic, high-throughput toxicokinetic (HTTK) predictions for compounds, including Funbound.plasma, molecular weight (g/mol), logP, logMA (membrane affinity), intrinsic clearance(uL/min/10⁶ cells), and pKa. These data have been compiled from multiple sources, and can be used to parameterize a variety of toxicokinetic models.

Usage

chem.physical_and_invitro.data

Format

A data.frame containing 565 rows and 33 columns.

Author(s)

John Wambaugh

Source

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

References

- DSStox database ([http:// www.epa.gov/ncct/dsstox](http://www.epa.gov/ncct/dsstox))
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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/1.73m².

References

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

convert_httk	<i>Converts HHTK-Pop virtual population into parameters relevant to an HHTK model.</i>
--------------	--

Description

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

Usage

```
convert_httk(indiv.model.bio, model, this.chem, adjusted.Funbound.plasma=T, regression=T,
             well.stirred.correction=T, restrictive.clearance=T)
```

Arguments

indiv.model.bio	A data.table containing the physiological parameters as expected by HHTK (from httkpop_bio) and Funbound.plasma and Clint values (from draw_fup_clint).
model	Which HHTK model to use. One of '1compartment', '3compartments', '3compartment', or 'pbtk'.
this.chem	CAS number for the chemical in the HHTK data set for which parameters are to be generated.
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 for model 1compartment elimination rate.

Value

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

References

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

draw_fup_clint	<i>Draw Funbound.plasma and Clint from censored or non-censored distributions.</i>
----------------	--

Description

Given a CAS in the HHTK data set, a virtual population from HHTK-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, nsamp, sigma.factor = 0.3, poormetab, fup.censor,
  Clint.vary = TRUE, lod = 0.01, adjusted.Funbound.plasma=T)
```

Arguments

this.chem	A CAS number in the HHTK data set
nsamp	The number of samples to draw.
sigma.factor	The coefficient of variance to assume. Default 0.3.
poormetab	Logical. Whether to include poor metabolizers in the Clint distribution or not.
fup.censor	Logical. Whether to draw Funbound.plasma from a censored distribution or not.
Clint.vary	Logical, default TRUE. Whether to treat Clint as fixed at its measured value (FALSE), or as a random variable (TRUE).
lod	The average limit of detection for Funbound.plasma, below which distribution will be censored if fup.censor is TRUE. Default 0.01.
adjusted.Funbound.plasma	Uses adjusted Funbound.plasma value if TRUE.

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.

estimate_gfr	<i>Predict GFR.</i>
--------------	---------------------

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.

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	<i>Predict GFR in children.</i>
------------------	---------------------------------

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/1.73m².

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.

References

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

export_pbtj_jarnac *Export model to jarnac.*

Description

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

Usage

```
export_pbtj_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.

Author(s)

Robert Pearce

Examples

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

export_pbt_k_sbml *Export model to sbml.*

Description

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

Usage

```
export_pbt_k_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.

Author(s)

Robert Pearce

Examples

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

`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

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

`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

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.

References

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

<code>get_cheminfo</code>	<i>Retrieve chemical information from HTKK package</i>
---------------------------	--

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 parameterized for a given species.

Usage

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

Arguments

<code>info</code>	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". <code>info="all"</code> gives all information for the model and species.
<code>species</code>	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
<code>exclude.fub.zero</code>	Whether or not to exclude chemicals with a fraction of unbound plasma equal to zero or include them with a value of <code>fub.lod.default</code> . Defaults to TRUE for '3compartmentss' and FALSE for pk models and schmitt.
<code>fub.lod.default</code>	Default value used for fraction of unbound plasma for chemicals where measured value was below the limit of detection. Default value is 0.0005.
<code>model</code>	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 <code>predict_partitioning_schmitt</code>).
<code>default.to.human</code>	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

<code>info</code>	Table/vector containing values specified in "info" for valid chemicals.
-------------------	---

Author(s)

John Wambaugh

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'.

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	<i>Converts the HTTK-Pop population data table to a table of the parameters needed by HTTK, for a specific chemical.</i>
-----------------	--

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, model, poormetab, fup.censor,
  sigma.factor = 0.3, Clint.vary = TRUE, lod = 0.01, adjusted.Funbound.plasma=T,
  regression=T, well.stirred.correction=T, restrictive.clearance=T)
```

Arguments

indiv_dt	A data table generated by <code>httkpop_generate()</code> .
chemcas	The CAS number of one of the HTTK chemicals (see get_cheminfo).
model	One of the HTTK models: "1compartment", "3compartmentss", "3compartment", or "pbt".
poormetab	TRUE (include poor metabolizers) or FALSE (exclude poor metabolizers)
fup.censor	TRUE (draw <code>Funbound.plasma</code> from a censored distribution) or FALSE (draw <code>Funbound.plasma</code> from a non-censored distribution)
sigma.factor	The coefficient of variation to use for <code>Clint</code> and <code>Funbound.plasma</code> distributions. Default value is 0.3.

