Package 'httk'

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Title High-Throughput Toxicokinetics

Description Pre-made models that can be rapidly tailored to various chemicals and species using chemical-specific in vitro data and physiological information. These tools allow incorporation of chemical toxicokinetics (``TK'') and in vitro-in vivo extrapolation (``IVIVE'') into bioinformatics, as described by Pearce et al. (2017) (<doi:10.18637/jss.v079.i04>). Chemical-specific in vitro data characterizing toxicokinetics have been obtained from relatively high-throughput experiments. The chemical-independent (``generic'') physiologically-based (``PBTK'') and empirical (for example, one compartment) ``TK'' models included here can be parameterized with in vitro data or in silico predictions which are provided for thousands of chemicals, multiple exposure routes, and various species. High throughput toxicokinetics (``HTTK'') is the combination of in vitro data and generic models. We establish the expected accuracy of HTTK for chemicals without in vivo data through statistical evaluation of HTTK predictions for chemicals where in vivo data do exist. The models are systems of ordinary differential equations that are developed in MCSim and solved using compiled (C-based) code for speed. A Monte Carlo sampler is included for simulating human biological variability (Ring et al., 2017 <doi:10.1016/j.envint.2017.06.004>) and propagating parameter uncertainty (Wambaugh et al., 2019 <doi:10.1093/toxsci/kfz205>). Empirically calibrated methods are included for predicting tissue:plasma partition coefficients and volume of distribution (Pearce et al., 2017 <doi:10.1007/s10928-017-9548-7>). These functions and data provide a set of tools for using IVIVE to convert concentrations from high-throughput screening experiments (for example, Tox21, ToxCast) to real-world exposures via reverse dosimetry (also known as ``RTK'') (Wetmore et al., 2015 <doi:10.1093/toxsci/kfv171>).

Depends R (>= 2.10)

Imports deSolve, msm, data.table, survey, mvtnorm, truncnorm, stats, graphics, utils, magrittr, purrr, methods, Rdpack (>= 2.3), ggplot2, dplyr

RdMacros Rdpack

Suggests knitr, rmarkdown, gplots, scales, EnvStats, MASS, RColorBrewer, stringr, reshape, viridis, gmodels, colorspace, cowplot, ggrepel, forcats, smatr, gridExtra, readxl, ks, testthat

License GPL-3

LazyData true

LazyDataCompression xz

Encoding UTF-8

VignetteBuilder knitr

RoxygenNote 7.3.2

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

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

NeedsCompilation yes

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

Description

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

Usage

```
add_chemtable(
  new.table,
  data.list,
  current.table = NULL,
  reference = NULL,
  species = NULL,
  overwrite = FALSE,
  sig.fig = 4,
  clint.pvalue.overwrite = TRUE,
  allow.na = FALSE
)
```

Arguments

new.table	Object of class data.frame containing one row per chemical, with each chemical minimally described by a CAS number.
data.list	This list identifies which properties are to be read from the table. Each item in the list should point to a column in the table new.table. Valid names in the list are: 'Compound', 'CAS', 'DSSTox.GSID' 'SMILES.desalt', 'Reference', 'Species', 'MW', 'logP', 'pKa_Donor', 'pKa_Accept', 'logMA', 'Clint', 'Clint.pValue', 'Funbound.plasma', 'Fabs', 'Fgut', 'Rblood2plasma'.
current.table	This is the table to which data are being added.
reference	This is the reference for the data in the new table. This may be omitted if a column in data.list gives the reference value for each chemical.
species	This is the species for the data in the new table. This may be omitted if a column in data.list gives the species value for each chemical or if the data are not species-specific (e.g., MW).
overwrite	If overwrite=TRUE then data in current.table will be replaced by any data in new.table that is for the same chemical and property. If overwrite=FALSE (DEFAULT) then new data for the same chemical and property are ignored. Funbound.plasma values of 0 (below limit of detection) are overwritten either way.
sig.fig	Sets the number of significant figures stored (defaults to 4)
clint.pvalue.overwrite	If TRUE then the Cl_int p-value is set to NA when the Cl_int value is changed unless a new p-value is provided. (defaults to TRUE)
allow.na	If TRUE (default is FALSE) then NA values are written to the table, otherwise they are ignored.

Value

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

Author(s)

John Wambaugh

Examples

```
library(httk)

my.new.data <- as.data.frame(c("A","B","C"),stringsAsFactors=FALSE)
my.new.data <- cbind(my.new.data,as.data.frame(c(
                     "111-11-2","222-22-0","333-33-5"),
                     stringsAsFactors=FALSE))
my.new.data <- cbind(my.new.data,as.data.frame(c("DTX1","DTX2","DTX3"),
                   stringsAsFactors=FALSE))
my.new.data <- cbind(my.new.data,as.data.frame(c(200,200,200)))
my.new.data <- cbind(my.new.data,as.data.frame(c(2,3,4)))
my.new.data <- cbind(my.new.data,as.data.frame(c(0.01,0.02,0.3)))
my.new.data <- cbind(my.new.data,as.data.frame(c(0,10,100)))
```

```
colnames(my.new.data) <- c("Name","CASRN","DTXSID","MW","LogP","Fup","CLint")

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

# Initialize a column describing proton donors ("acids")
my.new.data$pka.a <- NA
# set chemical C to an acid (pKa_donor = 5):
my.new.data[my.new.data$Name=="C","pka.a"] <- "5"
chem.physical_and_invitro.data <- add_chemtable(my.new.data,
                                  current.table=
                                    chem.physical_and_invitro.data,
                                 data.list=list(
                                 Compound="Name",
                                 CAS="CASRN",
                                 DTXSID="DTXSID",
                                 pKa_Donor="pka.a"),
                                 species="Human",
                                 reference="MyPaper 2015")

# Note Rblood2plasma and hepatic bioavailability change (relative to above):
parameterize_steadystate(chem.name="C")

# Initialize a column describing proton acceptors ("bases")
my.new.data$pka.b <- NA
# set chemical B to a base with multiple pka's (pKa_accept = 7 and 8):
my.new.data[my.new.data$Name=="B","pka.b"] <- "7;8"
chem.physical_and_invitro.data <- add_chemtable(my.new.data,
                                  current.table=
                                    chem.physical_and_invitro.data,
                                 data.list=list(
                                 Compound="Name",
                                 CAS="CASRN",
                                 DTXSID="DTXSID",
                                 pKa_Accept="pka.b"),
                                 species="Human",
                                 reference="MyPaper 2015")
# Note that average and max change (relative to above):
calc_css(chem.name="B")
```

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

Description

This function should usually not be called directly by the user. It is used by `httkpop_generate()` in "virtual-individuals" mode.

Usage

```
age_draw_smooth(gender, reth, nsamp, agelim_months, nhanes_mec_svy)
```

Arguments

`gender`	Gender. Either 'Male' or 'Female'.
`reth`	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.
`nhanes_mec_svy`	`surveydesign` object created from `mecdt` using `svydesign` (this is done in `httkpop_generate`)

Value

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

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

apply_clint_adjustment *Correct the measured intrinsive hepatic clearance for fraction free*

Description

This function uses the free fraction estimated from Kilford et al. (2008) to increase the in vitro measure intrinsic hepatic clearance. The assumption that chemical that is bound in vitro is not available to be metabolized and therefore the actual rate of clearance is actually faster. Note that in most high throughput TK models included in the package this increase is offset by the assumption of "restrictive clearance" – that is, the rate of hepatic metabolism is slowed to account for the free fraction of chemical in plasma. This adjustment was made starting in Wetmore et al. (2015) in order to better predict plasma concentrations.

Usage

```
apply_clint_adjustment(
  Clint,
  Fu_hep = NULL,
  Pow = NULL,
  pKa_Donor = NULL,
  pKa_Accept = NULL,
  suppress.messages = FALSE
)
```

Arguments

Clint	In vitro measured intrinsic hepatic clearance in units of (ul/min/million hepatocytes).
Fu_hep	Estimated fraction of chemical free for metabolism in the in vitro assay, estimated by default from the method of Kilford et al. (2008) using calc_hep_fu
Pow	The octanal:water equilibrium partition coefficient
pKa_Donor	A string containing hydrogen donor ionization equilibria, concatenated with commas. Can be "NA" if none exist.
pKa_Accept	A string containing hydrogen acceptance ionization equilibria, concatenated with commas. Can be "NA" if none exist.
suppress.messages	Whether or not the output message is suppressed.

Value

Intrinsic hepatic clearance increased to take into account binding in the in vitro assay

Author(s)

John Wambaugh

References

Kilford PJ, Gertz M, Houston JB, 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), 1194–1197. doi:10.1124/dmd.108.020834. Wetmore BA, Wambaugh JF, Allen B, Ferguson SS, Sochaski MA, Setzer RW, Houck KA, Strope CL, Cantwell K, Judson RS, others (2015). "Incorporating high-throughput exposure predictions with dosimetry-adjusted in vitro bioactivity to inform chemical toxicity testing." *Toxicological Sciences*, **148**(1), 121–136. doi:10.1093/toxsci/kfv171.

See Also

calc_hep_fu

---

apply_fup_adjustment *Correct the measured fraction unbound in plasma for lipid binding*

Description

This function uses the lipid binding correction estimated by Pearce et al. (2017) to decrease the fraction unbound in plasma (f_{up}). This correction assumes that there is additional in vivo binding to lipid, which has a greater impact on neutral lipophilic compounds.

Usage

```
apply_fup_adjustment(
  fup,
  fup.correction = NULL,
  Pow = NULL,
  pKa_Donor = NULL,
  pKa_Accept = NULL,
  suppress.messages = FALSE,
  minimum.Funbound.plasma = 1e-04
)
```

Arguments

fup	In vitro measured fraction unbound in plasma
fup.correction	Estimated correction to account for additional lipid binding in vivo (Pearce et al., 2017) from calc_fup_correction
Pow	The octanal:water equilibrium partition coefficient
pKa_Donor	A string containing hydrogen donor ionization equilibria, concatenated with commas. Can be "NA" if none exist.
pKa_Accept	A string containing hydrogen acceptance ionization equilibria, concatenated with commas. Can be "NA" if none exist.
suppress.messages	Whether or not the output message is suppressed.
minimum.Funbound.plasma	f_{up} is not allowed to drop below this value (default is 0.0001).

Value

Fraction unbound in plasma adjusted to take into account binding in the in vitro assay

Author(s)

John Wambaugh

References

Kilford PJ, Gertz M, Houston JB, 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), 1194–1197. doi:10.1124/dmd.108.020834. Wetmore BA, Wambaugh JF, Allen B, Ferguson SS, Sochaski MA, Setzer RW, Houck KA, Strope CL, Cantwell K, Judson RS, others (2015). "Incorporating high-throughput exposure predictions with dosimetry-adjusted in vitro bioactivity to inform chemical toxicity testing." *Toxicological Sciences*, **148**(1), 121–136. doi:10.1093/toxsci/kfv171.

See Also

calc_fup_correction

---

armitage_estimate_sarea

Estimate well surface area

Description

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

Usage

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

Arguments

tcdata	A data table with well_number corresponding to plate format, optionally include v_working, sarea, option.bottom, and option.plastic
this.well_number	For single value, plate format default is 384, used if is.na(tcdata)==TRUE

`this.cell_yield`
: For single value, optionally supply cell_yield, otherwise estimated based on well number

`this.v_working`
: For single value, optionally supply working volume, otherwise estimated based on well number (m^3)

Value

A data table composed of any input data.table *tcdata* with only the following columns either created or altered by this function:

Column Name	Description	Units
well_number	number of wells on plate	
sarea	surface area	m^2
cell_yield	number of cells	cells
v_working	working (filled) volume of each well	uL
v_total	total volume of each well	uL

Author(s)

Greg Honda

References

Armitage JM, Wania F, Arnot JA (2014). "Application of mass balance models and the chemical activity concept to facilitate the use of in vitro toxicity data for risk assessment." *Environmental science & technology*, **48**(16), 9770–9779. doi:10.1021/es501955g.

Honda GS, Pearce RG, Pham LL, Setzer RW, Wetmore BA, Sipes NS, Gilbert J, Franz B, Thomas RS, Wambaugh JF (2019). "Using the concordance of in vitro and in vivo data to evaluate extrapolation assumptions." *PloS one*, **14**(5), e0217564. doi:10.1371/journal.pone.0217564.

---

armitage_eval *Evaluate the updated Armitage model*

Description

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

Usage

```
armitage_eval(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  casrn.vector = NA_character_,
  nomconc.vector = 1,
  this.well_number = 384,
  this.FBSf = NA_real_,
  tcdata = NA,
  this.sarea = NA_real_,
  this.v_total = NA_real_,
  this.v_working = NA_real_,
  this.cell_yield = NA_real_,
  this.Tsys = 37,
  this.Tref = 298.15,
  this.option.kbsa2 = FALSE,
  this.option.swat2 = FALSE,
  this.pseudooct = 0.01,
  this.memblip = 0.04,
  this.nlom = 0.2,
  this.P_nlom = 0.035,
  this.P_dom = 0.05,
  this.P_cells = 1,
  this.csalt = 0.15,
  this.celldensity = 1,
  this.cellmass = 3,
  this.f_oc = 1,
  this.conc_ser_alb = 24,
  this.conc_ser_lip = 1.9,
  this.Vdom = 0,
  this.pH = 7,
  restrict.ion.partitioning = FALSE
)
```

Arguments

chem.cas	A single or vector of Chemical Abstracts Service Registry Number(s) (CAS-RN) of desired chemical(s).
chem.name	A single or vector of name(s)) of desired chemical(s).
dtxsid	A single or vector ofEPA's DSSTox Structure ID(s) (https://comptox.epa.gov/dashboard)
casrn.vector	A deprecated argument specifying a single or vector of Chemical Abstracts Service Registry Number(s) (CAS-RN) of desired chemical(s).
nomconc.vector	For vector or single value, micromolar (uM = umol/L) nominal concentration (e.g. AC50 value)

this.well_number
: For single value, plate format default is 384, used if is.na(tcdata)==TRUE. This value chooses default surface area settings for armitage_estimate_sarea based on the number of plates per well.

this.FBSf
: Fraction fetal bovine serum, must be entered by user.

tcdata
: A data.table with casrn, nomconc, MP, gkow, gkaw, gswat, sarea, v_total, v_working. Otherwise supply single values to this.params (e.g., this.sarea, this.v_total, etc.). Chemical parameters are taken from chem.physical_and_invitro.data.

this.sarea
: Surface area per well (m^2)

this.v_total
: Total volume per well (uL)

this.v_working
: Working volume per well (uL)

this.cell_yield
: Number of cells per well

this.Tsys
: System temperature (degrees C)

this.Tref
: Reference temperature (degrees K)

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

this.option.swat2
: Use alternative water solubility correction

this.pseudooct
: Pseudo-octanol cell storage lipid content

this.memblip
: Membrane lipid content of cells

this.nlom
: Structural protein content of cells

this.P_nlom
: Proportionality constant to octanol structural protein

this.P_dom
: Proportionality constant to dissolve organic material

this.P_cells
: Proportionality constant to octanol storage lipid

this.csalt
: Ionic strength of buffer (M = mol/L)

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

this.cellmass
: Mass per cell, ng/cell

this.f_oc
: Everything assumed to be like proteins

this.conc_ser_alb
: Mass concentration of albumin in serum (g/L)

this.conc_ser_lip
: Mass concentration of lipids in serum (g/L)

this.Vdom
: 0 ml, the volume of dissolved organic matter (DOM)

this.pH
: 7.0, pH of cell culture

restrict.ion.partitioning
: FALSE, Should we restrict the chemical available to partition to only the neutral fraction?

Value

Param	Description	Units
casrn	Chemical Abstracts Service Registry Number	character
nomconc	Nominal Concentration	uM=umol/L
well_number	Number of wells in plate (used to set default surface area)	unitless
sarea	Surface area of well	m^2
v_total	Total volume of well	uL
v_working	Filled volume of well	uL
cell_yield	Number of cells	cells
gkow	The log10 octanol to water (PC) (logP)	log10 unitless ratio
logHenry	The log10 Henry's law constant '	log10 unitless ratio
gswat	The log10 water solubility (logWSol)	log10 mg/L
MP	The chemical compound melting point	degrees Kelvin
MW	The chemical compound molecular weight	g/mol
gkaw	The air to water PC	unitless ratio
dsm		
duow		
duaw		
dumw		
gkmw	log10	
gkcw	The log10 cell/tissue to water PC	log10 unitless ratio
gkbsa	The log10 bovine serum albumin to water partitiion coefficient	unitless
gkpl	log10	
ksalt	Setschenow constant	L/mol
Tsys	System temperature	degrees C
Tref	Reference temperature	degrees K
option.kbsa2	Use alternative bovine-serum-albumin partitioning model	logical
option.swat2	Use alternative water solubility correction	logical
FBSf	Fraction fetal bovine serum	unitless
pseudooct	Pseudo-octanol cell storage lipid content	
memblip	Membrane lipid content of cells	
nlom	Structural protein content of cells	
P_nlom	Proportionality constant to octanol structural protein	unitless
P_dom	Proportionality constant to dissolved organic material (DOM)	unitless
P_cells	Proportionality constant to octanol storage lipid	unitless
csalt	Ionic strength of buffer	M=mol/L
celldensity	Cell density	kg/L, g/mL
cellmass	Mass per cell	ng/cell
f_oc		
cellwat		
Tcor		
Vm	Volume of media	L
Vwell	Volume of medium (aqueous phase only)	L
Vair	Volume of head space	L
Vcells	Volume of cells/tissue	L
Valb	Volume of serum albumin	L
Vslip	Volume of serum lipids	L

Vdom	Volume of dissolved organic matter	L
F_ratio		
gs1.GSE		
s1.GSE		
gss.GSE		
ss.GSE		
kmw		
kow	The octanol to water PC (i.e., 10^gkow)	unitless
kaw	The air to water PC (i.e., 10^gkaw)	unitless
swat	The water solubility (i.e., 10^gswat)	mg/L
kpl		
kcw	The cell/tissue to water PC (i.e., 10^gkcw)	unitless
kbsa	The bovine serum albumin to water PC	unitless
swat_L		
soct_L		
scell_L		
cinit	Initial concentration	uM=umol/L
mtot	Total micromoles	umol
cwat	Total concentration in water	uM=umol/L
cwat_s	Dissolved concentration in water	uM=umol/L
csat	Is the solution saturated (1/0)	logical
activity		
cair	Concentration in head space	uM=umol/L
calb	Concentration in serum albumin	uM=umol/L
cslip	Concentration in serum lipids	uM=umol/L
cdom	Concentration in dissolved organic matter	uM=umol/L
ccells	Concentration in cells	uM=umol/L
cplastic	Concentration in plastic	uM=umol/m^2
mwat_s	Mass dissolved in water	umols
mair	Mass in air/head space	umols
mbsa	Mass bound to bovine serum albumin	umols
mslip	Mass bound to serum lipids	umols
mdom	Mass bound to dissolved organic matter	umols
mcells	Mass in cells	umols
mplastic	Mass bond to plastic	umols
mprecip	Mass precipitated out of solution	umols
xwat_s	Fraction dissolved in water	fraction
xair	Fraction in the air	fraction
xbsa	Fraction bound to bovine serum albumin	fraction
xslip	Fraction bound to serum lipids	fraction
xdom	Fraction bound to dissolved organic matter	fraction
xcells	Fraction within cells	fraction
xplastic	Fraction bound to plastic	fraction
xprecip	Fraction precipitated out of solution	fraction
eta_free	Effective availability ratio	fraction
cfree.invitro	**Free concentration in the in vitro media** (use for Honda1 and Honda2)	fraction

Author(s)

Greg Honda

References

Armitage JM, Wania F, Arnot JA (2014). "Application of mass balance models and the chemical activity concept to facilitate the use of in vitro toxicity data for risk assessment." *Environmental science & technology*, **48**(16), 9770–9779. doi:10.1021/es501955g.

Honda GS, Pearce RG, Pham LL, Setzer RW, Wetmore BA, Sipes NS, Gilbert J, Franz B, Thomas RS, Wambaugh JF (2019). "Using the concordance of in vitro and in vivo data to evaluate extrapolation assumptions." *PloS one*, **14**(5), e0217564. doi:10.1371/journal.pone.0217564.

Examples

```
library(httk)

# Check to see if we have info on the chemical:
"80-05-7" %in% get_cheminfo()

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

# Check to see if we have info on the chemical:
"793-24-8" %in% get_cheminfo()

# Since we don't have any info, let's look up phys-chem from dashboard:
cheminfo <- data.frame(
  Compound="6-PPD",
  CASRN="793-24-8",
  DTXSID="DTXSID9025114",
  logP=4.27,
  logHenry=log10(7.69e-8),
  logWSol=log10(1.58e-4),
  MP= 99.4,
  MW=268.404
  )

# Add the information to HTTK's database:
chem.physical_and_invitro.data <- add_chemtable(
 cheminfo,
 current.table=chem.physical_and_invitro.data,
 data.list=list(
 Compound="Compound",
 CAS="CASRN",
  DTXSID="DTXSID",
  MW="MW",
  logP="logP",
```

```
  logHenry="logHenry",
  logWSol="logWSol",
  MP="MP"),
  species="Human",
  reference="CompTox Dashboard 31921")

# Run the Armitage et al. (2014) model:
out <- armitage_eval(
  casrn.vector = "793-24-8",
  this.FBSf = 0.1,
  this.well_number = 384,
  nomconc = 10)

print(out)
```

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

Description

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

Usage

```
armitage_input
```

Format

A data frame with 53940 rows and 10 variables:

MP

MW

casrn

compound_name

gkaw

gkow

gswat

Author(s)

Greg Honda

Source

https://www.diamondse.info/

References

Armitage JM, Wania F, Arnot JA (2014). "Application of mass balance models and the chemical activity concept to facilitate the use of in vitro toxicity data for risk assessment." *Environmental science & technology*, **48**(16), 9770–9779. doi:10.1021/es501955g.

Honda GS, Pearce RG, Pham LL, Setzer RW, Wetmore BA, Sipes NS, Gilbert J, Franz B, Thomas RS, Wambaugh JF (2019). "Using the concordance of in vitro and in vivo data to evaluate extrapolation assumptions." *PloS one*, **14**(5), e0217564. doi:10.1371/journal.pone.0217564.

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

Description

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

Usage

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

Arguments

`this.table`	Object of class data.frame containing one row per chemical.
`this.CAS`	The Chemical Abstracts Service registry number (CAS-RN) correponding to the parameter value
`compound.name`	A name associated with the chemical (defaults to NULL)
`this.property`	The property being added/modified.
`value`	The value being assigned to this.property.
`species`	This is the species for the data in the new table. This may be omitted if a column in data.list gives the species value for each chemical or if the data are not species-specific (e.g., MW).
`reference`	This is the reference for the data in the new table. This may be omitted if a column in data.list gives the reference value for each chemical.

overwrite	If overwrite=TRUE then data in current.table will be replaced by any data in new.table that is for the same chemical and property. If overwrite=FALSE (DEFAULT) then new data for the same chemical and property are ignored. Funbound.plasma values of 0 (below limit of detection) are overwritten either way.
sig.fig	Sets the number of significant figures stored (defaults to 4)
clint.pvalue.overwrite	If TRUE then the Cl_int p-value is set to NA when the Cl_int value is changed unless a new p-value is provided. (defaults to TRUE)
allow.na	If TRUE (default is FALSE) then NA values are written to the table, otherwise they are ignored.

Value

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

Author(s)

John Wambaugh

---

available_rblood2plasma

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

Description

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

Usage

```
available_rblood2plasma(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
  adjusted.Funbound.plasma = TRUE,
  class.exclude = TRUE,
  suppress.messages = FALSE
)
```

Arguments

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

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

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

`class.exclude` Exclude chemical classes identified as outside of domain of applicability by relevant modelinfo_[MODEL] file (default TRUE).

`suppress.messages`
Whether or not to display relevant warning messages to user.

Details

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

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

Value

The blood to plasma chemical concentration ratio – measured if available, calculated if not.

Author(s)

Robert Pearce

See Also

`calc_rblood2plasma`

`get_rblood2plasma`

Examples

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

---

aylward2014 *Aylward et al. 2014*

Description

Aylward et al. (2014) compiled measurements of the ratio of maternal to fetal cord blood chemical concentrations at birth for a range of chemicals with environmental routes of exposure, including bromodiphenyl ethers, fluorinated compounds, organochlorine pesticides, polyaromatic hydrocarbons, tobacco smoke components, and vitamins.

Usage

```
aylward2014
```

Format

data.frame

Source

Kapraun DF, Sfeir M, Pearce RG, Davidson-Fritz SE, Lumen A, Dallmann A, Judson RS, Wambaugh JF (2022). "Evaluation of a rapid, generic human gestational dose model." *Reproductive Toxicology*, **113**, 172–188. doi:10.1016/j.reprotox.2022.09.004.

References

Aylward LL, Hays SM, Kirman CR, Marchitti SA, Kenneke JF, English C, Mattison DR, Becker RA (2014). "Relationships of chemical concentrations in maternal and cord blood: a review of available data." *Journal of Toxicology and Environmental Health, Part B*, **17**(3), 175–203. doi:10.1080/10937404.2014.884956.

---

benchmark_httk *Assess the current performance of httk relative to historical benchmarks*

Description

The function performs a series of "sanity checks" and predictive performance benchmarks so that the impact of changes to the data, models, and implementation of the R package can be tested. Plots can be generated showing how the performance of the current version compares with past releases of httk.

Usage

```
benchmark_httk(
  basic.check = TRUE,
  calc_mc_css.check = TRUE,
  in_vivo_stats.check = TRUE,
  tissuepc.check = TRUE,
  suppress.messages = TRUE,
  make.plots = TRUE
)
```

Arguments

basic.check	Whether to run the basic checks, including uM and mg/L units for calc_analytic_css, calc_mc_css, and solve_pbtk as well as the number of chemicals with sufficient data to run the steady_state model (defaults to TRUE)
calc_mc_css.check	Whether to check the Monte Carlo sample. A comparison of the output of calc_mc_css to the SimCyp outputs reported in the Wetmore et al. (2012,2015) papers is performed. A comparison between the output of calc_analytic_css (no Monte Carlo) to the median of the output of calc_mc_css is also performed. (defaults to TRUE)
in_vivo_stats.check	Whether to compare the outputs of calc_mc_css and calc_tkstats to in vivo measurements of Css, AUC, and Cmax collected by Wambaugh et al. (2018). (defaults to TRUE)
tissuepc.check	Whether to compare the tissue-specific partition coefficient predictions from the calibrated Schmitt (2008) model to the in vivo data-derived estimates compiled by Pearce et al. (2017). (defaults to TRUE)
suppress.messages	Whether or not output messages are suppressed (defaults to TRUE)
make.plots	Whether current benchmarks should be plotted with historical performance (defaults to TRUE)

Details

Historically some refinements made to one aspect of httk have unintentionally impacted other aspects. Most notably errors have occasionally been introduced with respect to units (v1.9, v2.1.0). This benchmarking tool is intended to reduce the chance of these errors occurring in the future.

Past performance was retroactively evaluated by manually installing previous versions of the package from https://cran.r-project.org/src/contrib/Archive/httk/ and then adding the code for benchmark_httk at the command line interface.

The basic tests are important – if the output units for key functions are wrong, not much can be right. Past unit errors were linked to an incorrect unit conversions made within an individual function. Since the usage of convert_units became standard throughout httk, unit problems are hopefully less likely.

There are two Monte Carlo tests. One compares calc_mc_css 95th percentile steady-state plasma concentrations for a 1 mg/kg/day exposure against the Css values calculated by SimCyp and reported in Wetmore et al. (2012,2015). These have gradually diverged as the assumptions for httk have shifted to better describe non-pharmaceutical, commercial chemicals.

The in vivo tests are in some ways the most important, as they establish the overall predictability for httk for Cmax, AUC, and Css. The in vivo statistics are currently based on comparisons to the in vivo data compiled by Wambaugh et al. (2018). We see that when the tissue partition coefficient calibrations were introduced in v1.6 that the overall predictability for in vivo endpoints was reduced (increased RMSLE). If this phenomena continues as new in vivo evaluation data become available, we may need to revisit whether evaluation against experimentally-derived partition coefficients can actually be used for calibration, or just merely for establishing confidence intervals.

The partition coefficient tests provide an important check of the httk implementation of the Schmitt (2008) model for tissue:plasma equilibrium distribution. These predictions heavily rely on accurate description of tissue composition and the ability to predict the ionization state of the compounds being modeled.

Value

named list, whose elements depend on the selected checks

basic	A list with four metrics: N.steadystate – Number of chemicals with sufficient data for steady-state IVIVE c
calc_mc_css	A list with four metrics: RMSLE.Wetmore – Root mean squared log10 error (RMSLE) in predicted Css be
in_vivo_stats	A list with two metrics: RMSLE.InVivoCss – RMSLE between the predictions of `calc_analytic_css` an
units.plot	A ggplot2 figure showing units tests of various functions. Output is generated for mg/L and uM, and then t
invivo.rmsle.plot	A ggplot2 figure comparing model predictions to in vivo measured values. Output generated is the root me
model.rmsle.plot	A ggplot2 figure comparing various functions values against values predicted by other models (chiefly Sim
count.plot	A ggplot2 figure showing count of chemicals of various functions. Output generated is a count of the chem

Author(s)

John Wambaugh

References

Davidson-Fritz SE, Ring CL, Evans MV, Schacht CM, Chang X, Breen M, Honda GS, Kenyon E, Linakis MW, Meade A, others (2025). "Enabling Transparent Toxicokinetic Modeling for Public Health Risk Assessment." *PLOS ONE*, **20**(4), 1-40. doi:10.1371/journal.pone.0321321.

`blood_mass_correct` *Find average blood masses by age.*

Description

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

Usage

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

Arguments

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

Value

A vector of blood masses in kg.

Author(s)

Caroline Ring

References

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

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

`blood_weight` *Predict blood mass.*

Description

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

Usage

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

Arguments

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

Value

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

Author(s)

Caroline Ring

References

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

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

`bmiage` *CDC BMI-for-age charts*

Description

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

Usage

```
bmiage
```

Format

A data.table with 434 rows and 5 variables:

Sex Female or Male

Agemos Age in months

P5 The 5th percentile BMI for the corresponding sex and age

P85 The 85th percentile BMI for the corresponding sex and age

P95 The 95th percentile BMI for the corresponding sex and age

Details

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

Underweight <5th percentile

Normal weight 5th-85th percentile

Overweight 85th-95th percentile

Obese >=95th percentile

Author(s)

Caroline Ring

Source

https://www.cdc.gov/growthcharts/data/zscore/bmiagerev.csv

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

body_surface_area *Predict body surface area.*

Description

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

Usage

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

Arguments

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

Value

A vector of body surface areas in cm^2.

Author(s)

Caroline Ring

References

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

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

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

bone_mass_age *Predict bone mass*

Description

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

Usage

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

Arguments

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

Value

Vector of bone masses.

Author(s)

Caroline Ring

References

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

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

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

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

`brain_mass` *Predict brain mass.*

Description

Predict brain mass from gender and age.

Usage

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

Arguments

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

Value

A vector of brain masses in kg.

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

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

Description

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

Usage

```
calc_analytic_css(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  species = "human",
  daily.dose = NULL,
  dose = 1,
  dose.units = "mg/kg/day",
  route = "oral",
  output.units = "uM",
  model = "pbtk",
  concentration = "plasma",
  suppress.messages = FALSE,
  tissue = NULL,
  bioactive.free.invivo = FALSE,
  IVIVE = NULL,
  parameterize.args.list = list(),
  ...
)
```

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_pbtk (for model = 'pbtk'), parameterize_3comp (for model = '3compartment), parameterize_1comp(for model = '1compartment') or parameterize_steadystate (for model = '3compartmentss'), overrides chem.name and chem.cas.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
daily.dose	Total daily dose, mg/kg BW.
dose	The amount of chemial to which the individual is exposed.
dose.units	The units associated with the dose received.
route	Route of exposure (either "oral", "iv", or "inhalation" default "oral").
output.units	Units for returned concentrations, defaults to uM (specify units = "uM") but can also be mg/L.
model	Model used in calculation,'gas_pbtk' for the gas pbtk model, 'pbtk' for the multiple compartment model, '3compartment' for the three compartment model, '3compartmentss' for the three compartment steady state model, and '1compartment' for one compartment model.
concentration	Desired concentration type: 'blood','tissue', or default 'plasma'. In the case that the concentration is for plasma, selecting "blood" will use the blood:plasma ratio

to estimate blood concentration. In the case that the argument 'tissue' specifies a particular tissue of the body, concentration defaults to 'tissue' – that is, the concentration in the If cocentration is set to 'blood' or 'plasma' and 'tissue' specifies a specific tissue then the value returned is for the plasma or blood in that specific tissue.

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

`tissue`
: Desired steady state tissue concentration. Default is of NULL typically gives whole body plasma concentration.

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

`IVIVE`
: Honda et al. (2019) identified four plausible sets of assumptions for *in vitro-in vivo* extrapolation (IVIVE) assumptions. Argument may be set to "Honda1" through "Honda4". If used, this function overwrites the tissue, restrictive.clearance, and bioactive.free.invivo arguments. See Details below for more information.

`parameterize.args.list`
: List of arguments passed to model's associated parameterization function, including default.to.human, adjusted.Funbound.plasma, regression, and minimum.Funbound.plasma. The default.to.human argument substitutes missing animal values with human values if true, adjusted.Funbound.plasma returns adjusted Funbound.plasma when set to TRUE along with parition coefficients calculated with this value, regression indicates whether or not to use the regressions in calculating partition coefficients, and minimum.Funbound.plasma is the value to which Monte Carlo draws less than this value are set (default is 0.0001 – half the lowest measured Fup in our dataset).

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

Details

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

Only four sets of IVIVE assumptions that performed well in Honda et al. (2019) are currently included in `honda.ivive`: "Honda1" through "Honda4". The use of max (peak) concentration can not be currently be calculated with `calc_analytic_css`. The httk default settings correspond to "Honda3":

	In Vivo Conc.	Metabolic Clearance	Bioactive Chemical Conc. *In Vivo*	TK Statistic Used*	Bioactive C
Honda1	Veinous (Plasma)	Restrictive	Free	Mean Conc. In Vivo	
Honda2	Veinous	Restrictive	Free	Mean Conc. In Vivo	
Honda3	Veinous	Restrictive	Total	Mean Conc. In Vivo	
Honda4	Target Tissue	Non-restrictive	Total	Mean Conc. In Vivo	

"Honda1" uses plasma concentration, restrictive clearance, and treats the unbound invivo concentration as bioactive. For IVIVE, any input nominal concentration in vitro should be converted to cfree.invitro using armitage_eval, otherwise performance will be the same as "Honda2".