<code>Clint.vary</code>	TRUE (sample <code>Clint</code> values) or FALSE (hold <code>Clint</code> fixed). Default TRUE. If <code>Clint.vary</code> is FALSE, then <code>poormetab</code> will have no effect.
<code>lod</code>	The average limit of detection for <code>Funbound.plasma</code> . if <code>fup.censor == TRUE</code> , the <code>Funbound.plasma</code> distribution will be censored below <code>lod/2</code> . Default value is 0.01.
<code>adjusted.Funbound.plasma</code>	Uses adjusted <code>Funbound.plasma</code> when set to TRUE along with partition coefficients calculated with this value.
<code>regression</code>	Whether or not to use the regressions in calculating partition coefficients.
<code>well.stirred.correction</code>	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.
<code>restrictive.clearance</code>	Protein binding not taken into account (set to 1) in liver clearance if FALSE for model 1compartment elimination rate.

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`.

```
@examples set.seed(42) indiv_examp <- httkpop_generate(method="d", nsamp=100) httk_param
<- get_httk_param(indiv_dt=indiv_examp, chemcas="80-05-7", model="1compartment", poormetab=TRUE,
fup.censor=TRUE)
```

References

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

`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.

Author(s)

Robert Pearce

Examples

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

get_weight_class	<i>Given vectors of age, BMI, recumbent length, weight, and gender, categorizes weight classes using CDC and WHO categories.</i>
------------------	--

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'.

References

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

get_wetmore_cheminfo *Get Wetmore Chemical Information.*

Description

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

Usage

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

Arguments

info	A single character vector (or collection of character vectors) from "Compound", "CAS", "MW", "Raw.Exposure", "r2", "p.val", "Concentration.uM.", "Css_lower_5th_perc.mg.L.", "Css_median_perc.mg.L.", "Css_upper_5th_perc.mg.L." 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., Strobe, 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_wetmore_cheminfo()
get_wetmore_cheminfo(info=c('CAS', 'MW'))

## End(Not run)
```

get_wetmore_css	<i>Get Wetmore Css</i>
-----------------	------------------------

Description

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

Usage

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

Arguments

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

Author(s)

John Wambaugh

References

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

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

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

Examples

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

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

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

```
get_wetmore_oral_equiv
```

Get Wetmore Oral Equivalent Dose

Description

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

Usage

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

Arguments

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

Value

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

Author(s)

John Wambaugh

References

- Wetmore, B.A., Wambaugh, J.F., Ferguson, S.S., Sochaski, M.A., Rotroff, D.M., Freeman, K., Clewell, H.J., Dix, D.H., Andersen, M.E., Houck, K.A., Allen, B., Judson, R.S., Sing, R., Kavlock, R.J., Richard, A.M., and Thomas, R.S., "Integration of Dosimetry, Exposure and High-Throughput Screening Data in Chemical Toxicity Assessment," *Toxicological Sciences* 125 157-174 (2012)
- Wetmore, B.A., Wambaugh, J.F., Ferguson, S.S., Li, L., Clewell, H.J. III, Judson, R.S., Freeman, K., Bao, W, Sochaski, M.A., Chu T.-M., Black, M.B., Healy, E, Allen, B., Andersen M.E., Wolfinger, R.D., and Thomas R.S., "The Relative Impact of Incorporating Pharmacokinetics on Predicting in vivo Hazard and Mode-of-Action from High-Throughput in vitro Toxicity Assays" *Toxicological Sciences*, 132:327-346 (2013).
- Wetmore, B. A., Wambaugh, J. F., Allen, B., Ferguson, S. S., Sochaski, M. A., Setzer, R. W., Houck, K. A., Strope, C. L., Cantwell, K., Judson, R. S., LeCluyse, E., Clewell, H.J. III, Thomas, R.S., and Andersen, M. E. (2015). "Incorporating High-Throughput Exposure Predictions with Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing" *Toxicological Sciences*, kfv171.

Examples

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

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

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.

References

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

howgate	<i>Howgate 2006</i>
---------	---------------------

Description

This data set is only used in Vignette 5.

Usage

```
howgate
```

httkpop_bio	<i>Convert HHTK-Pop-generated parameters to HHTK physiological parameters</i>
-------------	---

Description

Convert HHTK-Pop-generated parameters to HHTK 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 HHTK 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.

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. <code>list(Male=100,Female=100)</code> . 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 <code>c(0,79)</code> . 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 <code>c(0,959)</code> , 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 <code>c('Underweight', 'Normal', 'Overweight', 'Obese')</code> . User-supplied vector must contain one or more of these strings.
gfr_category	The kidney function categories to include in the population. Default is <code>c('Normal', 'Kidney Disease', 'Kidney Failure')</code> , to include all kidney function levels.
reths	Optional: a character vector giving the races/ethnicities to include in the population. Default is <code>c('Mexican American', 'Other Hispanic', 'Non-Hispanic White', 'Non-Hispanic Black', 'Other')</code> . 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.

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')`. 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', 'Overweight')`. 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.

References

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

httkpop_generate	<i>Generate a virtual population</i>
------------------	--------------------------------------

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. <code>nsamp</code> need not be provided if <code>gendernum</code> is provided.
gendernum	Optional: A named list giving the numbers of male and female individuals to include in the population, e.g. <code>list(Male=100,Female=100)</code> . Default is <code>NULL</code> , meaning both males and females are included, in their proportions in the NHANES data. If both <code>nsamp</code> and <code>gendernum</code> are provided, they must agree (i.e., <code>nsamp</code> must be the sum of <code>gendernum</code>).
agelim_years	Optional: A two-element numeric vector giving the minimum and maximum ages (in years) to include in the population. Default is <code>c(0,79)</code> . If only a single value is provided, both minimum and maximum ages will be set to that value; e.g. <code>agelim_years=3</code> is equivalent to <code>agelim_years=c(3,3)</code> . If <code>agelim_years</code> is provided and <code>agelim_months</code> is not, <code>agelim_years</code> will override the default value of <code>agelim_months</code> .

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', 'Overweight'). 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', 'End Stage Kidney Disease'), 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'). 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.

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,
#include 80 females and 20 males,
#include only ages 20-65,
#include only Mexican American and
#Non-Hispanic Black individuals,
#include 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. <code>list(Male=100,Female=100)</code> . 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 <code>c(0,79)</code> . 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 <code>c(0, 959)</code> , 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 <code>c('Underweight', 'Normal', 'Overweight', 'Obese')</code> . User-supplied vector must contain one or more of these strings.
gfr_category	The kidney function categories to include in the population. Default is <code>c('Normal', 'Kidney Disease', 'Kidney Failure')</code> , to include all kidney function levels.
reths	Optional: a character vector giving the races/ethnicities to include in the population. Default is <code>c('Mexican American', 'Other Hispanic', 'Non-Hispanic White', 'Non-Hispanic Black', 'Other')</code> , 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.

References

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

in.list	<i>Convenience Boolean (yes/no) functions to identify chemical membership in several key lists.</i>
---------	---

Description

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

Usage

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

Arguments

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

Details

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

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

ExpoCast: ExpoCast (Exposure Forecaster) is an U.S. EPA research project to generate tentative 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 Survey (NHANES) is an on-going survey to characterize the health and biometrics (e.g., weight, height) of the U.S. population. One set of measurements includes the quantification of xenobiotic chemicals in various samples (blood, serum, urine) of the thousands of surveyed individuals. (CDC, 2014)

Value

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

Author(s)

John Wambaugh

References

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

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

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

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

Examples

```
httk.table <- get_cheminfo(info=c("CAS", "Compound"))
httk.table[, "Rat"] <- ""
httk.table[, "NHANES"] <- ""
httk.table[, "Tox21"] <- ""
httk.table[, "ToxCast"] <- ""
httk.table[, "ExpoCast"] <- ""
httk.table[, "PBTk"] <- ""
# To make this example run quickly, this loop is only over the first fifty
# chemicals. To build a table with all available chemicals use:
```



```

# for (this.cas in httpk.table$CAS)
for (this.cas in httpk.table$CAS[1:50])
{
  this.index <- httpk.table$CAS==this.cas
  if (is.nhanes(this.cas)) httpk.table[this.index,"NHANES"] <- "Y"
  if (is.tox21(this.cas)) httpk.table[this.index,"Tox21"] <- "Y"
  if (is.toxcast(this.cas)) httpk.table[this.index,"ToxCast"] <- "Y"
  if (is.expocast(this.cas)) httpk.table[this.index,"ExpoCast"] <- "Y"
  if (is.httpk(this.cas,model="PBTK")) httpk.table[this.index,"PBTK"] <- "Y"
  if (is.httpk(this.cas,species="rat")) httpk.table[this.index,"Rat"] <- "Y"
}

```

is_in_inclusive	<i>Checks whether a value, or all values in a vector, is within inclusive limits</i>
-----------------	--

Description

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

Usage

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

Arguments

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

Value

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

johnson	<i>Johnson 2006</i>
---------	---------------------

Description

This data set is only used in Vignette 5.

Usage