Value

Steady state plasma concentration in specified units

Author(s)

Robert Pearce, John Wambaugh, Greg Honda, Miyuki Breen

References

Honda GS, Pearce RG, Pham LL, Setzer RW, Wetmore BA, Sipes NS, Gilbert J, Franz B, Thomas RS, Wambaugh JF (2019). "Using the concordance of in vitro and in vivo data to evaluate extrapolation assumptions." *PloS one*, **14**(5), e0217564. doi:10.1371/journal.pone.0217564.

See Also

calc_css

Examples

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


# Test that the underlying PK models give the same answers:
calc_analytic_css(chem.cas="15972-60-8")
calc_analytic_css(chem.cas="15972-60-8",model="1compartment")
calc_analytic_css(chem.cas="15972-60-8",model="pbtk")
calc_analytic_css(chem.cas="15972-60-8",model="3compartment")

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

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

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

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

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

# Try various chemicals with differing parameter sources/issues:
calc_analytic_css(chem.name="Betaxolol")
calc_analytic_css(chem.name="Tacrine",model="pbtk")
```

```
calc_analytic_css(chem.name="Dicofol",model="1compartment")
calc_analytic_css(chem.name="Diflubenzuron",model="3compartment")
calc_analytic_css(chem.name="Theobromine",model="3compartmentss")

# permutations on steady-state for the 1compartment model
calc_analytic_css(chem.name="bisphenol a",
                  model="1compartment")
calc_analytic_css(chem.cas="80-05-7",
                  model="1compartment")
calc_analytic_css(parameters=parameterize_1comp(chem.cas="80-05-7"),
                  model="1compartment")
calc_analytic_css(chem.cas="80-05-7",
                  model="1compartment",
                  tissue="liver")
calc_analytic_css(chem.cas="80-05-7",
                  model="1compartment",
                  tissue="brain")

# permutations on steady-state for the 3compartment model
calc_analytic_css(chem.cas="80-05-7",
                  model="3compartment")
calc_analytic_css(parameters=parameterize_3comp(chem.cas="80-05-7"),
                  model="3compartment")
calc_analytic_css(chem.name="bisphenol a",
                  model="3compartment",
                  tissue="liver")
calc_analytic_css(chem.name="bisphenol a",
                  model="3compartment",
                  tissue="brain")

# permurtations on steady-state for the pbtk model:
calc_analytic_css(chem.cas="80-05-7",
                  model="pbtk")
calc_analytic_css(parameters=parameterize_pbtk(chem.cas="80-05-7"),
                  model="pbtk")
calc_analytic_css(chem.name="bisphenol a",
                  model="pbtk",
                  tissue="liver")
calc_analytic_css(chem.name="bisphenol a",
                  model="pbtk",
                  tissue="brain")

# Test oral absorption functionality:
# By default we now include calculation of Fabs and Fgut (always had Fhep):
calc_analytic_css(chem.name="bisphenol a",
                  model="pbtk")
# Therefore if we set Fabs = Fgut = 1 with keetit100=TRUE, we should get a
# higher predicted plasma steady-state concentration:
calc_analytic_css(chem.name="bisphenol a",
                  model="pbtk",
                  Caco2.options=list(keepit100=TRUE))
```

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

Description

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

Usage

```
calc_analytic_css_1comp(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  dosing = list(daily.dose = 1),
  hourly.dose = NULL,
  dose.units = "mg",
  concentration = "plasma",
  suppress.messages = FALSE,
  recalc.blood2plasma = FALSE,
  tissue = NULL,
  restrictive.clearance = TRUE,
  bioactive.free.invivo = FALSE,
  Caco2.options = list(),
  ...
)
```

Arguments

`chem.name`	Either the chemical name, CAS number, or the parameters must be specified.
`chem.cas`	Either the chemical name, CAS number, or the parameters must be specified.
`dtxsid`	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
`parameters`	Chemical parameters from parameterize_pbtk (for model = 'pbtk'), parameterize_3comp (for model = '3compartment), parameterize_1comp(for model = '1compartment') or parameterize_steadystate (for model = '3compartmentss'), overrides chem.name and chem.cas.
`dosing`	List of dosing metrics used in simulation, which includes the namesake entries of a model's associated dosing.params. For steady-state calculations this is likely to be either "daily.dose" for oral exposures or "Cinhaled" for inhalation.
`hourly.dose`	Hourly dose rate mg/kg BW/h.
`dose.units`	The units associated with the dose received.

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

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

`recalc.blood2plasma`
Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters. Use this if you have altered hematocrit, Funbound.plasma, or Krbc2pu.

`tissue` Desired tissue conentration (defaults to whole body concentration.)

`restrictive.clearance`
If TRUE (default), then only the fraction of chemical not bound to protein is available for metabolism in the liver. If FALSE, then all chemical in the liver is metabolized (faster metabolism due to rapid off-binding).

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

`Caco2.options` A list of options to use when working with Caco2 apical to basolateral data `Caco2.Pab`, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = `Fabs`. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = `Fgut`. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See `get_fbio` for further details.

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

Value

Steady state plasma concentration in mg/L units

Author(s)

Robert Pearce and John Wambaugh

See Also

`calc_analytic_css`

`parameterize_1comp`

`calc_analytic_css_3comp` *Calculate the analytic steady state concentration for model 3compartment*

Description

This function calculates the analytic steady state plasma or blood concentrations as a result of constant oral infusion dosing. The three compartment model (Pearce et al. 2017) describes the amount of chemical in three key tissues of the body: the liver, the portal vein (essentially, oral absorption from the gut), and a systemic compartment ("sc") representing the rest of the body. See `solve_3comp` for additional details. The analytical steady-state solution for the the three compartment model is:

$$C_{plasma}^{ss} = \frac{dose}{f_{up} * Q_{GFR} + Cl_h + \frac{Cl_h}{Q_l}\frac{f_{up}}{R_{b:p}}Q_{GFR}}$$

$$C_{blood}^{ss} = R_{b:p} * C_{plasma}^{ss}$$

where Q_GFR is the glomerular filtration rate in the kidney, Q_l is the total liver blood flow (hepatic artery plus total vein), Cl_h is the chemical-specific whole liver metabolism clearance (scaled up from intrinsic clearance, which does not depend on flow), f_up is the chemical-specific fraction unbound in plasma, R_b:p is the chemical specific ratio of concentrations in blood:plasma.

Usage

```
calc_analytic_css_3comp(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  dosing = list(daily.dose = 1),
  hourly.dose = NULL,
  dose.units = "mg",
  concentration = "plasma",
  suppress.messages = FALSE,
  recalc.blood2plasma = FALSE,
  tissue = NULL,
  restrictive.clearance = TRUE,
  bioactive.free.invivo = FALSE,
  Caco2.options = list(),
  ...
)
```

Arguments

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

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

parameters — Chemical parameters from parameterize_pbtk (for model = 'pbtk'), parameterize_3comp (for model = '3compartment), parameterize_1comp(for model = '1compartment') or parameterize_steadystate (for model = '3compartmentss'), overrides chem.name and chem.cas.

dosing — List of dosing metrics used in simulation, which includes the namesake entries of a model's associated dosing.params. For steady-state calculations this is likely to be either "daily.dose" for oral exposures or "Cinhaled" for inhalation.

hourly.dose — Hourly dose rate mg/kg BW/h.

dose.units — The units associated with the dose received.

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

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

recalc.blood2plasma — Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters. Use this if you have altered hematocrit, Funbound.plasma, or Krbc2pu.

tissue — Desired tissue conentration (defaults to whole body concentration.)

restrictive.clearance — If TRUE (default), then only the fraction of chemical not bound to protein is available for metabolism in the liver. If FALSE, then all chemical in the liver is metabolized (faster metabolism due to rapid off-binding).

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

Caco2.options — A list of options to use when working with Caco2 apical to basolateral data Caco2.Pab, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = Fabs. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = Fgut. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See get_fbio for further details.

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

Value

Steady state plasma concentration in mg/L units

Author(s)

Robert Pearce and John Wambaugh

References

Pearce RG, Setzer RW, Strope CL, Wambaugh JF, Sipes NS (2017). "Httk: R package for high-throughput toxicokinetics." *Journal of Statistical Software*, **79**(4), 1. doi:10.18637/jss.v079.i04.

See Also

calc_analytic_css

parameterize_3comp

`calc_analytic_css_3comp2` *Calculate the analytic steady state concentration for model 3compartment*

Description

This function calculates the analytic steady state plasma or blood concentrations as a result of constant oral infusion dosing. The three compartment model (Pearce et al. 2017) describes the amount of chemical in three key tissues of the body: the liver, the portal vein (essentially, oral absorption from the gut), and a systemic compartment ("sc") representing the rest of the body. See solve_3comp for additional details. The analytical steady-state solution for the the three compartment model is:

$$C^{ss}_{plasma} = \frac{dose}{f_{up} * Q_{GFR} + Cl_h + \frac{Cl_h}{Q_l}\frac{f_{up}}{R_{b:p}}Q_{GFR}}$$

$$C^{ss}_{blood} = R_{b:p} * C^{ss}_{plasma}$$

where Q_GFR is the glomerular filtration rate in the kidney, Q_l is the total liver blood flow (hepatic artery plus total vein), Cl_h is the chemical-specific whole liver metabolism clearance (scaled up from intrinsic clearance, which does not depend on flow), f_up is the chemical-specific fraction unbound in plasma, R_b:p is the chemical specific ratio of concentrations in blood:plasma.

Usage

```
calc_analytic_css_3comp2(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  dosing = list(daily.dose = 1),
  hourly.dose = NULL,
  dose.units = "mg",
  concentration = "plasma",
  suppress.messages = FALSE,
  recalc.blood2plasma = FALSE,
  tissue = NULL,
  route = "oral",
```

```
  restrictive.clearance = TRUE,
  bioactive.free.invivo = FALSE,
  Caco2.options = list(),
  exhalation = TRUE,
  ...
)
```

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_pbtk (for model = 'pbtk'), parameterize_3comp (for model = '3compartment), parameterize_1comp(for model = '1compartment') or parameterize_steadystate (for model = '3compartmentss'), overrides chem.name and chem.cas.
dosing	List of dosing metrics used in simulation, which includes the namesake entries of a model's associated dosing.params. For steady-state calculations this is likely to be either "daily.dose" for oral exposures or "Cinhaled" for inhalation.
hourly.dose	Hourly dose rate mg/kg BW/h.
dose.units	The units associated with the dose received.
concentration	Desired concentration type, 'blood' or default 'plasma'.
suppress.messages	Whether or not the output message is suppressed.
recalc.blood2plasma	Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters. Use this if you have altered hematocrit, Funbound.plasma, or Krbc2pu.
tissue	Desired tissue conentration (defaults to whole body concentration.)
route	Route of exposure ("inhalation" or [DEFAULT] "oral").
restrictive.clearance	If TRUE (default), then only the fraction of chemical not bound to protein is available for metabolism in the liver. If FALSE, then all chemical in the liver is metabolized (faster metabolism due to rapid off-binding).
bioactive.free.invivo	If FALSE (default), then the total concentration is treated as bioactive in vivo. If TRUE, the the unbound (free) plasma concentration is treated as bioactive in vivo. Only works with tissue = NULL in current implementation.
Caco2.options	A list of options to use when working with Caco2 apical to basolateral data Caco2.Pab, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = Fabs. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral,

	otherwise fgut.oral = Fgut. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See get_fbio for further details.
exhalation	A Boolean (TRUE/FALSE) indicating whether exhalation is included as a route of potential clearance (Defaults to TRUE).
...	Additional parameters passed to parameterize function if parameters is NULL.

Value

Steady state plasma concentration in mg/L units

Author(s)

Robert Pearce and John Wambaugh

References

Pearce RG, Setzer RW, Strope CL, Wambaugh JF, Sipes NS (2017). "Httk: R package for high-throughput toxicokinetics." *Journal of Statistical Software*, **79**(4), 1. doi:10.18637/jss.v079.i04.

See Also

calc_analytic_css

parameterize_3comp

---

calc_analytic_css_3compss

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

---

Description

This function calculates the steady state plasma or venous blood concentrations as a result of constant oral infusion dosing. The equation, initally used for high throughput in vitro-in vivo extrapolation in (Rotroff et al. 2010) and later given in (Wetmore et al. 2012), assumes that the concentration is the inverse of the total clearance, which is the sum of hepatic metabolism and renal filatrion:

$$C^{ss}_{plasma} = \frac{dose}{f_{up} * Q_{GFR} + Cl_h}$$

$$C^{ss}_{blood} = R_{b:p} * C^{ss}_{plasma}$$

where Q_GFR is the glomerular filtration rate in the kidney, Cl_h is the chemical-specific whole liver metabolism clearance (scaled up from intrinsic clearance, which does not depend on flow), f_up is the chemical-specific fraction unbound in plasma, R_b:p is the chemical specific ratio of concentrations in blood:plasma.

Usage

```
calc_analytic_css_3compss(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  dosing = list(daily.dose = 1),
  hourly.dose = NULL,
  dose.units = "mg",
  concentration = "plasma",
  suppress.messages = FALSE,
  recalc.blood2plasma = FALSE,
  tissue = NULL,
  restrictive.clearance = TRUE,
  bioactive.free.invivo = FALSE,
  Caco2.options = list(),
  ...
)
```

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_pbtk (for model = 'pbtk'), parameterize_3comp (for model = '3compartment), parameterize_1comp(for model = '1compartment') or parameterize_steadystate (for model = '3compartmentss'), overrides chem.name and chem.cas.
dosing	List of dosing metrics used in simulation, which includes the namesake entries of a model's associated dosing.params. For steady-state calculations this is likely to be either "daily.dose" for oral exposures or "Cinhaled" for inhalation.
hourly.dose	Hourly dose rate mg/kg BW/h.
dose.units	The units associated with the dose received.
concentration	Desired concentration type, 'blood' or default 'plasma'.
suppress.messages	Whether or not the output message is suppressed.
recalc.blood2plasma	Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters. Use this if you have 'altered hematocrit, Funbound.plasma, or Krbc2pu.
tissue	Desired tissue concentration (defaults to whole body concentration.)
restrictive.clearance	If TRUE (default), then only the fraction of chemical not bound to protein is available for metabolism in the liver. If FALSE, then all chemical in the liver is metabolized (faster metabolism due to rapid off-binding).

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

`Caco2.options`
: A list of options to use when working with Caco2 apical to basolateral data `Caco2.Pab`, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = `Fabs`. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = `Fgut`. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See `get_fbio` for further details.

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

Details

This equation is a simplification of the steady-state plasma concentration in the three-comprtment model (see `solve_3comp`), neglecting a higher order term that causes this Css to be higher for very rapidly cleared chemicals.

Value

Steady state plasma concentration in mg/L units

Author(s)

Robert Pearce and John Wambaugh

References

Rotroff DM, Wetmore BA, Dix DJ, Ferguson SS, Clewell HJ, Houck KA, LeCluyse EL, Andersen ME, Judson RS, Smith CM, others (2010). "Incorporating human dosimetry and exposure into high-throughput in vitro toxicity screening." *Toxicological Sciences*, **117**(2), 348–358. doi:10.1093/toxsci/kfq220.

Wetmore BA, Wambaugh JF, Ferguson SS, Sochaski MA, Rotroff DM, Freeman K, Clewell III HJ, Dix DJ, Andersen ME, Houck KA, others (2012). "Integration of dosimetry, exposure, and high-throughput screening data in chemical toxicity assessment." *Toxicological Sciences*, **125**(1), 157–174. doi:10.1093/toxsci/kfr254.

See Also

`calc_analytic_css`

`parameterize_steadystate`

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

Description

This function calculates the analytic steady state concentration (mg/L) as a result of constant oral infusion dosing. Concentrations are returned for plasma by default, but various tissues or blood concentrations can also be given as specified.

Usage