```
johnson
```

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.

References

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

liver_mass_children *Predict liver mass for children.*

Description

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

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.

References

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

load_sipes2017	<i>Load data from Sipes et al 2017.</i>
----------------	---

Description

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

Usage

```
load_sipes2017(overwrite=F)
```

Arguments

overwrite	If overwrite=TRUE then existing data in chem.physical_and_invitro.data will be replaced by any data in Sipes2017 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	An updated version of chem.physical_and_invitro.data.
------------	---

Author(s)

Robert Pearce

Examples

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

lump_tissues	<i>Lump tissue parameters</i>
--------------	-------------------------------

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

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

Value

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

References

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

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

Description

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

Usage

```
mcnally_dt
```

Format

A data.table with variables:

tissue Body tissue

gender Gender: Male or Female

mass_ref Reference mass in kg, from Reference Man

mass_cv Coefficient of variation for mass

mass_dist Distribution for mass: Normal or Log-normal

flow_ref Reference flow in L/h, from Reference Man

flow_cv Coefficient of variation for flow (all normally distributed)

height_ref Reference heights (by gender)

CO_ref Reference cardiac output by gender

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

Source

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

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 parameters 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 parameter). This argument should be a list of sub-lists. Each sublist is named for a parameter in "params" and contains two elements: "cv" (coefficient of variation) and "LOD" (limit of detection), below which parameter values are censored. New values are sampled with mean equal to the value in "params" and standard deviation equal to the mean times the cv. Censored values are sampled on a uniform distribution between 0 and the limit of detection.
samples	This argument is the number of samples to be generated for calculating quantiles.
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 htkk jss paper:
## Not run:
library(ggplot2)
library(scales)
vary.params <- NULL
params <- parameterize_pbtck(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 = "pbtck", 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.

Source

www.cdc.gov/nhanes/nhanes_questionnaires.htm

Obach2008

Published Pharmacokinetic Parameters from Obach et al. 2008

Description

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

Usage

Obach2008

Format

A data.frame containing 670 rows and 8 columns.

References

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

onlyp

NHANES Exposure Data

Description

This data set is only used in Vignette 6.

Usage

onlyp

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.

References

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

parameterize_1comp *Parameterize_1comp*

Description

This function initializes the parameters needed in the function solve_1comp.

Usage

```
parameterize_1comp(chem.cas=NULL,chem.name=NULL,species="Human",
  default.to.human=F,adjusted.funbound.plasma=T,regression=T,
  restrictive.clearance=T,well.stirred.correction=T,
  suppress.messages=F)
```

Arguments

chem.name	Either the chemical name or the CAS number must be specified.
chem.cas	Either the chemical name or the CAS number must be specified.
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.

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. Only included for the conversion of plasma outputs.
hepatic.bioavailability	Fraction of dose remaining after first pass clearance, calculated from the corrected well-stirred model.

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.fub = F,
                  clint.pvalue.threshold=0.05,adjusted.funbound.plasma=T,
                  regression=T,suppress.messages=F)
```

Arguments

chem.name	Either the chemical name or the CAS number must be specified.
chem.cas	Either the chemical name or the CAS number must be specified.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
default.to.human	Substitutes missing animal values with human values if true.
force.human.clint.fub	Forces use of human values for hepatic intrinsic clearance and fraction of unbound plasma if true.
clint.pvalue.threshold	Hepatic clearances with clearance assays having p-values greater than the threshold are set to zero.
adjusted.funbound.plasma	Returns 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.
suppress.messages	Whether or not the output message is suppressed.

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_pbt *Parameterize_PBT*

Description

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

Usage

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

Arguments

chem.name	Either the chemical name or the CAS number must be specified.
chem.cas	Either the chemical name or the CAS number must be specified.
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_pbt only works with the default parameters.
force.human.clint.fub	Forces use of human values for hepatic intrinsic clearance and fraction of unbound plasma if true.
clint.pvalue.threshold	Hepatic clearances with clearance assays having p-values greater than the threshold are set to zero.
adjusted.funbound.plasma	Returns 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.
suppress.messages	Whether or not the output message is suppressed.

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.
Qcardiac	Cardiac Output, L/h/kg BW ^{3/4} .
Qgfr	Glomerular Filtration Rate, L/h/kg BW ^{3/4} , volume of fluid filtered from kidney and excreted.
Qgut	Fraction of cardiac output flowing to the gut.
Qkidney	Fraction of cardiac output flowing to the kidneys.
Qliver	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.
Vgut	Volume of the gut per kg body weight, L/kg BW.
Vkidney	Volume of the kidneys per kg body weight, L/kg BW.
Vliver	Volume of the liver per kg body weight, L/kg BW.
Vlung	Volume of the lungs per kg body weight, L/kg BW.
Vrest	Volume of the rest of the body per kg body weight, L/kg BW.
Vvein	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_pbtck(chem.cas='80-05-7')

parameters <- parameterize_pbtck(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_pbtck(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.fub=F)
```

Arguments

<code>chem.name</code>	Either the chemical name or the CAS number must be specified.
<code>chem.cas</code>	Either the chemical name or the CAS number must be specified.
<code>species</code>	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
<code>default.to.human</code>	Substitutes missing fraction of unbound plasma with human values if true.
<code>force.human.fub</code>	Returns human fraction of unbound plasma in calculation for rats if true.

Details

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

force.human.fub 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 equilibrium constant(s)
pKa_Accept	compound H association equilibrium 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 ('3compartments').

Usage

```
parameterize_steadystate(chem.cas=NULL,chem.name=NULL,species="Human",
  Clint.pvalue.threshold=0.05,default.to.human=F,
  human.Clint.fub=F,adjusted.Funbound.plasma=T,
  restrictive.clearance=T)
```

Arguments

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

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.
Qtotall.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.

Usage

pc.data

Format

A data.frame.

Author(s)

Jimena Davis and Robert Pearce

References

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

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

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

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

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

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

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

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

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

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

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

physiology.data

Species-specific physiology parameters

Description

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

Usage

physiology.data

Format

A data.frame containing 11 rows and 7 columns.

Author(s)

John Wambaugh and Nisha Sipes

Source

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

References

Davies, B. and Morris, T. (1993). *Physiological Parameters in Laboratory Animals and Humans*. *Pharmaceutical Research* 10(7), 1093-1095, 10.1023/a:1018943613122. Anderson and Holford (2009) Robertshaw, D., *Temperature Regulation and Thermal Environment*, in *Dukes' Physiology of Domestic Animals*, 12th ed., Reece W.O., Ed. Copyright 2004 by Cornell University. Stammers (1926) *The blood count and body temperature in normal rats* Gordon (1993) *Temperature Regulation in Laboratory Rodents*

predict_partitioning_schmitt

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

Description

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

Usage

```
predict_partitioning_schmitt(chem.name=NULL,chem.cas=NULL,species="Human",
                             default.to.human=F,parameters=NULL,
                             adjusted.Funbound.plasma=T, regression=T,
                             regression.list=c('brain','adipose','gut','heart','kidney',
                                                'liver','lung','muscle','skin','spleen','bone'),
                             tissues=NULL)
```

Arguments

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

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 ($K_{tissue2pu} * Funbound.plasma$) calculated with the corrected Funbound.plasma value and divided by this value to get $K_{tissue2pu}$. 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

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.

sipes.data	<i>Sipes et al. 2017 data</i>
------------	-------------------------------

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

```
sipes.data
```

Format

```
data.frame
```

Author(s)

Nisha Sipes

Source

ADMET, Simulations Plus

References

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

skeletal_muscle_mass *Predict skeletal muscle mass.*

Description

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

Usage

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

Arguments

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

Details

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

Value

Vector of skeletal muscle masses in kg.

References

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

See Also

[skeletal_muscle_mass_children](#)

skeletal_muscle_mass_children

Predict skeletal muscle mass for children.

Description

For individuals under age 18, predict skeletal muscle mass from gender and age, using a nonlinear equation from 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.

References

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

skin_mass_bosgra

Predict skin mass.

Description

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

Usage

skin_mass_bosgra(BSA)

Arguments

BSA Vector of body surface areas in cm².

Value

Vector of skin masses in kg.

References

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

solve_1comp	<i>Solve one compartment TK model</i>
-------------	---------------------------------------

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.cas=NULL,chem.name=NULL,times=NULL,parameters=NULL,daily.dose=1,
dose=NULL,doses.per.day=NULL, days=10,tsteps = 4, suppress.messages=F,
species='Human',output.units='uM',plots=F,initial.values=NULL,
iv.dose=F,method="lsoda",rtol=1e-8,atol=1e-12,
default.to.human=F,dosing.matrix=NULL,recalc.elimination=F,
adjusted.funbound.plasma=T,regression=T,restrictive.clearance=T,
well.stirred.correction=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.
times	Optional time sequence for specified number of days.
parameters	Chemical parameters from parameterize_1comp function, overrides chem.name and chem.cas.
days	Length of the simulation.
tsteps	The number time steps per hour.
daily.dose	Total daily dose, mg/kg BW.
dose	Amount of a single dose, mg/kg BW. Overwrites daily.dose.
doses.per.day	Number of doses per day.
species	Species desired (either "Rat", "Rabbit", "Dog", or default "Human").
iv.dose	Simulates a single i.v. dose if true.
output.units	Desired units (either "mg/L", "mg", "umol", or default "uM").
initial.values	Vector containing the initial concentrations or amounts of the chemical in specified tissues with units corresponding to output.units. Defaults are zero.
suppress.messages	Whether or not the output message is suppressed.
plots	Plots all outputs if true.

<code>method</code>	Method used by integrator (deSolve).
<code>rtol</code>	Argument passed to integrator (deSolve).
<code>atol</code>	Argument passed to integrator (deSolve).
<code>default.to.human</code>	Substitutes missing rat values with human values if true.
<code>dosing.matrix</code>	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.
<code>recalc.elimination</code>	Whether or not to recalculate the elimination rate.
<code>adjusted.funbound.plasma</code>	Uses adjusted <code>Funbound.plasma</code> when set to TRUE along with volume of distribution calculated with this value.
<code>regression</code>	Whether or not to use the regressions in calculating partition coefficients in volume of distribution calculation.
<code>restrictive.clearance</code>	In calculating elimination rate, protein binding is not taken into account (set to 1) in liver clearance if FALSE.
<code>well.stirred.correction</code>	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.
<code>...</code>	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.

AUC is area under plasma concentration curve.

Value

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

Author(s)

Robert Pearce

Examples