```
calc_analytic_css_pbtk(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  dosing = list(daily.dose = 1),
  hourly.dose = NULL,
  dose.units = "mg",
  concentration = "plasma",
  suppress.messages = FALSE,
  recalc.blood2plasma = FALSE,
  tissue = NULL,
  restrictive.clearance = TRUE,
  bioactive.free.invivo = FALSE,
  Caco2.options = list(),
  ...
)
```

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_pbtk (for model = 'pbtk'), parameterize_3comp (for model = '3compartment), parameterize_1comp(for model = '1compartment') or parameterize_steadystate (for model = '3compartmentss'), overrides chem.name and chem.cas.
dosing	List of dosing metrics used in simulation, which includes the namesake entries of a model's associated dosing.params. For steady-state calculations this is likely to be either "daily.dose" for oral exposures or "Cinhaled" for inhalation.
hourly.dose	Hourly dose rate mg/kg BW/h.

`dose.units` The units associated with the dose received.

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

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

`recalc.blood2plasma` Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters. Use this if you have altered hematocrit, Funbound.plasma, or Krbc2pu.

`tissue` Desired tissue conentration (defaults to whole body concentration.)

`restrictive.clearance` If TRUE (default), then only the fraction of chemical not bound to protein is available for metabolism in the liver. If FALSE, then all chemical in the liver is metabolized (faster metabolism due to rapid off-binding).

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

`Caco2.options` A list of options to use when working with Caco2 apical to basolateral data `Caco2.Pab`, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = `Fabs`. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = `Fgut`. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See `get_fbio` for further details.

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

Details

The PBTK model (Pearce et al. 2017) predicts the amount of chemical in various tissues of the body. A system of ordinary differential equations describes how the amounts in each tissue change as a function of time. The analytic steady-state equation was found by algebraically solving for the tissue concentrations that result in each equation being zero – thus determining the concentration at which there is no change over time as the result of a fixed infusion dose rate.

The analytical solution is:

$$C_{ven}^{ss} = \frac{doserate * \frac{Q_{liver}+Q_{gut}}{\frac{f_{up}}{R_{b:p}} * Cl_{metabolism} + (Q_{liver}+Q_{gut})}}{Q_{cardiac} - \frac{(Q_{liver}+Q_{gut})^2}{\frac{f_{up}}{R_{b:p}} * Cl_{metabolism} + (Q_{liver}+Q_{gut})} - \frac{(Q_{kidney})^2}{\frac{f_{up}}{R_{b:p}} * Q_{GFR} + Q_{kideny}} - Q_{rest}}$$

$$C_{plasma}^{ss} = \frac{C_{ven}^{ss}}{R_{b:p}}$$

$$C_{tissue}^{ss} = \frac{K_{tissue:fuplasma} * f_{up}}{R_{b:p}} * C_{ven}^{ss}$$

where Q_cardiac is the cardiac output, Q_gfr is the glomerular filtration rate in the kidney, other Q's indicate blood flows to various tissues, Cl_metabolism is the chemical-specific whole liver metabolism clearance, f_up is the chemical-specific fraction unbound in plasma, R_b2p is the chemical specific ratio of concentrations in blood:plasma, K_tissue2fuplasma is the chemical- and tissue-specific equilibrium partition coefficient and dose rate has units of mg/kg/day.

Value

Steady state plasma concentration in mg/L units

Author(s)

Robert Pearce and John Wambaugh

References

Pearce RG, Setzer RW, Strope CL, Wambaugh JF, Sipes NS (2017). "Httk: R package for high-throughput toxicokinetics." *Journal of Statistical Software*, **79**(4), 1. doi:10.18637/jss.v079.i04.

See Also

calc_analytic_css

parameterize_pbtk

`calc_analytic_css_sumclearances` *Calculate the steady state concentration for the sum of clearances steady-state model with exhalation*

Description

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

Usage

```
calc_analytic_css_sumclearances(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  dosing = list(daily.dose = 1),
  hourly.dose = NULL,
  dose.units = "mg",
  concentration = "plasma",
  species = "human",
  Caco2.options = NULL,
```

```
  suppress.messages = FALSE,
  recalc.blood2plasma = FALSE,
  tissue = NULL,
  route = "oral",
  restrictive.clearance = TRUE,
  bioactive.free.invivo = FALSE,
  ...
)
```

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_sumclearances overrides chem.name and chem.cas.
dosing	List of dosing metrics used in simulation, which includes the namesake entries of a model's associated dosing.params. For steady-state calculations this is likely to be either "daily.dose" for oral exposures or "Cinhaled" for inhalation.
hourly.dose	Hourly dose rate mg/kg BW/h.
dose.units	The units associated with the dose received.
concentration	Desired concentration type, 'blood' or default 'plasma'.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
Caco2.options	A list of options to use when working with Caco2 apical to basolateral data Caco2.Pab, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = Fabs. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = Fgut. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See get_fbio for further details.
suppress.messages	Whether or not the output message is suppressed.
recalc.blood2plasma	Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters. Use this if you have 'altered hematocrit, Funbound.plasma, or Krbc2pu.
tissue	Desired tissue concentration (defaults to whole body concentration.)
route	Route of exposure ("inhalation" or [DEFAULT] "oral").
restrictive.clearance	If TRUE (default), then only the fraction of chemical not bound to protein is available for metabolism in the liver. If FALSE, then all chemical in the liver is metabolized (faster metabolism due to rapid off-binding).

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

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

Value

Steady state plasma concentration in mg/L units

Author(s)

John Wambaugh

See Also

calc_analytic_css

parameterize_steadystate

---

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

Description

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

Usage

```
calc_css(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  species = "Human",
  f = 0.01,
  daily.dose = 1,
  doses.per.day = 3,
  dose.units = "mg/kg",
  route = "oral",
  days = 21,
  output.units = "uM",
  suppress.messages = FALSE,
  tissue = NULL,
  model = "pbtk",
```

```
  f.change = 1e-05,
  dosing = NULL,
  parameterize.args.list = list(),
  ...
)
```

Arguments

chem.name	Either the chemical name, CAS number, or parameters must be specified.
chem.cas	Either the chemical name, CAS number, or parameters must be specified.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_pbtk function, overrides chem.name and chem.cas.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
f	Fractional distance from the final steady state concentration that the average concentration must come within to be considered at steady state.
daily.dose	Total daily dose, mg/kg BW.
doses.per.day	Number of oral doses per day.
dose.units	The units associated with the dose received.
route	Route of exposure (either "oral", "iv", or "inhalation" default "oral").
days	Initial number of days to run simulation that is multiplied on each iteration.
output.units	Units for returned concentrations, defaults to uM (specify units = "uM") but can also be mg/L.
suppress.messages	Whether or not to suppress messages.
tissue	Desired tissue concentration (default value is NULL, will depend on model – see steady.state.compartment in model.info file for further details.)
model	Model used in calculation, 'pbtk' for the multiple compartment model,'3compartment' for the three compartment model, and '1compartment' for the one compartment model.
f.change	Fractional change of daily steady state concentration reached to stop calculating.
dosing	The dosing object for more complicated scenarios. Defaults to repeated daily.dose spread out over doses.per.day
parameterize.args.list	Named list of any additional arguments passed to model parameterization function (other than the already-named arguments). Default 'list()' to pass no additional arguments.
...	Additional arguments passed to solve_model (defaults model is "pbtk").

Value

frac	Ratio of the mean concentration on the day steady state is reached (baed on doses.per.day) to the analytical Css (based on infusion dosing).
max	The maximum concentration of the simulation.
avg	The average concentration on the final day of the simulation.
the.day	The day the average concentration comes within 100 * p percent of the true steady state concentration.

Author(s)

Robert Pearce, John Wambaugh

See Also

calc_analytic_css

Examples

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


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

out <- solve_pbtk(chem.name = "Bisphenol A",
  days = 50,
  daily.dose=1,
  doses.per.day = 3)
plot.data <- as.data.frame(out)

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

print(c.vs.t)


calc_css(chem.name='nicotine', model="1compartment")

calc_css(chem.name='nicotine', model="3compartment")

calc_css(chem.name="endrin")
```

calc_dow *Calculate the distribution coefficient*

Description

This function estimates the ratio of the equilibrium concentrations of a compound in octanol and water, taking into account the charge of the compound. Given the pH, we assume the neutral (uncharged) fraction of compound partitions according to the hydrophobicity (P_{ow}). We assume that only a fraction alpha (defaults to 0.001 – Schmitt (2008)) of the charged compound partitions into lipid (octanol):

$$D_{ow} = P_{ow} * (F_{neutral} + \alpha * F_{charged})$$

Fractions charged are calculated according to hydrogen ionization equilibria (pKa_Donor, pKa_Accept) using calc_ionization.

Usage

```
calc_dow(
  Pow = NULL,
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  pH = NULL,
  pKa_Donor = NULL,
  pKa_Accept = NULL,
  fraction_charged = NULL,
  alpha = 0.001
)
```

Arguments

Pow	Octanol:water partition coefficient (ratio of concentrations)
chem.cas	Either the chemical name or the CAS number must be specified.
chem.name	Either the chemical name or the CAS number must be specified.
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from a parameterize_MODEL function, overrides chem.name and chem.cas.
pH	pH where ionization is evaluated.
pKa_Donor	Compound H dissociation equilibirum constant(s). Overwrites chem.name and chem.cas.
pKa_Accept	Compound H association equilibirum constant(s). Overwrites chem.name and chem.cas.
fraction_charged	Fraction of chemical charged at the given pH

alpha — Ratio of Distribution coefficient D of totally charged species and that of the neutral form

Value

Distribution coefficient (numeric)

Author(s)

Robert Pearce and John Wambaugh

References

Schmitt W (2008). "General approach for the calculation of tissue to plasma partition coefficients." *Toxicology in vitro*, **22**(2), 457–467. doi:10.1016/j.tiv.2007.09.010.

Pearce RG, Setzer RW, Davis JL, Wambaugh JF (2017). "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." *Journal of pharmacokinetics and pharmacodynamics*, **44**, 549–565. doi:10.1007/s1092801795487.

Strope CL, Mansouri K, Clewell III HJ, Rabinowitz JR, Stevens C, Wambaugh JF (2018). "High-throughput in-silico prediction of ionization equilibria for pharmacokinetic modeling." *Science of The Total Environment*, **615**, 150–160. doi:10.1016/j.scitotenv.2017.09.033.

See Also

calc_ionization

---

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

Description

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

Usage

```
calc_elimination_rate(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  species = "Human",
  model = "3compartmentss",
  suppress.messages = TRUE,
  ...
)
```

Arguments

chem.cas	Either the cas number or the chemical name must be specified.
chem.name	Either the chemical name or the cas number must be specified.
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_steadystate or 1compartment function, overrides chem.name and chem.cas.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
model	The model used to calculate total clearance (defaults to "3compartmentss")
suppress.messages	Whether or not the output message is suppressed.
...	Additional parameters passed to parameterize function if parameters is NULL.

Details

Elimination rate calculated by dividing the total clearance (using the default -stirred hepatic model) by the volume of distribution. When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Value

Elimination rate
: Units of 1/h.

Author(s)

John Wambaugh

References

Schmitt W (2008). "General approach for the calculation of tissue to plasma partition coefficients." *Toxicology in vitro*, **22**(2), 457–467. doi:10.1016/j.tiv.2007.09.010.

Dawson DE, Ingle BL, Phillips KA, Nichols JW, Wambaugh JF, Tornero-Velez R (2021). "Designing QSARs for Parameters of High-Throughput Toxicokinetic Models Using Open-Source Descriptors." *Environmental Science & Technology*, **55**(9), 6505-6517. doi:10.1021/acs.est.0c06117, PMID: 33856768, https://doi.org/10.1021/acs.est.0c06117.

Kilford PJ, Gertz M, Houston JB, 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), 1194–1197. doi:10.1124/dmd.108.020834.

See Also

calc_total_clearance for calculation of total clearance

calc_vdist for calculation of volume of distribution

Examples

```
calc_elimination_rate(chem.name="Bisphenol A")

## Not run:

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

# non-restrictive clearance should be faster:
kelim1 <- calc_elimination_rate(chem.cas="80-05-7")
kelim2 <- calc_elimination_rate(chem.cas="80-05-7",
                                restrictive.clearance=FALSE)
if (!(kelim2 > kelim1)) stop("kelim2 is not faster than kelim1")

## End(Not run)
```

`calc_fbio.oral` *Functions for calculating the bioavaialble fractions from oral doses*

Description

These functions calculate the fraction of chemical absorbed from the gut based upon in vitro measured Caco-2 membrane permeability data. Caco-2 permeabilities (10^{-6} cm/s) are related to effective permeability based on Yang et al. (2007). These functions calculate the fraction absorbed (calc_fabs.oral – S Darwich et al. (2010) and Yu and Amidon (1999)), the fraction surviving first pass gut metabolism (calc_fgut.oral), and the overall systemic oral bioavailability (calc_fbio.oral). Note that the first pass hepatic clearance is calculated within the parameterization and other functions. using `calc_hep_bioavailability` Absorption rate is calculated according to Fick's law (LennernÄs (1997)) assuming low blood concentrations.

Usage

```
calc_fbio.oral(
  parameters = NULL,
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
  suppress.messages = FALSE,
  ...
)

calc_fabs.oral(
  parameters = NULL,
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
```

```
  suppress.messages = FALSE,
  Caco2.Pab.default = 1.6
)

calc_peff(
  parameters = NULL,
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
  suppress.messages = FALSE,
  Caco2.Pab = NULL,
  parameterize.args.list = list()
)

calc_kgutabs(
  parameters = NULL,
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
  suppress.messages = FALSE,
  parameterize.args.list = list()
)

calc_fgut.oral(
  parameters = NULL,
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
  suppress.messages = FALSE,
  Caco2.Pab.default = 1.6,
  parameterize.args.list = list()
)
```

Arguments

parameters	(List) A list of the parameters (Caco2.Pab, Funbound.Plasma, Rblood2plasma, Clint, BW, Qsmallintestine, Fabs, Fgut) used in the calculation, either supplied by user or calculated in parameterize_steadystate.
chem.cas	(Character) Chemical CAS number. (Defaults to 'NULL'.) (Note: Either the chemical name, CAS number, or EPA's DSSTox Structure ID must be specified).
chem.name	(Character) Chemical name. (Defaults to 'NULL'.) (Note: Either the chemical name, CAS number, or EPA's DSSTox Structure ID must be specified).
dtxsid	(Character) EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard). (Defaults to 'NULL'.) (Note: Either the chemical name, CAS number, or EPA's DSSTox Structure ID must be specified).

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

`suppress.messages` (Logical) Whether or not the output message is suppressed. (Defaults to 'FALSE'.)

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

`Caco2.Pab.default` (Numeric) Caco2 apical to basolateral data. (Defaults to 1.6.) (Not applicable for 'calc_fbio.oral'.)

`Caco2.Pab` (Numeric) Caco2 apical to basolaterial permeability used by calc_peff

`parameterize.args.list` List of arguments passed to `parameterize_steadystate`

Details

We assume that systemic oral bioavailability (F_{bio}) consists of three components: (1) the fraction of chemical absorbed from intestinal lumen into enterocytes (F_{abs}), (2) the fraction surviving intestinal metabolism (F_{gut}), and (3) the fraction surviving first-pass hepatic metabolism (F_{hep}). This function returns ($F_{abs} * F_{gut}$).

We model systemic oral bioavailability as $F_{bio} = F_{abs} * F_{gut} * F_{hep}$. F_{hep} is estimated from in vitro TK data using `calc_hep_bioavailability`. If F_{bio} has been measured in vivo and is found in table `chem.physical_and_invitro.data` then we set $F_{abs} * F_{gut}$ to the measured value divided by F_{hep}. Otherwise, if Caco2 membrane permeability data or predictions are available F_{abs} is estimated using `calc_fgut.oral`. Intrinsic hepatic metabolism is used to very roughly estimate (F_{gut}) using `calc_fgut.oral`. If argument keepit100 is used then there is complete absorption from the gut (that is, $F_{abs} = F_{gut} = 1$).

Value

`fbio.oral` Oral bioavailability, the fraction of oral dose reaching systemic distribution in the body.

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

`fgut.oral` Fraction of chemical surviving first pass metabolism in the gut.

`fhep.oral` Fraction of chemical surviving first pass hepatic clearance.

`kgutabs` Rate of absorption from gut (1/h).

Functions

- `calc_fabs.oral()`: Calculate the fraction absorbed in the gut (Darwich et al., 2010)
- `calc_peff()`: Calculate the effective gut permeability rate (10^-4 cm/s)
- `calc_kgutabs()`: Calculate the gut absorption rate (1/h)
- `calc_fgut.oral()`: Calculate the fraction of chemical surviving first pass metabolism in the gut

Author(s)

Gregory Honda and John Wambaugh

References

S Darwich A, Neuhoff S, Jamei M, Rostami-Hodjegan A (2010). "Interplay of metabolism and transport in determining oral drug absorption and gut wall metabolism: a simulation assessment using the 'Advanced Dissolution, Absorption, Metabolism (ADAM)' model." *Current drug metabolism*, **11**(9), 716–729. doi:10.2174/138920010794328913.

Yang J, Jamei M, Yeo KR, Tucker GT, Rostami-Hodjegan A (2007). "Prediction of intestinal first-pass drug metabolism." *Current drug metabolism*, **8**(7), 676–684. doi:10.2174/138920007782109733.

Honda GS, Kenyon EM, Davidson-Fritz S, Dinallo R, El Masri H, Korol-Bexell E, Li L, Angus D, Pearce RG, Sayre RR, others (2025). "Impact of gut permeability on estimation of oral bioavailability for chemicals in commerce and the environment." *ALTEX-Alternatives to animal experimentation*, **42**(1), 56–74. doi:10.14573/altex.2403271.

Yu LX, Amidon GL (1999). "A compartmental absorption and transit model for estimating oral drug absorption." *International journal of pharmaceutics*, **186**(2), 119–125. doi:10.1016/S0378-5173(99)001477.

LennernÄs H (1997). "Human jejunal effective permeability and its correlation with preclinical drug absorption models." *Journal of Pharmacy and Pharmacology*, **49**(7), 627–638. doi:10.1111/j.20427158.1997.tb06084.x.

`calc_fetal_phys` *Calculate maternal-fetal physiological parameters*

Description

This function uses the equations from Kapraun (2019) to calculate chemical- independent physiological paramreters as a function of gestational age in weeks.