```
solve_1comp(chem.name='Bisphenol-A',days=1)
```

 solve_3comp

Solve_3comp

Description

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

Usage

```
solve_3comp(chem.name = NULL, chem.cas = NULL, times=NULL,
            parameters=NULL, days=10, tsteps = 4, daily.dose = 1,dose=NULL,
            doses.per.day=NULL, initial.values=NULL,plots=F, suppress.messages=F,
            species="Human", iv.dose=F,output.units='uM',
            method="lsoda",rtol=1e-8,
            atol=1e-12,default.to.human=F,recalc.blood2plasma=F,
            recalc.clearance=F,dosing.matrix=NULL,adjusted.funbound.plasma=T,
            regression=T,restrictive.clearance = 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.
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).

<code>rtol</code>	Argument passed to integrator (deSolve).
<code>atol</code>	Argument passed to integrator (deSolve).
<code>default.to.human</code>	Substitutes missing animal values with human values if true (hepatic intrinsic clearance or fraction of unbound plasma).
<code>recalc.blood2plasma</code>	Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters, calculated with hematocrit, Funbound.plasma, and Krbc2pu.
<code>recalc.clearance</code>	Recalculates the the hepatic clearance (Clmetabolism) with new million.cells.per.gliver parameter.
<code>dosing.matrix</code>	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.
<code>adjusted.Funbound.plasma</code>	Uses adjusted Funbound.plasma when set to TRUE along with partition coefficients calculated with this value.
<code>regression</code>	Whether or not to use the regressions in calculating partition coefficients.
<code>restrictive.clearance</code>	Protein binding not taken into account (set to 1) in liver clearance if FALSE.
<code>...</code>	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.

Value

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

Author(s)

John Wambaugh and Robert Pearce

Examples

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

 solve_pbt

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_pbt(chem.name = NULL, chem.cas = NULL, times=NULL, parameters=NULL,
          days=10, tsteps = 4, daily.dose=1,dose = NULL,doses.per.day=NULL,
          initial.values=NULL,plots=F,suppress.messages=F,species="Human",
          iv.dose=F,output.units='uM',method="lsoda",rtol=1e-8,atol=1e-12,
          default.to.human=F,recalc.blood2plasma=F,recalc.clearance=F,
          dosing.matrix=NULL,adjusted.funbound.plasma=T,regression=T,
          restrictive.clearance = 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.
times	Optional time sequence for specified number of days. Dosing sequence begins at the beginning of times.
parameters	Chemical parameters from parameterize_pbt 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).

<code>default.to.human</code>	Substitutes missing animal values with human values if true (hepatic intrinsic clearance or fraction of unbound plasma).
<code>recalc.blood2plasma</code>	Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters, calculated with hematocrit, <code>Funbound.plasma</code> , and <code>Krbc2pu</code> .
<code>recalc.clearance</code>	Recalculates the the hepatic clearance (<code>Clmetabolism</code>) with new <code>million.cells.per.gliv</code> parameter.
<code>dosing.matrix</code>	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.
<code>adjusted.Funbound.plasma</code>	Uses adjusted <code>Funbound.plasma</code> when set to TRUE along with partition coefficients calculated with this value.
<code>regression</code>	Whether or not to use the regressions in calculating partition coefficients.
<code>restrictive.clearance</code>	Protein binding not taken into account (set to 1) in liver clearance if FALSE.
<code>...</code>	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.