Usage

```
calc_fetal_phys(week = 12, ...)
```

Arguments

`week`	Gestational week
`...`	Additional arguments to parameterize_fetal_pbtk

Details

$$BW = pre_pregnant_BW + BW_cubic_theta1 * tw + BW_cubic_theta2 * tw^2 + BW_cubic_theta3 * tw^3$$

$$Wadipose = Wadipose_linear_theta0 + Wadipose_linear_theta1 * tw;$$

$$Wfkidney = 0.001 * Wfkidney_gompertz_theta0 * exp(Wfkidney_gompertz_theta1 / Wfkidney_gompertz_theta2 * (1 - ex$$

$$Wfthyroid = 0.001*Wfthyroid_gompertz_theta0*exp(Wfthyroid_gompertz_theta1/Wfthyroid_gompertz_theta2*(1-$$

$$Wfliver = 0.001*Wfliver_gompertz_theta0*exp(Wfliver_gompertz_theta1/Wfliver_gompertz_theta2*(1-exp(-Wf$$

$$Wfbrain = 0.001*Wfbrain_gompertz_theta0*exp(Wfbrain_gompertz_theta1/Wfbrain_gompertz_theta2*(1-exp(-W$$

$$Wfgut = 0.001*Wfgut_gompertz_theta0*exp(Wfgut_gompertz_theta1/Wfgut_gompertz_theta2*(1-exp(-Wfgut_gom$$

$$Wflung = 0.001*Wflung_gompertz_theta0*exp(Wflung_gompertz_theta1/Wflung_gompertz_theta2*(1-exp(-Wflu$$

$$hematocrit = (hematocrit_quadratic_theta0+hematocrit_quadratic_theta1*tw+hematocrit_quadratic_theta2*pow(tw,$$

$$Rblood2plasma = 1 - hematocrit + hematocrit * Krbc2pu * Fraction_unbound_plasma;$$

$$fhematocrit = (fhematocrit_cubic_theta1*tw+fhematocrit_cubic_theta2*pow(tw,2)+fhematocrit_cubic_theta3*pow($$

$$Rfblood2plasma = 1-fhematocrit+fhematocrit*Kfrbc2pu*Fraction_unbound_plasma_fetus;$$

$$fBW = 0.001*fBW_gompertz_theta0*exp(fBW_gompertz_theta1/fBW_gompertz_theta2*(1-exp(-fBW_gompertz_th$$

$$Vplacenta = 0.001*(Vplacenta_cubic_theta1*tw+Vplacenta_cubic_theta2*pow(tw,2)+Vplacenta_cubic_theta3*pow(tw$$

$$Vamnf = 0.001*Vamnf_logistic_theta0/(1+exp(-Vamnf_logistic_theta1*(tw-Vamnf_logistic_theta2)));$$

$$Vplasma = Vplasma_mod_logistic_theta0/(1+exp(-Vplasma_mod_logistic_theta1*(tw-Vplasma_mod_logistic_theta2)))$$

$$Vrbcs = hematocrit/(1 - hematocrit) * Vplasma;$$

$$Vven = venous_blood_fraction * (Vrbcs + Vplasma);$$

$$Vart = arterial_blood_fraction * (Vrbcs + Vplasma);$$

$$Vadipose = 1/adipose_density * Wadipose;$$

$$Vffmx = 1/ffmx_density*(BW-Wadipose-(fBW+placenta_density*Vplacenta+amnf_density*Vamnf));$$

$$Vallx = Vart + Vven + Vthyroid + Vkidney + Vgut + Vliver + Vlung;$$

$$Vrest = Vffmx - Vallx;$$

$$Vfart = 0.001 * arterial_blood_fraction * fblood_weight_ratio * fBW;$$

$$Vfven = 0.001 * venous_blood_fraction * fblood_weight_ratio * fBW;$$

$$Vfkidney = 1/kidney_density * Wfkidney;$$

$$Vfthyroid = 1/thyroid_density * Wfthyroid;$$

$$Vfliver = 1/liver_density * Wfliver;$$

$$Vfbrain = 1/brain_density * Wfbrain;$$

$$Vfgut = 1/gut_density * Wfgut;$$

$$Vflung = 1/lung_density * Wflung;$$

$$Vfrest = fBW-(Vfart+Vfven+Vfbrain+Vfkidney+Vfthyroid+Vfliver+Vfgut+Vflung);$$

$$Qcardiac = 24*(Qcardiac_cubic_theta0+Qcardiac_cubic_theta1*tw+Qcardiac_cubic_theta2*pow(tw,2)+Qcardiac_cubic$$

$$Qgut = 0.01*(Qgut_percent_initial+(Qgut_percent_terminal-Qgut_percent_initial)/term*tw)*Qcardiac;$$

$$Qkidney = 24*(Qkidney_cubic_theta0+Qkidney_cubic_theta1*tw+Qkidney_cubic_theta2*pow(tw,2)+Qkidney_cubic_he$$

$$Qliver = 0.01*(Qliver_percent_initial+(Qliver_percent_terminal-Qliver_percent_initial)/term*tw)*Qcardiac;$$

$$Qthyroid = 0.01*(Qthyroid_percent_initial+(Qthyroid_percent_terminal-Qthyroid_percent_terminal)/term*tw)*Qc$$

$$Qplacenta = 24 * Qplacenta_linear_theta1 * 1000 * Vplacenta;$$

$$Qadipose = 0.01*(Qadipose_percent_initial+(Qadipose_percent_terminal-Qadipose_percent_initial)/term*tw)*Qcar$$

$$Qrest = Qcardiac - (Qgut + Qkidney + Qliver + Qthyroid + Qplacenta + Qadipose);$$

$$Qgfr = 60*24*0.001*(Qgfr_quadratic_theta0+Qgfr_quadratic_theta1*tw+Qgfr_quadratic_theta2*pow(tw,2));$$

$$Qfrvtl = 60*24*0.001*Qfrvtl_logistic_theta0/(1+exp(-Qfrvtl_logistic_theta1*(tw-Qfrvtl_logistic_theta2)));$$

$$Qflvtl = 60*24*0.001*Qflvtl_logistic_theta0/(1+exp(-Qflvtl_logistic_theta1*(tw-Qflvtl_logistic_theta2)));$$

$$Qfda = 60*24*0.001*Qfda_logistic_theta0/(1+exp(-Qfda_logistic_theta1*(tw-Qfda_logistic_theta2)));$$

$$Qfartb = Qflvtl + Qfda;$$

$$Qfcardiac = Qfartb;$$

$$Qflung = Qfrvtl - Qfda;$$

$$Qfplacenta = 60*24*0.001*Qfplacenta_logistic_theta0/(1+exp(-Qfplacenta_logistic_theta1*(tw-Qfplacenta_logis$$

$$Qfdv = 60*24*0.001*Qfdv_gompertz_theta0*exp(Qfdv_gompertz_theta1/Qfdv_gompertz_theta2*(1-exp(-Qfdv_gom$$

$$Qfgut = Qfgut_percent/Qfnonplacental_percent * (1 - Qfplacenta/Qfartb) * Qfartb;$$

$$Qfkidney = Qfkidney_percent/Qfnonplacental_percent*(1-Qfplacenta/Qfartb)*Qfartb;$$

$$Qfbrain = Qfbrain_percent/Qfnonplacental_percent * (1 - Qfplacenta/Qfartb) * Qfartb;$$

$$Qfliver = Qfliver_percent/(100-(Qbrain_percent+Qkidney_percent+Qgut_percent))*(1-(Qfbrain_percent+Qfkid$$

$$Qfthyroid = Qfthyroid_percent/(100-(Qbrain_percent+Qkidney_percent+Qgut_percent))*(1-(Qfbrain_percent+Q$$

$$Qfrest = Qfcardiac-(Qfplacenta+Qfgut+Qfliver+Qfthyroid+Qfkidney+Qfbrain);$$

$$Qfbypass = Qfcardiac - Qflung;$$

Value

list containing:

`BW`	Maternal body weight, kg
`Wadipose`	Maternal adipose fraction of total weight
`Wfkidney`	Fetal kidney fraction of total weight
`Wfthyroid`	Fetal thyroid fraction of total weight
`Wfliver`	Fetal liver fraction of total weight
`Wfbrain`	Fetal brain fraction of total weight
`Wfgut`	Fetal gut fraction of total weight
`Wflung`	Fetal lung fraction of total weight
`hematocrit`	Maternal hematocrit fraction of blood

Rblood2plasma	Maternal Rblood2plasma
fhematocrit	Fetal hematocrit fraction of blood
Rfblood2plasma	Fetal Rfblood2plasma
fBW	Fetal body weight, kg
Vplacenta	Volume of Vplacenta, L
Vamnf	Volume of amniotic fluid, L
Vplasma	Maternal volume of plasma, L
Vrbcs	Maternal volume of red blood cells, L
Vven	Maternal volume of venous blood, L
Vart	Maternal volume of arterial blood, L
Vadipose	Maternal volume of adipose, L
Vffmx	Fetal volume ofVffmx, L
Vallx	Vallx, L
Vrest	Maternal volume of rest of body, L
Vfart	Fetal volume of arterial blood, L
Vfven	Fetal volume of venous blood, L
Vfkidney	Fetal volume of kidney, L
Vfthyroid	Fetal volume of thyroid, L
Vfliver	Fetal volume of liver, L
Vfbrain	Fetal volume of brain, L
Vfgut	Fetal volume of gut, L
Vflung	Fetal volume of lung, L
Vfrest	Fetal volume of rest of body, L
Qcardiac	Maternal cardiac output blood flow, L/day
Qgut	Maternal blood flow to gut, L/day
Qkidney	Maternal blood flow to kidney, L/day
Qliver	Maternal blood flow to liver, L/day
Qthyroid	Maternal blood flow to thyroid, L/day
Qplacenta	Maternal blood flow to placenta, L/day
Qadipose	Maternal blood flow to adipose, L/day
Qrest	Maternal blood flow to rest, L/day
Qgfr	Maternal glomerular filtration rate in kidney, L/day
Qfrvtl	Fetal blood flow to right ventricle, L/day
Qflvtl	Fetal blood flow to left ventircle, L/day
Qfda	Fetal blood flow to Qfda, L/day
Qfartb	Fetal blood flow to Qfartb, L/day
Qfcardiac	Fetal cardiac output blood flow, L/day

Qflung	Fetal blood flow to lung, L/day
Qfplacenta	Fetal blood flow to placenta, L/day
Qfdv	Fetal blood flow to Qfdv, L/day
Qfgut	Fetal blood flow to gut, L/day
Qfkidney	Fetal blood flow to kidney, L/day
Qfbrain	Fetal blood flow to brain, L/day
Qfliver	Fetal blood flow to liver, L/day
Qfthyroid	Fetal blood flow to thyroid, L/day
Qfrest	Fetal blood flow to rest, L/day
Qfbypass	Fetal blood flow to Qfbypass, L/day

Author(s)

John Wambaugh

References

Kapraun DF, Wambaugh JF, Setzer RW, Judson RS (2019). "Empirical models for anatomical and physiological changes in a human mother and fetus during pregnancy and gestation." *PLOS ONE*, **14**(5), 1-56. doi:10.1371/journal.pone.0215906.

---

calc_fup_correction *Calculate the correction for lipid binding in plasma binding assay*

Description

Poulin and Haddad (2012) observed "...that for a highly lipophilic compound, the calculated f_{up} is by far [less than] the experimental values observed under in vitro conditions." Pearce et al. (2017) hypothesized that there was additional lipid binding in vivo that acted as a sink for lipophilic compounds, reducing the effective f_{up} in vivo. It is possible that this is due to the binding of lipophilic compounds on the non plasma-side of the rapid equilibrium dialysis plates (Waters et al., 2008). Pearce et al. (2017) compared predicted and observed tissue partition coefficients for a range of compounds. They showed that predictions were improved by adding additional binding proportional to the distribution coefficient D_{ow} (calc_dow) and the fractional volume of lipid in plasma (F_{lipid}). We calculate F_{lipid} as the sum of the physiological plasma neutral lipid fractional volume and 30 percent of the plasma neutral phospholipid fractional volume. We use values from Peyret et al. (2010) for rats and Poulin and Haddad (2012) for humans. The estimate of 30 percent of the neutral phospholipid volume as neutral lipid was used for simplictity's sake in place of our membrane affinity predictor. To account for additional binding to lipid, plasma to water partitioning ($K_{plasma:water} = \frac{1}{f_{up}}$) is increased as such:

$$f_{up}^{corrected} = \frac{1}{f_{up}^{corrected}} = \frac{1}{K_{nL}^{pl} * F_{lipid} + \frac{1}{f_{up}^{invitro}}}$$

Usage

```
calc_fup_correction(
  fup = NULL,
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  Flipid = NULL,
  plasma.pH = 7.4,
  dow74 = NULL,
  species = "Human",
  default.to.human = FALSE,
  force.human.fup = FALSE,
  suppress.messages = FALSE
)
```

Arguments

fup	Fraction unbound in plasma, if provided this argument overides values from argument parameters and chem.physical_and_invitro.data
chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Parameters from the appropriate parameterization function for the model indicated by argument model
Flipid	The fractional volume of lipid in plasma (from physiology.data)
plasma.pH	pH of plasma (default 7.4)
dow74	The octanol-water distribution ratio (DOW).
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
default.to.human	Substitutes missing fraction of unbound plasma with human values if true.
force.human.fup	Returns human fraction of unbound plasma in calculation for rats if true. When species is specified as rabbit, dog, or mouse, the human unbound fraction is substituted.
suppress.messages	Whether or not the output message is suppressed.

Details

Note that octanal:water partitioning above 1:1,000,000 ($LogD_{ow} > 6$) are truncated at 1:1,000,000 because greater partitioning would likely take longer than protein binding assay itself.

Value

A numeric fraction unpbound in plasma between zero and one

Author(s)

John Wambaugh

References

Pearce RG, Setzer RW, Davis JL, Wambaugh JF (2017). "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." *Journal of pharmacokinetics and pharmacodynamics*, **44**, 549–565. doi:10.1007/s1092801795487.

Peyret T, Poulin P, Krishnan K (2010). "A unified algorithm for predicting partition coefficients for PBPK modeling of drugs and environmental chemicals." *Toxicology and applied pharmacology*, **249**(3), 197–207. doi:10.1016/j.taap.2010.09.010.

Poulin P, Haddad S (2012). "Advancing prediction of tissue distribution and volume of distribution of highly lipophilic compounds from a simplified tissue-composition-based model as a mechanistic animal alternative method." *Journal of pharmaceutical sciences*, **101**(6), 2250–2261. doi:10.1002/jps.23090.

Schmitt W (2008). "General approach for the calculation of tissue to plasma partition coefficients." *Toxicology in vitro*, **22**(2), 457–467. doi:10.1016/j.tiv.2007.09.010.

Waters NJ, Jones R, Williams G, Sohal B (2008). "Validation of a rapid equilibrium dialysis approach for the measurement of plasma protein binding." *Journal of pharmaceutical sciences*, **97**(10), 4586–4595. doi:10.1002/jps.21317.

See Also

apply_fup_adjustment

calc_dow

`calc_half_life` *Calculates the half-life for a one compartment model.*

Description

This function calculates the half life 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_half_life(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
```

```
  species = "Human",
  model = "3compartmentss",
  suppress.messages = TRUE,
  ...
)
```

Arguments

chem.cas	Either the cas number or the chemical name must be specified.
chem.name	Either the chemical name or the cas number must be specified.
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_steadystate or 1compartment function, overrides chem.name and chem.cas.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
model	The model used to calculate elimination rate (defaults to "3compartmentss")
suppress.messages	Whether or not the output message is suppressed.
...	Additional parameters passed to parameterize function if parameters is NULL.

Details

Half life is calculated by dividing the natural-log of 2 by the elimination rate from the one compartment model.

Value

Half life	Units of h.

Author(s)

Sarah E. Davidson

See Also

calc_elimination_rate

Examples

```
calc_half_life(chem.name="Bisphenol A")

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

calc_half_life(chem.cas="80-05-7")

# Volatiles are outside the domain of default model:
try(calc_half_life(
     chem.name="toluene"))
```

```
# We can turn off physchem checking:
calc_half_life(
     chem.name="toluene",
     physchem.exclude=FALSE)

# Or use an appropriate model for volatiles:
calc_half_life(
     chem.name="toluene",
     model="sumclearances")

# PFAS are outside the domain:
try(calc_half_life(
     dtxsid="DTXSID8031865",
     model="sumclearances"))

# Can turn off chemical class checking:
calc_half_life(
  dtxsid="DTXSID8031865",
  model="sumclearances",
  class.exclude=FALSE,
  suppress.messages=TRUE)

# For a metabolized compound, non-restrictive clearance should be faster:
h1 <- calc_half_life(
  chem.name="toluene",
  model="sumclearances",
  suppress.messages=TRUE)
h2 <- calc_half_life(
  chem.name="toluene",
  model="sumclearances",
  restrictive.clearance=FALSE,
  suppress.messages=TRUE)
# Check that h2 < h1:
if (!(h2 < h1)) stop("h2 not less than h1")

# Change species:
calc_half_life(
  dtxsid="DTXSID8031865",
  species="rat",
  model="sumclearances",
  default.to.human=TRUE,
  class.exclude=FALSE,
  physchem.exclude=FALSE,
  suppress.messages=TRUE)
```

`calc_hepatic_clearance` *Calculate the hepatic clearance (deprecated).*

Description

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

Usage

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

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_steadystate function, overrides chem.name and chem.cas.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
default.to.human	Substitutes missing animal values with human values if true.
hepatic.model	Model used in calculating hepatic clearance, unscaled, parallel tube, dispersion, or default well-stirred.
suppress.messages	Whether or not to suppress the output message.
well.stirred.correction	Uses correction in calculation of hepatic clearance for well-stirred model if TRUE for hepatic.model well-stirred. This assumes clearance relative to amount unbound in whole blood instead of plasma, but converted to use with plasma concentration.
restrictive.clearance	Protein binding not taken into account (set to 1) in liver clearance if FALSE.
adjusted.Funbound.plasma	Whether or not to use Funbound.plasma adjustment if calculating Rblood2plasma.
...	Additional parameters passed to parameterize_steadystate if parameters is NULL.

Value

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

Author(s)

John Wambaugh and Robert Pearce

References

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

Examples

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

---

calc_hep_bioavailability

Calculate first pass heaptic metabolism

Description

For models that don't described first pass blood flow from the gut, need to cacluate a hepatic bioavailability, that is, the fraction of chemical systemically available after metabolism during the first pass through the liver (Rowland, 1973 Equation 29, where k21 is blood flow through the liver and k23 is clearance from the liver in Figure 1 in that paper).

Usage

```
calc_hep_bioavailability(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  restrictive.clearance = TRUE,
  default.to.human = FALSE,
  flow.34 = TRUE,
  suppress.messages = FALSE,
  species = "Human"
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Parameters from the appropriate parameterization function for the model indicated by argument model
restrictive.clearance	Protein binding not taken into account (set to 1) in liver clearance if FALSE.
default.to.human	Substitutes missing animal values with human values if true (hepatic intrinsic clearance or fraction of unbound plasma).
flow.34	A logical constraint
suppress.messages	Whether or not to suppress the output message.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").