Value

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

Author(s)

John Wambaugh and Robert Pearce

Examples

```
solve_pbt(chem.name='Bisphenol-A',dose=.5,days=1,doses.per.day=2,tsteps=2)
out <- solve_pbt(chem.name='bisphenola',dose=0,output.units='mg',
                plots=TRUE,initial.values=c(Agut=200))
## Not run:
parameters <- parameterize_pbt(chem.name = "triclosan", species = "rat")
parameters["Funbound.plasma"] <- 0.1
```



```
out <- solve_pbtck(parameters=parameters)

library("ggplot2")
out <- solve_pbtck(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.

References

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

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

Description

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

Usage

```
spline_heightweight
```

Format

A data.table with 6 variables:

g Gender: Male or Female

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

height_spline A list of smooth.spline objects, each giving a smoothed relationship between log height in cm and age in months

weight_spline A list of smooth.spline objects, each giving a smoothed relationship between log body weight in kg and age in months

hw_kde A list of kde objects; each is a 2-D KDE of the distribution of log height and log body weight residuals about the smoothing splines.

References

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

spline_hematocrit	<i>Smoothing splines for log hematocrit vs. age in months, and KDE residuals, by race and gender.</i>
-------------------	---

Description

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

Usage

```
spline_hematocrit
```

Format

A data.table with 6 variables:

gender Gender: Male or Female

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

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

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

References

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

spline_serumcreat	<i>Smoothing splines for log serum creatinine vs. age in months, along with KDE residuals, by race and gender.</i>
-------------------	--

Description

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

Usage

```
spline_serumcreat
```

Format

A data.table with 6 variables:

gender Gender: Male or Female

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

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

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

References

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

`tc.dt`*Toxcast Data*

Description

This data set is used in Vignette 6.

Usage`tc.dt`

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

Description

This data set contains values from Schmitt (2008) and Ruark et al. (2014) describing the composition of specific tissues and from Birnbaum et al. (1994) describing volumes of and blood flows to those tissues, allowing parameterization of toxicokinetic models for human, mouse, rat, dog, or rabbit. Tissue volumes were calculated by converting the fractional mass of each tissue with its density (both from ICRP), lumping the remaining tissues into the rest-of-body, excluding the mass of the gastrointestinal contents

Usage`tissue.data`**Format**

A data.frame containing 13 rows and 20 columns.

Author(s)

John Wambaugh, Robert Pearce, and Nisha Sipes

Source

Pearce et al. (2017), in preparation,

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

References

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

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

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

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

tissue_masses_flows	<i>Given a data.table describing a virtual population by the NHANES quantities, generates HHTK physiological parameters for each individual.</i>
---------------------	--

Description

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

Usage

```
tissue_masses_flows(tmf_dt)
```

Arguments

tmf_dt	A data.table generated by <code>gen_age_height_weight()</code> , containing variables gender, reth, age_months, age_years, weight, and height.
--------	--

Value

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

References

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

tissue_scale	<i>Allometric scaling.</i>
--------------	----------------------------

Description

Allometrically scale a tissue mass or flow based on $\text{height}^{3/4}$.

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`.

References

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

Wetmore.data	<i>Published toxicokinetic predictions based on in vitro data</i>
--------------	---

Description

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

Usage