Value

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

Author(s)

John Wambaugh

References

Rowland M, Benet LZ, Graham GG (1973). "Clearance concepts in pharmacokinetics." *Journal of pharmacokinetics and biopharmaceutics*, **1**(2), 123–136. doi:10.1007/BF01059626.

---

calc_hep_clearance *Calculate the hepatic clearance.*

Description

This function calculates the hepatic clearance in plasma for using the "well-stirred" model by default. Other scaling options from (Ito and Houston 2004) are also available. Parameters for scaling from flow-free intrinsic-hepatic clearance to whole-liver metabolism rate are taken from (Carlile et al. 1997). In vitro measured hepatic clearace is corrected for estimated binding in the in vitro clearance assay using the model of (Kilford et al. 2008). The agument restrictive.clearance (defaults to TRUE) describes the significance (or lack thereof) of plasma protein binding in metabolism. Restrictive clearance assumes that only the free fraction of chemical in plasma is available for

metabolism. Non-restrictive clearance assumes that the compound is weakly bound to plasma protein and any free chemical metabolized is instantly replaced. For non-restrictive clearance the effective fup = 1.

Usage

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

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_steadystate function, overrides chem.name and chem.cas.
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 the (Yang et al. 2007) blood:plasma ratio correction in the calculation of hepatic clearance for well-stirred model if TRUE if argument hepatic.model = "well-stirred".
restrictive.clearance	If TRUE (default) the rate of metabolism is restricted to the unbound fraction of chemical. If FALSE the free fraction is set to 1 (that is, plasma protein binding is weak and metabolzied chemical is rapidly replaced)
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
adjusted.Funbound.plasma	Uses the (Pearce et al. 2017) lipid binding adjustment for Funbound.plasma (which also impacts partition coefficients such as blood:plasma ratio) when set to TRUE (Default).
...	Additional parameters passed to parameterize_steadystate if parameters is NULL.

Value

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

Author(s)

John Wambaugh and Robert Pearce

References

Carlile DJ, Zomorodi K, Houston JB (1997). "Scaling factors to relate drug metabolic clearance in hepatic microsomes, isolated hepatocytes, and the intact liver: studies with induced livers involving diazepam." *Drug metabolism and disposition*, **25**(8), 903–911.

Ito K, Houston JB (2004). "Comparison of the use of liver models for predicting drug clearance using in vitro kinetic data from hepatic microsomes and isolated hepatocytes." *Pharmaceutical research*, **21**, 785–792. doi:10.1023/B:PHAM.0000026429.12114.7d.

Kilford PJ, Gertz M, Houston JB, 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), 1194–1197. doi:10.1124/dmd.108.020834.

Pearce RG, Setzer RW, Davis JL, Wambaugh JF (2017). "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." *Journal of pharmacokinetics and pharmacodynamics*, **44**, 549–565. doi:10.1007/s1092801795487.

Yang J, Jamei M, Yeo KR, Rostami-Hodjegan A, Tucker GT (2007). "Misuse of the well-stirred model of hepatic drug clearance." *Drug Metabolism and Disposition*, **35**(3), 501–502. doi:10.1124/dmd.106.013359.

Examples

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

---

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

Description

This function uses the method from Kilford et al. (2008) to calculate the fraction of unbound chemical in the hepatocyte intrinsic clearance assay. The bound chemical is presumed to be unavailable during the performance of the assay, so this fraction can be used to increase the apparent clearance rate to better estimate in vivo clearance. For bases, the fraction of chemical unbound in hepatocyte clearance assays (fu_{hep}) is calculated in terms of $logP_{ow}$ but for neutrual and acidic compounds

we use $logD_{ow}$ (from calc_dow). Here we denote the appropriate partition coefficient as "logP/D". Kilford et al. (2008) calculates

$$fu_{hep} = \frac{1}{1 + 125 * V_R * 10^{0.072 * logP * D^2 + 0.067 * logP/D - 1.126}}$$

Usage

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

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Parameters from the appropriate parameterization function for the model indicated by argument model
Vr	Ratio of cell volume to incubation volume. Default (0.005) is taken from
pH	pH of the incupation medium.

Details

Note that octanal:water partitioning above 1:1,000,000 ($LogP_{ow} > 6$) are truncated at 1:1,000,000 because greater partitioning would likely take longer than hepatocyte assay itself.

Value

A numeric fraction between zero and one

Author(s)

John Wambaugh and Robert Pearce

References

Kilford PJ, Gertz M, Houston JB, 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), 1194–1197. doi:10.1124/dmd.108.020834.

Wetmore BA, Wambaugh JF, Allen B, Ferguson SS, Sochaski MA, Setzer RW, Houck KA, Strope CL, Cantwell K, Judson RS, others (2015). "Incorporating high-throughput exposure predictions with dosimetry-adjusted in vitro bioactivity to inform chemical toxicity testing." *Toxicological Sciences*, **148**(1), 121–136. doi:10.1093/toxsci/kfv171.

See Also

apply_clint_adjustment

---

calc_ionization *Calculate the ionization.*

Description

This function calculates the ionization of a compound at a given pH. The pKa's are either entered as parameters or taken from a specific compound in the package. The arguments pKa_Donor and pKa_Accept may be single numbers, characters, or vectors. We support characters because there are many instances with multiple predicted values and all those values can be included by concatenating with commas (for example, pKa_Donor = "8.1,8.6". Finally, pka_Donor and pKa_Accept may be vectors of characters representing different chemicals or instances of chemical parameters to allow for uncertainty analysis. A null value for pKa_Donor or pKa_Accept is interpretted as no argument provided, while " " is taken as a prediction of no ionization possible at any pH.

Usage

```
calc_ionization(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  pH = NULL,
  pKa_Donor = NULL,
  pKa_Accept = NULL,
  return_charge_matrix = FALSE
)
```

Arguments

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

parameters	Chemical parameters from a parameterize_MODEL function, overrides chem.name and chem.cas.
pH	pH where ionization is evaluated.
pKa_Donor	Compound H dissociation equilibirum constant(s). Overwrites chem.name and chem.cas.
pKa_Accept	Compound H association equilibirum constant(s). Overwrites chem.name and chem.cas.
return_charge_matrix	If TRUE, the function returns a table describing each ionization state considered by the calculations in this function (defaults to FALSE)

Details

It is very important to note that pKb = 14 - pKa. But if a predictor gives us a doinor pKa, we just accept it as a pKa.

For hydrogen donor sites, a hydrogen is present in the molecule that can be donated to the solution if the concentration of hydrogens gets low enough. This causes the molecule to become more negatively charged. This is an acid. For hydrogen acceptor suits a location exist in the molecule that can accept an additional history if the concentration of hydrogens gets sufficiently high. This causes the molecule to become more positively charged. This is a base.

We make several assumptions about ionization in order to make our calculations. First, we assume ionization is either due to either "donating" (losing) a hydrogen ion (a positively charge proton) to the solution or by "accepting" (gaining) a hydrogen ion from the solution. Generally, acids are hydrogen donors and bases are hydrogen acceptors. Second, pH is the negative log10 concentration of hydrogen atoms. The lower the pH, the more hydrogen atoms. So, acids donate their hydrogen atoms as pH of the solution increases. Bases accept their hydrogen atoms as pH decreases. Third, each predicted pKa is a prediction that a specific location (or site) on molecule X can either donate or accept a hydrogen. Fourth, the pKa value indicates the pH at which half of the molecules of X have ionized at the site, and half have not. The concentration of the two forms are equal. Fifth, if there are N pKa's for molecule X, then there are N sites that can ionize. Technically this means that there are 2^N different ionization states for molecule X (where each site is or is not ionized). However, pKa predictors give the equlibrium only for pairs of ionization states. So, we only consider N + 1 ionizations states for X – the state immediately above and below each pKa.

To understand the different charge states we annotate the nonionizable backbone of a molecule as "X". For each site on X that is capable of donating a hydrogen we add a "D" to the right of "X". For each site on X that has accepted a hydrogen, we add a "A" to the right of "X". We read the A's and D's from left to right, with the one occuring at the lowest pH first. So a typical acid ionization would be: XD -> X- and a typical base ionization would be XA+ -> X. Where things get complicated is if there are multiple donor and acceptor states. In particular, it is possible for a compound to have a net zero charge, but be simultaneously positively and negatively charged. Such a state is called a Zwitter ion. For example: XDAA+ -> XAA++ -> XA+ -> XA -> X- . The state XA is technically neutral because X has donated one hydrogen, but also accepted one hydrogen. XA is a Zwitter ion.

Each pKa gives the equlibrium ratio of two states pH - pKa = log10[X/XD] for donation or pOH - pka = log10[X/XA] for accepting. pOH = 14 - pH. Separating the logarithm into log10[X] - log10[XD] lets us see that Cn = Xn - Xn-1 where Cn = pH -pKa for donor pKa's and Cn = 14 - pH - pKa for acceptor pKa's. We can rewrite log10Xn = Sum_i=1:n Ci + log10X1. So we can calculate each Xn by summing all the ratios between Xn and the lowest state (X1). Then, by requiring that

all Xi sum to 1, we have: 1 = Sum_i=1:N 10^Xi = Sum_i=1:N 10^(Sum_j=1:i (Cj + log10X1)) = X1 * Sum_i=1:N 10^(Sum_j=1:i Cj) so that X1 = 1 / Sum_i=1:N 10^(Sum_j=1:i Cj)

The sum im the denominator is the ratio from X1 to each state (including X1). We use a table called "charge_matrix" to keep track of all N + 1 ionization states and the ratio of each state to the next. We use these ratios to calculate

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

`charge_matrix`
: Description of each ionization state if argument return_charge_matrix==TRUE

Author(s)

Robert Pearce and John Wambaugh

References

Pearce RG, Setzer RW, Davis JL, Wambaugh JF (2017). "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." *Journal of pharmacokinetics and pharmacodynamics*, **44**, 549–565. doi:10.1007/s1092801795487.

Strope CL, Mansouri K, Clewell III HJ, Rabinowitz JR, Stevens C, Wambaugh JF (2018). "High-throughput in-silico prediction of ionization equilibria for pharmacokinetic modeling." *Science of The Total Environment*, **615**, 150–160. doi:10.1016/j.scitotenv.2017.09.033.

Examples

```
# Neutral compound:
calc_ionization(chem.name="Acetochlor",pH=7.4)

# Donor pKa's 9.78,10.39 -- Should be almost all neutral at plasma pH:
out <- calc_ionization(chem.name='bisphenola',pH=7.4)
print(out)
out[["fraction_neutral"]]==max(unlist(out))

# Donor pKa's 9.78,10.39 -- Should be almost all negative (anion) at higher pH:
out <- calc_ionization(chem.name='bisphenola',pH=11)
print(out)
out[["fraction_negative"]]==max(unlist(out))

# Ficticious compound, should be almost all all negative (anion):
```

```
out <- calc_ionization(pKa_Donor=8,pKa_Accept="1,4",pH=9)
print(out)
out[["fraction_negative"]]>0.9

# Donor pKa 6.54 -- Should be mostly negative (anion):
out <- calc_ionization(chem.name='Acephate',pH=7)
print(out)
out[["fraction_negative"]]==max(unlist(out))

#Acceptor pKa's "9.04,6.04"  -- Should be almost all positive (cation) at plasma pH:
out <- calc_ionization(chem.cas="145742-28-5",pH=7.4)
print(out)
out[["fraction_positive"]]==max(unlist(out))

#Ficticious Zwitteron:
out <- calc_ionization(pKa_Donor=6,pKa_Accept="8",pH=7.4)
print(out)
out[["fraction_zwitter"]]==max(unlist(out))
```

`calc_kair` *Calculate air:matrix partition coefficients*

Description

This function uses the methods colleced by Linakis et al. (2020) to calculate air partition coefficients for blood, water, and mucus.

Usage

```
calc_kair(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  species = "Human",
  adjusted.Funbound.plasma = TRUE,
  fup.lod.default = 0.005,
  force.human.clint.fup = FALSE,
  minimum.Funbound.plasma = 1e-04,
  default.to.human = FALSE,
  suppress.messages = FALSE,
  pH = 7.4,
  alpha = 0.001
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Parameters from the appropriate parameterization function for the model indicated by argument model. Can include parameters "logHenry" and "body_temp", but if not included standard values are looked up from httk tables.
species	Species used for body temperature, defaults to "Human"
adjusted.Funbound.plasma	Uses Pearce et al. (2017) lipid binding adjustment for Funbound.plasma (which impacts partition coefficients) when set to TRUE (Default).
fup.lod.default	Default value used for fraction of unbound plasma for chemicals where measured value was below the limit of detection. Default value is 0.0005.
force.human.clint.fup	Uses human hepatic intrinsic clearance and fraction of unbound plasma in calculation of partition coefficients for rats if true.
minimum.Funbound.plasma	Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).
default.to.human	Substitutes missing species-specific values with human values if TRUE (default is FALSE).
suppress.messages	Whether or not the output messages are suppressed.
pH	pH where ionization is evaluated.
alpha	Ratio of Distribution coefficient D of totally charged species and that of the neutral form

Details

The blood:air partition coefficient (PB:A) was calculated as

$$P_{B:A} = \frac{P_{B:A} * R_{B:P}}{f_{up}}$$

where P_B:A is the blood:air partition, RB:P is the blood:plasma partition ratio, fup is the fraction unbound in the plasma, and P_W:A is the water:air partition coefficient:

$$\frac{R * T_{body}}{HLC * P}$$

where R is the gas constant (8.314 J/mol/K), T_body is the species-specific body temperature (K) from physiology.data, HLC is the Henry's Law Constant (atm*m^3 / mol), and P is conversion factor from atmospheres to Pascals (1 atm = 101325 Pa).

In the isopropanol PBTK model published by Clewell et al. (2001) it was noted that certain chemicals are likely to be absorbed into the mucus or otherwise trapped in the upper respiratory tract (URT). Following Scott (2014), the air:mucus partition coefficient (PA:M) calculated as

$$log_{10}(\frac{1}{K_{water2air}}) - (log_{10}(P_{ow}) - 1) * 0.524$$

where Pow is the octanol/water partition coefficient

Value

A named list containing the blood:air, water:air, and mucus:air partition coefficients

Author(s)

John Wambaugh and Matt Linakis

References

Linakis MW, Sayre RR, Pearce RG, Sfeir MA, Sipes NS, Pangburn HA, Gearhart JM, Wambaugh JF (2020). "Development and evaluation of a high-throughput inhalation model for organic chemicals." *Journal of exposure science & environmental epidemiology*, **30**(5), 866–877. doi:10.1038/s41370-0200238y.

Clewell III, Harvey J., et al. "Development of a physiologically based pharmacokinetic model of isopropanol and its metabolite acetone." Toxicological Sciences 63.2 (2001): 160-172.

Scott, John W., et al. "Tuning to odor solubility and sorption pattern in olfactory epithelial responses." Journal of Neuroscience 34.6 (2014): 2025-2036.

See Also

calc_dow

---

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

Description

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

Usage

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

Arguments

Rb2p	The chemical blood:plasma concentration ratop
Funbound.plasma	The free fraction of chemical in the presence of plasma protein Rblood2plasma.
hematocrit	Overwrites default hematocrit value in calculating Rblood2plasma.
default.to.human	Substitutes missing animal values with human values if true.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
suppress.messages	Determine whether to display certain usage feedback.

Value

The red blood cell to unbound chemical in plasma partition coefficient.

Author(s)

John Wambaugh and Robert Pearce

References

Pearce RG, Setzer RW, Davis JL, Wambaugh JF (2017). "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." *Journal of pharmacokinetics and pharmacodynamics*, **44**, 549–565. doi:10.1007/s1092801795487.

Ruark CD, Hack CE, Robinson PJ, Mahle DA, Gearhart JM (2014). "Predicting passive and active tissue: plasma partition coefficients: interindividual and interspecies variability." *Journal of pharmaceutical sciences*, **103**(7), 2189–2198. doi:10.1002/jps.24011.

calc_ma *Calculate the membrane affinity*

Description

Membrane affinity (MA) is the membrane:water partition coefficient. MA chacterizes chemical partitioning into membranes formed from neutral phospholipids (K_{nPL}). Pearce et al. (2017) compared five different methods for predicting membrane affinity using measured data for 59 compounds. The method of Yun and Edgington (2013) was identified as the best:

$$MA = 10^(1.294 + 0.304 * log_{10}(P_{ow}))$$

Usage

```
calc_ma(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  suppress.messages = FALSE
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Parameters from the appropriate parameterization function for the model indicated by argument model
suppress.messages	Whether or not the output message is suppressed.

Value

A numeric fraction unpbound in plasma between zero and one

Author(s)

John Wambaugh

References

Pearce RG, Setzer RW, Davis JL, Wambaugh JF (2017). "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." *Journal of pharmacokinetics and pharmacodynamics*, **44**, 549–565. doi:10.1007/s1092801795487.

Yun YE, Edginton AN (2013). "Correlation-based prediction of tissue-to-plasma partition coefficients using readily available input parameters." *Xenobiotica*, **43**(10), 839–852. doi:10.3109/00498254.2013.770182.

`calc_maternal_bw` *Calculate maternal body weight*

Description

This function initializes the parameters needed in the functions solve_fetal_pbtk by calling solve_pbtk and adding additional parameters.

Usage

```
calc_maternal_bw(week = 12)
```

Arguments

`week`	Gestational week

Details

BW <- params$pre_pregnant_BW + params$BW_cubic_theta1 * tw + params$BW_cubic_theta2 * tw^2 + params$BW_cubic_theta3 * tw^3

Value

`BW`	Maternal Body Weight, kg.

Author(s)

John Wambaugh

References

Kapraun DF, Wambaugh JF, Setzer RW, Judson RS (2019). "Empirical models for anatomical and physiological changes in a human mother and fetus during pregnancy and gestation." *PLOS ONE*, **14**(5), 1-56. doi:10.1371/journal.pone.0215906.

`calc_mc_css` *Distribution of chemical steady state concentration with uncertainty and variability*

Description

For a given chemical and fixed dose rate this function determines a distribution of steady-state concentrations reflecting measurement uncertainty an population variability. Uncertainty and variability are simulated via the Monte Carlo method – many sets of model parameters are drawn according to probability distributions described in Ring et al. (2017) (doi:10.1016/j.envint.2017.06.004) for human variability and Wambaugh et al. (2019) (doi:10.1093/toxsci/kfz205) for measurement uncertainty. Monte Carlo samples are generated by the function `create_mc_samples`. To allow rapid application of the Monte Carlo method we make use of analytical solutions for the steady-state concentration for a particular model via a given route (when available) as opposed to solving the model numerically (that is, using differential equations). For each sample of the Monte Carlo method (as specified by argument `samples`) the parameters for the analytical solution are varied. An ensemble of steady-state predictions are produced, though by default only the quantiles specified by argument `which.quantile` are provided. If the full set of predicted values are desired use set the argument `return.samples` to `TRUE`.

Usage

```
calc_mc_css(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  samples = 1000,
  which.quantile = 0.95,
  species = "Human",
  daily.dose = 1,
  suppress.messages = FALSE,
  model = "3compartmentss",
  httkpop = TRUE,
  httkpop.dt = NULL,
  invitrouv = TRUE,
  calcrb2p = TRUE,
  censored.params = list(),
  vary.params = list(),
  return.samples = FALSE,
  tissue = NULL,
  concentration = "plasma",
  output.units = "mg/L",
  invitro.mc.arg.list = NULL,
  httkpop.generate.arg.list = list(method = "direct resampling"),
  convert.httkpop.arg.list = NULL,
  parameterize.args.list = NULL,
```

```
  calc.analytic.css.arg.list = NULL,
  Caco2.options = NULL
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Parameters from the appropriate parameterization function for the model indicated by argument model
samples	Number of samples generated in calculating quantiles.
which.quantile	Which quantile from Monte Carlo simulation is requested. Can be a vector.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human"). Species must be set to "Human" to run httkpop model.
daily.dose	Total daily dose, mg/kg BW.
suppress.messages	Whether or not to suppress output message.
model	Model used in calculation,'gas_pbtk' for the gas pbtk model, 'pbtk' for the multiple compartment model, '3compartment' for the three compartment model, '3compartmentss' for the three compartment steady state model, and '1compartment' for one compartment model. This only applies when httkpop=TRUE and species="Human", otherwise '3compartmentss' is used.
httkpop	Whether or not to use population generator and sampler from httkpop. This is overwrites censored.params and vary.params and is only for human physiology. Species must also be set to 'Human'.
httkpop.dt	A data table generated by httkpop_generate. This defaults to NULL, in which case httkpop_generate is called to generate this table.
invitrouv	Logical to indicate whether to include in vitro parameters in uncertainty and variability analysis
calcrb2p	Logical determining whether or not to recalculate the chemical ratio of blood to plasma
censored.params	The parameters listed in censored.params are sampled from a normal distribution that is censored for values less than the limit of detection (specified separately for each parameter). This argument should be a list of sublists. Each sublist is named for a parameter in "parameters" and contains two elements: "CV" (coefficient of variation) and "LOD" (limit of detection, below which parameter values are censored. New values are sampled with mean equal to the value in "parameters" and standard deviation equal to the mean times the CV. Censored values are sampled on a uniform distribution between 0 and the limit of detection. Not used with httkpop model.

vary.params — The parameters listed in vary.params are sampled from a normal distribution that is truncated at zero. This argument should be a list of coefficients of variation (CV) for the normal distribution. Each entry in the list is named for a parameter in "parameters". New values are sampled with mean equal to the value in "parameters" and standard deviation equal to the mean times the CV. Not used with httkpop model.

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

tissue — Desired steady state tissue concentration. Default is of NULL typically gives whole body plasma concentration.

concentration — Desired concentration type: 'blood','tissue', or default 'plasma'. In the case that the concentration is for plasma, selecting "blood" will use the blood:plasma ratio to estimate blood concentration. In the case that the argument 'tissue' specifies a particular tissue of the body, concentration defaults to 'tissue' – that is, the concentration in the If cocentration is set to 'blood' or 'plasma' and 'tissue' specifies a specific tissue then the value returned is for the plasma or blood in that specific tissue.

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

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

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

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

parameterize.args.list — A list of arguments to be passed to the model parameterization function (that is, parameterize_MODEL) corresponding to argument "model". (Defaults to NULL.)

calc.analytic.css.arg.list — Additional parameters passed to

Caco2.options — Arguments describing how to handle Caco2 absorption data that are passed to invitro_mc and the parameterize_[MODEL] functions. See get_fbio for further details.

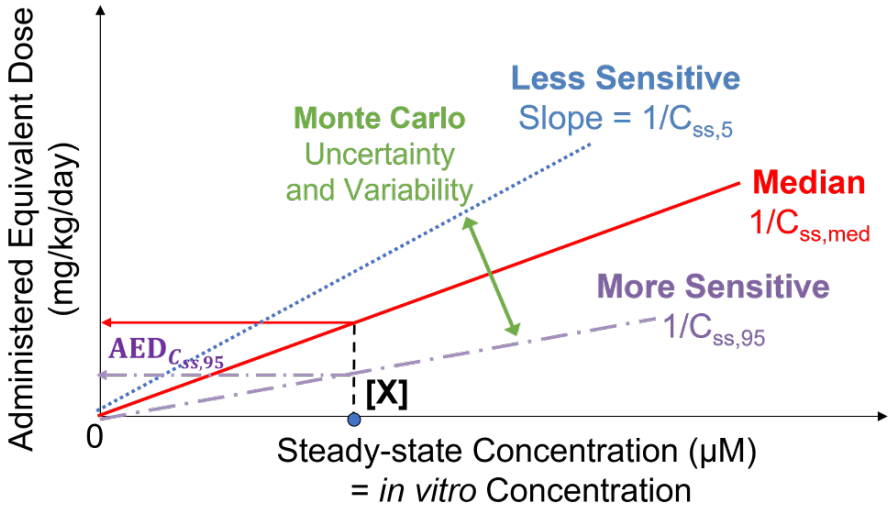
calc_analytic_css.

Details

The chemical-specific steady-state concentration for a dose rate of 1 mg/kg body weight/day can be used for in *in vitro-in vivo* extrapolation (IVIVE) of a bioactive *in vitro* concentration by dividing the *in vitro* concentration by the steady-state concentration to predict a dose rate (mg/kg/day) that would produce that concentration in plasma. Using quantiles of the distribution (such as the upper 95th percentile) allow incorporation of uncertainty and variability into IVIVE.

Reverse Dosimetry Toxicodynamic IVIVE

$$\mathbf{AED}_{C_{ss,95}} = \frac{[X]}{C_{ss,95}}$$



altalt

Figure from Breen et al. (2021) (doi:10.1080/17425255.2021.1935867) shows reverse dosimetry toxicodynamic IVIVE. Equivalent external dose is determined by solving the TK model in reverse by deriving the external dose (that is, TK model input) that produces a specified internal concentration (that is, TK model output). Reverse dosimetry and IVIVE using HTTK relies on the linearity of the models. We calculate a scaling factor to relate *in vitro* concentrations (uM) to administered equivalent doses (AED). The scaling factor is the inverse of the steady state plasma concentration (Css) predicted for a 1 mg/kg/day exposure dose rate. We use Monte Carlo to simulate variability and propagate uncertainty; for example, to calculate an upper 95th percentile Css,95 for individuals who get higher plasma concentrations from the same exposure.

The Monte Carlo methods used here were recently updated and described by Breen et al. (submitted).

httk-pop is used only for humans. For non-human species biological variability is simulated by drawing parameters from uncorellated log-normal distributions.

Chemical-specific httk data are available primarily for human and for a few hundred chemicals in rat. All in silico predictions are for human. Thus, when species is specified as rabbit, dog, or mouse, the user can choose to set the argument `default.to.human` to `TRUE` so that this function uses the appropriate physiological data (volumes and flows) but substitutes human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

If the argument `tissue` is used, the steady-state concentration in that tissue, if available, is provided. If that tissue is included in the model used (specified by arguement `model`) then the actual tissue concentration is provided. Otherwise, the tissue-specific partition coefficient is used to estimate the concentration from the plasma.

The six sets of plausible IVIVE assumptions identified by Honda et al. (2019) (doi:10.1371/journal.pone.0217564) are:

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

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

Value

Quantiles (specified by which.quantile) of the distribution of plasma steady-stae concentration (Css) from the Monte Carlo simulation

Author(s)

Caroline Ring, Robert Pearce, John Wambaugh, Miyuki Breen, and Greg Honda

References

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

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

Honda GS, Pearce RG, Pham LL, Setzer RW, Wetmore BA, Sipes NS, Gilbert J, Franz B, Thomas RS, Wambaugh JF (2019). "Using the concordance of in vitro and in vivo data to evaluate extrapolation assumptions." *PloS one*, **14**(5), e0217564. doi:10.1371/journal.pone.0217564.

Rowland M, Benet LZ, Graham GG (1973). "Clearance concepts in pharmacokinetics." *Journal of pharmacokinetics and biopharmaceutics*, **1**(2), 123–136. doi:10.1007/BF01059626.

See Also

calc_analytic_css

create_mc_samples

Examples

```
# Set the number of samples (NSAMP) low for rapid testing, increase NSAMP
# for more stable results. Default value is 1000:
NSAMP = 10

# Basic in vitro - in vivo extrapolation with httk, convert 3 uM in vitro
# concentration of chemical with CAS 2451-62-9 to mg/kg/day:
set.seed(1234)
3/calc_mc_css(chem.cas="2451-62-9", samples=NSAMP, output.units="uM")
```

```
# The significant digits should give the same answer as:
set.seed(1234)
calc_mc_oral_equiv(chem.cas="2451-62-9", conc=3, samples=NSAMP)

 set.seed(1234)
 calc_mc_css(chem.name='Bisphenol A', output.units='uM',
             samples=NSAMP, return.samples=TRUE)

 set.seed(1234)
 calc_mc_css(chem.name='Bisphenol A', output.units='uM',
             samples=NSAMP,
             httkpop.generate.arg.list=list(method='vi'))

 # The following example should result in an error since we do not
 # estimate tissue partitioning with '3compartmentss'.
 set.seed(1234)
 try(calc_mc_css(chem.name='2,4-d', which.quantile=.9,
             samples=NSAMP,
             httkpop=FALSE, tissue='heart'))

# But heart will work with PBTK, even though it's lumped since we estimate
# a partition coefficient before lumping:
 set.seed(1234)
 calc_mc_css(chem.name='2,4-d', model='pbtk',
             samples=NSAMP,
             which.quantile=.9, httkpop=FALSE, tissue='heart')

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

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

 set.seed(1234)
 # Standard HTTK Monte Carlo
 calc_mc_css(chem.cas="90-43-7", model="pbtk", samples=NSAMP)
 set.seed(1234)
 # HTTK Monte Carlo with no measurement uncertainty (pre v1.10.0):
 calc_mc_css(chem.cas="90-43-7",
 model="pbtk",
 samples=NSAMP,
 invitro.mc.arg.list = list(
   adjusted.Funbound.plasma = TRUE,
   poormetab = TRUE,
   fup.censored.dist = FALSE,
   fup.lod = 0.01,
   fup.meas.cv = 0.0,
   clint.meas.cv = 0.0,
```

```
  fup.pop.cv = 0.3,
  clint.pop.cv = 0.3))

# HTTK Monte Carlo with no HTTK-Pop physiological variability):
set.seed(1234)
calc_mc_css(chem.cas="90-43-7",model="pbtk",samples=NSAMP,httkpop=FALSE)

# HTTK Monte Carlo with no in vitro uncertainty and variability):
set.seed(1234)
calc_mc_css(chem.cas="90-43-7",model="pbtk",samples=NSAMP,invitrouv=FALSE)

# HTTK Monte Carlo with no HTTK-Pop and no in vitro uncertainty and variability):
set.seed(1234)
calc_mc_css(chem.cas="90-43-7" ,model="pbtk",
            samples=NSAMP, httkpop=FALSE, invitrouv=FALSE)

# Should be the same as the mean result:
calc_analytic_css(chem.cas="90-43-7",model="pbtk",output.units="mg/L")

# HTTK Monte Carlo using basic Monte Carlo sampler:
set.seed(1234)
calc_mc_css(chem.cas="90-43-7",
            model="pbtk",
            samples=NSAMP,
            httkpop=FALSE,
            invitrouv=FALSE,
            vary.params=list(Pow=0.3))

# The following will not work because Diquat dibromide monohydrate's
# Henry's Law Constant (-3.912) is higher than that of Acetone (~-4.5):
try(calc_mc_css(chem.cas="6385-62-2"))

# However, we can turn off checking for phys-chem properties, since we know
# that  Diquat dibromide monohydrate is not too volatile:
calc_mc_css(chem.cas="6385-62-2", parameterize.args.list =list(physchem.exclude=FALSE))

# We can also use the Monte Carlo functions by passing a table
# where each row represents a different Monte Carlo draw of parameters:
p <- create_mc_samples(chem.cas="80-05-7")
# Use data.table for steady-state plasma concentration (Css) Monte Carlo:
calc_mc_css(parameters=p)
# Using the same table gives the same answer:
calc_mc_css(parameters=p)
# Use Css for 1 mg/kg/day for simple reverse toxicokinetics
# in Vitro-In Vivo Extrapolation to convert 15 uM to mg/kg/day:
15/calc_mc_css(parameters=p, output.units="uM")
# Can do the same with calc_mc_oral_equiv:
calc_mc_oral_equiv(15, parameters=p)

# HTTK Monte Carlo using basic Monte Carlo sampler:
set.seed(1234)
calc_mc_css(chem.cas="90-43-7",
  model="pbtk",
```

```
  samples=NSAMP,
  httkpop=FALSE,
  invitrouv=FALSE,
  vary.params=list(Pow=0.3))

# make sure the oral equivalent function works:
set.seed(1234)
calc_mc_oral_equiv(chem.name="bisphenol a",conc=10,samples=NSAMP)
set.seed(1234)
# Do the calculation manually to make sure units are correct:
signif(10/calc_mc_css(chem.name="bisphenol a",samples=NSAMP,output.units="uM"),4)

# do test of passing data.table of parameters
set.seed(1234)
parameter.dt <- create_mc_samples(chem.cas="335104-84-2",
                                  model="pbtk",
                                  samples=NSAMP)
calc_mc_oral_equiv(conc=100,
                   parameters=parameter.dt,
                   model="pbtk",
                   samples=NSAMP)

# do test of passing single set of parameters
params <- parameterize_steadystate(chem.cas="80-05-7")
css3 <- calc_analytic_css(
  parameters=params,
  output.units = "uM",
  model = "3compartmentss",
  species = "Human")
set.seed(1234)
css4 <- calc_mc_css(
  parameters=params,
  output.units = "uM",
  model = "3compartmentss",
  species = "Human",
  httkpop=FALSE,
  invitrouv=FALSE,
  return.samples=TRUE,
  samples=NSAMP)
set.seed(1234)
css5 <- calc_mc_css(
  parameters=params,
  output.units = "uM",
  model = "3compartmentss",
  species = "Human",
  httkpop=TRUE,
  invitrouv=TRUE,
  return.samples=TRUE,
  samples=NSAMP)

# If we turn off all the montecarlo the samples should all be the same and
# give us the same result as calc_analytic_css:
set.seed(1234)
```

```
css1 <- calc_mc_css(
  chem.cas = "80-05-7",
  output.units = "uM",
  model = "3compartmentss",
  species = "Human",
  httkpop=FALSE,
  invitrouv=FALSE,
  return.samples=TRUE,
  samples=NSAMP)
set.seed(1234)
css2 <- calc_analytic_css(
  chem.cas = "80-05-7",
  output.units = "uM",
  model = "3compartmentss",
  species = "Human")
# These values should be the same:
all(mean(abs(signif((css1-css2)/css2,4)))<0.001)
css2/css3==1
# Because we can't recalculate Rblood2plasma for 3compartmentss this is not
# quite the same but should be close:
unique(css4)/css2