```
Wetmore.data
```

Format

A data.frame containing 577 rows and 20 columns.

Source

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

References

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

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

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

Wetmore2012

Published toxicokinetic predictions based on in vitro data from Wetmore et al. 2012.

Description

This data set overlaps with Wetmore.data and is used only in Vignette 4 for steady state concentration.

Usage

Wetmore2012

Format

A data.frame containing 13 rows and 15 columns.

References

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

wfl

WHO weight-for-length charts

Description

Charts giving weight-for-length percentiles for boys and girls under age 2.

Usage

wfl

Format

A data.table object with variables

Sex 'Male' or 'Female'

Length length in cm

L, M, S LMS parameters; see 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

Source

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

Index

*Topic **Export**

export_pbtck_jarnac, 43
export_pbtck_sbml, 44

*Topic **Monte Carlo**

calc_mc_css, 20
calc_mc_oral_equiv, 23
get_wetmore_css, 53
get_wetmore_oral_equiv, 54
monte_carlo, 70

*Topic **Parameter**

available_rblood2plasma, 7
calc_elimination_rate, 16
calc_hepatic_clearance, 17
calc_ionization, 19
calc_rblood2plasma, 24
calc_total_clearance, 27
calc_vdist, 28
get_rblood2plasma, 50
lump_tissues, 68
parameterize_1comp, 75
parameterize_3comp, 77
parameterize_pbtck, 79
parameterize_schmitt, 81
parameterize_steadystate, 82
predict_partitioning_schmitt, 86

*Topic **Retrieval**

get_cheminfo, 47
get_wetmore_cheminfo, 52

*Topic **Solve**

calc_analytic_css, 12
calc_stats, 25
solve_1comp, 91
solve_3comp, 93
solve_pbtck, 95

*Topic **Statistics**

calc_stats, 25

*Topic **Steady State**

calc_css, 14
calc_mc_css, 20

calc_mc_oral_equiv, 23

*Topic **Wetmore**

get_wetmore_cheminfo, 52
get_wetmore_css, 53
get_wetmore_oral_equiv, 54

*Topic **datasets**

age_dist_smooth, 6
bmiage, 9
chem.invivo.PK.aggregate.data, 29
chem.invivo.PK.data, 30
chem.invivo.PK.summary.data, 33
chem.lists, 36
chem.physical_and_invitro.data, 37
howgate, 57
johnson, 65
mcnally_dt, 69
nhanes_mec_svy, 73
Obach2008, 74
onlyp, 74
pc.data, 84
physiology.data, 85
sipes.data, 88
spline_heightweight, 98
spline_hematocrit, 98
spline_serumcreat, 99
tc.dt, 100
tissue.data, 100
Wetmore.data, 102
Wetmore2012, 103
wfl, 104

*Topic **package**

httk-package, 4

add_chemtable, 5
age_dist_smooth, 6
age_draw_smooth, 7
available_rblood2plasma, 7

blood_mass_correct, 8
blood_weight, 8, 9

- bmiage, 9
- body_surface_area, 10
- bone_mass_age, 11
- brain_mass, 12

- calc_analytic_css, 12
- calc_css, 14
- calc_elimination_rate, 16
- calc_hepatic_clearance, 17
- calc_ionization, 19
- calc_mc_css, 20
- calc_mc_oral_equiv, 23
- calc_rblood2plasma, 24
- calc_stats, 25
- calc_total_clearance, 27
- calc_vdist, 28
- chem.in_vivo.PK.aggregate.data, 29
- chem.in_vivo.PK.data, 30
- chem.in_vivo.PK.summary.data, 33
- chem.lists, 36
- chem.physical_and_in_vitro.data, 37
- ckd_epi_eq, 39
- convert_httk, 40

- draw_fup_clint, 40, 41

- estimate_gfr, 42
- estimate_gfr_ped, 42
- estimate_hematocrit, 43
- export_pbt_k_jarnac, 43
- export_pbt_k_sbml, 44

- gen_age_height_weight, 45
- gen_height_weight, 46
- get_cheminfo, 47, 49
- get_gfr_category, 48
- get_httk_params, 49
- get_rblood2plasma, 50
- get_weight_class, 51
- get_wetmore_cheminfo, 52
- get_wetmore_css, 53
- get_wetmore_oral_equiv, 54

- hematocrit_infants, 56
- howgate, 57
- httk (httk-package), 4
- httk-package, 4
- httkpop_bio, 40, 57
- httkpop_direct_resample, 58

- httkpop_direct_resample_inner, 59
- httkpop_generate, 60
- httkpop_virtual_indiv, 62

- in.list, 63
- is.expocast (in.list), 63
- is.httk (in.list), 63
- is.nhanes (in.list), 63
- is.pharma (in.list), 63
- is.tox21 (in.list), 63
- is.toxcast (in.list), 63
- is_in_inclusive, 65

- johnson, 65

- kidney_mass_children, 66

- liver_mass_children, 66
- load_sipes2017, 67
- lump_tissues, 68
- lung_mass_children, 69

- mcnally_dt, 69
- monte_carlo, 70

- nhanes_mec_svy, 73

- Obach2008, 74
- onlyp, 74

- pancreas_mass_children, 75
- parameterize_1comp, 75
- parameterize_3comp, 77
- parameterize_pbt_k, 79
- parameterize_schmitt, 81
- parameterize_steadystate, 82
- pc.data, 84
- physiology.data, 85
- predict_partitioning_schmitt, 86

- r_left_censored_norm, 87
- rfun, 87

- sipes.data, 88
- Sipes2017 (sipes.data), 88
- skeletal_muscle_mass, 89
- skeletal_muscle_mass_children, 89, 90
- skin_mass_bosgra, 90
- solve_1comp, 91
- solve_3comp, 93

solve_pbt, [95](#)
spleen_mass_children, [97](#)
spline_heightweight, [98](#)
spline_hematocrit, [98](#)
spline_serumcreat, [99](#)

tc.dt, [100](#)
tissue.data, [100](#)
tissue_masses_flows, [101](#)
tissue_scale, [102](#)

Wetmore.data, [102](#)
Wetmore2012, [103](#)
wfl, [104](#)