# Now test that MC works across different models:
set.seed(1234)
calc_mc_css(chem.cas="15972-60-8",model="3compartment",samples=NSAMP)
set.seed(1234)
calc_mc_css(chem.cas="15972-60-8",model="1compartment",samples=NSAMP)
set.seed(1234)
calc_mc_css(chem.cas="15972-60-8",model="pbtk",samples=NSAMP)

# Should be the same as the mean result:
calc_analytic_css(chem.cas="90-43-7",model="pbtk",output.units="mg/L")
```

`calc_mc_oral_equiv` *Calculate Monte Carlo Oral Equivalent Dose*

Description

This function converts a chemical plasma concentration to an oral adminstered equivalent dose (AED) using a concentration obtained from `calc_mc_css`. This function uses reverse dosimetry-based '*in vitro-in vivo* extrapolation (IVIVE) for high throughput risk screening. The user can input the chemical and *in vitro* bioactive concentration, select the TK model, and then automatically predict the *in vivo* AED which would produce a body concentration equal to the *in vitro* bioactive concentration. This function relies on the Monte Carlo method (via funcion `create_mc_samples` to simulate both uncertainty and variability so that the result is a distribution of equivalent doses, from which we provide specific quantiles (specified by `which.quantile`), though the full set of predictions can be obtained by setting `return.samples` to `TRUE`.

Usage

```
calc_mc_oral_equiv(
  conc,
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  which.quantile = 0.95,
  species = "Human",
  input.units = "uM",
  output.units = "mgpkgpday",
  suppress.messages = FALSE,
  return.samples = FALSE,
  restrictive.clearance = TRUE,
  bioactive.free.invivo = FALSE,
  tissue = NULL,
  concentration = "plasma",
  IVIVE = NULL,
  model = "3compartmentss",
  Caco2.options = list(),
  calc.analytic.css.arg.list = list(),
  ...
)
```

Arguments

conc	Bioactive in vitro concentration in units of uM.
chem.name	Either the chemical name or the CAS number must be specified.
chem.cas	Either the CAS number or the chemical name must be specified.
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Parameters from the appropriate parameterization function for the model indicated by argument model
which.quantile	Which quantile from Monte Carlo steady-state simulation (calc_mc_css) is requested. Can be a vector. Note that 95th concentration quantile is the same population as the 5th dose quantile.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
input.units	Units of given concentration, default of uM but can also be mg/L.
output.units	Units of dose, default of 'mgpkgpday' for mg/kg BW/ day or 'umolpkgpday' for umol/ kg BW/ day.
suppress.messages	Suppress text messages.
return.samples	Whether or not to return the vector containing the samples from the simulation instead of the selected quantile.
restrictive.clearance	Protein binding not taken into account (set to 1) in liver clearance if FALSE.

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

`tissue`
: Desired steady state tissue concentration. Default is of NULL typically gives whole body plasma concentration.

`concentration`
: Desired concentration type: 'blood','tissue', or default 'plasma'. In the case that the concentration is for plasma, selecting "blood" will use the blood:plasma ratio to estimate blood concentration. In the case that the argument 'tissue' specifies a particular tissue of the body, concentration defaults to 'tissue' – that is, the concentration in the If cocentration is set to 'blood' or 'plasma' and 'tissue' specifies a specific tissue then the value returned is for the plasma or blood in that specific tissue.

`IVIVE`
: Honda et al. (2019) identified six plausible sets of assumptions for *in vitro-in vivo* extrapolation (IVIVE) assumptions. Argument may be set to "Honda1" through "Honda6". If used, this function overwrites the tissue, restrictive.clearance, and bioactive.free.invivo arguments. See Details below for more information.

`model`
: Model used in calculation,'gas_pbtk' for the gas pbtk model, '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.

`Caco2.options`
: A list of options to use when working with Caco2 apical to basolateral data `Caco2.Pab`, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = `Fabs`. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = `Fgut`. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See `get_fbio` for further details.

`calc.analytic.css.arg.list`
: A list of options to pass to the analytic steady-state calculation function. This includes 'restrictive.clearance', 'bioactive.free.invivo', 'IVIVE', 'wellstirred.correction', and 'adjusted.Funbound.plasma'.

`...`
: Additional parameters passed to `calc_mc_css` for httkpop and variance of parameters.

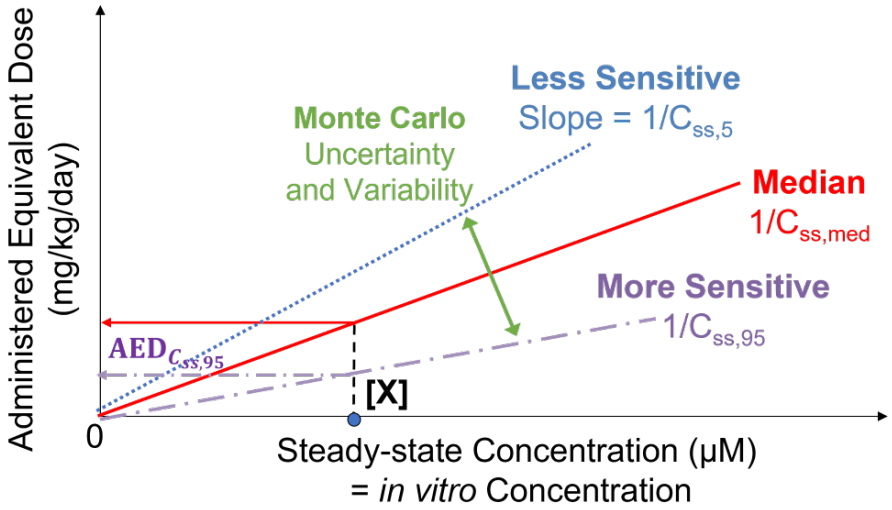
Details

The chemical-specific steady-state concentration for a dose rate of 1 mg/kg body weight/day can be used for in IVIVE of a bioactive *in vitro* concentration by dividing the *in vitro* concentration by the steady-state concentration to predict a dose rate (mg/kg/day) that would produce that concentration in plasma. Using quantiles of the distribution (such as the upper 95th percentile) allow incorporation of uncertainty and variability into IVIVE.

This approach relies on thelinearity of the models to calculate a scaling factor to relate in vitro concentrations (uM) with AED. The scaling factor is the inverse of the steady-state plasma concentration (Css) predicted for a 1 mg/kg/day exposure dose rate where *in vitro* concentration [X] and Css must be in the same units. Note that it is typical for *in vitro* concentrations to be reported in units of uM and Css in units of mg/L, in which case one must be converted to the other.

Reverse Dosimetry Toxicodynamic IVIVE

$$\mathbf{AED}_{C_{ss,95}} = \frac{[X]}{C_{ss,95}}$$



altalt

Figure from Breen et al. (2021) (doi:10.1080/17425255.2021.1935867) shows reverse dosimetry toxicodynamic IVIVE. Equivalent external dose is determined by solving the TK model in reverse by deriving the external dose (that is, TK model input) that produces a specified internal concentration (that is, TK model output). Reverse dosimetry and IVIVE using HTTK relies on the linearity of the models. We calculate a scaling factor to relate *in vitro* concentrations (uM) to AEDs. The scaling factor is the inverse of the Css predicted for a 1 mg/kg/day exposure dose rate. We use Monte Carlo to simulate variability and propagate uncertainty; for example, to calculate an upper 95th percentile Css,95 for individuals who get higher plasma concentrations from the same exposure.

The Monte Carlo methods used here were recently updated and described by Breen et al. (submitted).

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

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

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

The six sets of plausible IVIVE assumptions identified by Honda et al. (2019) (doi:10.1371/journal.pone.0217564) are:

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

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

Value

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

Author(s)

John Wambaugh

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

Wetmore BA, Wambaugh JF, Allen B, Ferguson SS, Sochaski MA, Setzer RW, Houck KA, Strope CL, Cantwell K, Judson RS, others (2015). "Incorporating high-throughput exposure predictions with dosimetry-adjusted in vitro bioactivity to inform chemical toxicity testing." *Toxicological Sciences*, **148**(1), 121–136. doi:10.1093/toxsci/kfv171.

Honda GS, Pearce RG, Pham LL, Setzer RW, Wetmore BA, Sipes NS, Gilbert J, Franz B, Thomas RS, Wambaugh JF (2019). "Using the concordance of in vitro and in vivo data to evaluate extrapolation assumptions." *PloS one*, **14**(5), e0217564. doi:10.1371/journal.pone.0217564.

Rowland M, Benet LZ, Graham GG (1973). "Clearance concepts in pharmacokinetics." *Journal of pharmacokinetics and biopharmaceutics*, **1**(2), 123–136. doi:10.1007/BF01059626.

See Also

`calc_mc_css`

`create_mc_samples`

Examples

```
# Set the number of samples (NSAMP) low for rapid testing, increase NSAMP
# for more stable results. Default value is 1000:
NSAMP = 10
```

```
# Basic in vitro - in vivo extrapolation with httk, convert 0.5 uM in vitro
# concentration of chemical Surinabant to mg/kg/day:
set.seed(1234)
0.5/calc_mc_css(chem.name="Surinabant", samples=NSAMP, output.units="uM")

# The significant digits should give the same answer as:
set.seed(1234)
calc_mc_oral_equiv(chem.name="Surinabant",conc=0.5,samples=NSAMP)

# Note that we use set.seed to get the same sequence of random numbers for
# the two different function calls (calc_mc_css and calc_mc_oral_equiv)

# The following example should result in an error since we do not
# estimate tissue partitioning with '3compartmentss'.
set.seed(1234)
try(calc_mc_oral_equiv(0.1, chem.cas="34256-82-1",
                       which.quantile=c(0.05,0.5,0.95),
                       samples=NSAMP,
                       tissue='brain'))

set.seed(1234)
calc_mc_oral_equiv(0.1,chem.cas="34256-82-1", model='pbtk',
                   samples=NSAMP,
                   which.quantile=c(0.05,0.5,0.95), tissue='brain')

# The following will not work because Diquat dibromide monohydrate's
# Henry's Law Constant (-3.912) is higher than that of Acetone (~-4.5):
try(calc_mc_oral_equiv(3, chem.cas="6385-62-2"))

# However, we can turn off checking for phys-chem properties, since we know
# that  Diquat dibromide monohydrate is not too volatile:
calc_mc_oral_equiv(3, chem.cas="6385-62-2", parameterize.args.list =list(physchem.exclude=FALSE))

# We can also use the Monte Carlo functions by passing a table
# where each row represents a different Monte Carlo draw of parameters:
p <- create_mc_samples(chem.cas="80-05-7")
# Use data.table for steady-state plasma concentration (Css) Monte Carlo:
calc_mc_css(parameters=p)
# Using the same table gives the same answer:
calc_mc_css(parameters=p)
# Use Css for 1 mg/kg/day for simple reverse toxicokinetics
# in Vitro-In Vivo Extrapolation to convert 15 uM to mg/kg/day:
15/calc_mc_css(parameters=p, output.units="uM")
# Can do the same with calc_mc_oral_equiv:
calc_mc_oral_equiv(15, parameters=p)
```

---

calc_mc_tk *Conduct multiple TK simulations using Monte Carlo*

Description

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

Usage

```
calc_mc_tk(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  samples = 1000,
  species = "Human",
  suppress.messages = FALSE,
  model = "pbtk",
  httkpop = TRUE,
  httkpop.dt = NULL,
  invitrouv = TRUE,
  calcrb2p = TRUE,
  censored.params = list(),
  vary.params = list(),
  return.samples = FALSE,
  tissue = NULL,
  output.units = "mg/L",
 solvemodel.arg.list = list(times = c(0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5)),
  Caco2.options = list(),
  invitro.mc.arg.list = NULL,
  httkpop.generate.arg.list = list(method = "direct resampling"),
  convert.httkpop.arg.list = NULL,
  parameterize.args.list = NULL,
  return.all.sims = FALSE
)
```

Arguments

chem.cas	Either the CAS number, parameters, or the chemical name must be specified.
chem.name	Either the chemical parameters, name, or the CAS number must be specified.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Parameters from parameterize_steadystate. Not used with httkpop model.
samples	Number of samples generated in calculating quantiles.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human"). Species must be set to "Human" to run httkpop model.
suppress.messages	Whether or not to suppress output message.
model	Model used in calculation: 'pbtk' for the multiple compartment model,'3compartment' for the three compartment model, '3compartmentss' for the three compartment

steady state model, and '1compartment' for one compartment model. This only applies when httkpop=TRUE and species="Human", otherwise '3compartmentss' is used.

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

`httkpop.dt` A data table generated by `httkpop_generate`. This defaults to NULL, in which case `httkpop_generate` is called to generate this table.

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

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

`censored.params`
The parameters listed in censored.params are sampled from a normal distribution that is censored for values less than the limit of detection (specified separately for each parameter). This argument should be a list of sub-lists. Each sublist is named for a parameter in "parameters" and contains two elements: "CV" (coefficient of variation) and "LOD" (limit of detection, below which parameter values are censored. New values are sampled with mean equal to the value in "parameters" and standard deviation equal to the mean times the CV. Censored values are sampled on a uniform distribution between 0 and the limit of detection. Not used with httkpop model.

`vary.params` The parameters listed in vary.params are sampled from a normal distribution that is truncated at zero. This argument should be a list of coefficients of variation (CV) for the normal distribution. Each entry in the list is named for a parameter in "parameters". New values are sampled with mean equal to the value in "parameters" and standard deviation equal to the mean times the CV. Not used with httkpop model.

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

`tissue` Desired steady state tissue conentration.

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

`solvemodel.arg.list`
Additional arguments ultimately passed to `solve_model`

`Caco2.options` A list of options to use when working with Caco2 apical to basolateral data `Caco2.Pab`, default is Caco2.options = list(Caco2.default = 2, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = `Fabs`. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = `Fgut`. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings.

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

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

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

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

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

Details

The Monte Carlo methods used here were recently updated and described by Breen et al. (submitted).

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

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

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

The six sets of plausible *in vitro-in vivo* extrpolation (IVIVE) assumptions identified by Honda et al. (2019) (doi:10.1371/journal.pone.0217564) are:

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

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

Value

If return.all.sims == FALSE (default) a list with:

`means`
: The mean concentration for each model compartment as a function of time across the Monte Carlo simulation

`sds`
: The standard deviation for each model compartment as a function of time across the Monte Carlo simulation

If return.all.sums == TRUE then a list is returned with:

`stats`
: The list of means and sds from return.all.sums=FALSE

`sims`
: The concentration vs. time results for each compartment for every (samples) set of parameters in the Monte Carlo simulation

Author(s)

John Wambaugh

See Also

create_mc_samples

Examples

```
NSAMP <- 50
chemname="Abamectin"
times<- c(0,0.25,0.5,0.75,1,1.5,2,2.5,3,4,5)
age.ranges <- seq(6,80,by=10)
forward <- NULL
for (age.lower in age.ranges)
{
  label <- paste("Ages ",age.lower,"-",age.lower+4,sep="")
  set.seed(1234)
  forward[[label]] <- calc_mc_tk(
                        chem.name=chemname,
                        samples=NSAMP,
                        httkpop.generate.arg.list=list(
                          method="d",
                          agelim_years = c(age.lower, age.lower+9)),
                        solvemodel.arg.list = list(
                          times=times))
}

set.seed(1234)
# well-behaved chemical with a measured Rblood2plasma:
lapply(calc_mc_tk(chem.cas="80-05-7",samples=NSAMP),function(x) x[-2,])
```

---

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

Description

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

Usage

```
calc_rblood2plasma(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
```

```
  hematocrit = NULL,
  Krbc2pu = NULL,
  Funbound.plasma = NULL,
  default.to.human = FALSE,
  species = "Human",
  adjusted.Funbound.plasma = TRUE,
  class.exclude = TRUE,
  suppress.messages = TRUE
)
```

Arguments

chem.cas	Either the CAS number or the chemical name must be specified.
chem.name	Either the chemical name or the CAS number must be specified.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Parameters from parameterize_schmitt
hematocrit	Overwrites default hematocrit value in calculating Rblood2plasma.
Krbc2pu	The red blood cell to unbound plasma chemical partition coefficient, typically from predict_partitioning_schmitt
Funbound.plasma	The fraction of chemical unbound (free) in the presence of plasma protein
default.to.human	Substitutes missing animal values with human values if true.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
adjusted.Funbound.plasma	Whether or not to use Funbound.plasma adjustment.
class.exclude	Exclude chemical classes identified as outside of domain of applicability by relevant modelinfo_[MODEL] file (default TRUE).
suppress.messages	Determine whether to display certain usage feedback.

Details

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

Value

The blood to plasma chemical concentration ratio

Author(s)

John Wambaugh and Robert Pearce

References

Schmitt W (2008). "General approach for the calculation of tissue to plasma partition coefficients." *Toxicology in vitro*, **22**(2), 457–467. doi:10.1016/j.tiv.2007.09.010.

Pearce RG, Setzer RW, Davis JL, Wambaugh JF (2017). "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." *Journal of pharmacokinetics and pharmacodynamics*, **44**, 549–565. doi:10.1007/s1092801795487.

Ruark CD, Hack CE, Robinson PJ, Mahle DA, Gearhart JM (2014). "Predicting passive and active tissue: plasma partition coefficients: interindividual and interspecies variability." *Journal of pharmaceutical sciences*, **103**(7), 2189–2198. doi:10.1002/jps.24011.

Examples

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

`calc_stats` *Calculate toxicokinetic summary statistics (deprecated).*

Description

#' This function is included for backward compatibility. It calls `calc_tkstats` which calculates the area under the curve, the mean, and the peak values for the venous blood or plasma concentration of a specified chemical or all chemicals if none is specified for the multiple compartment model with a given number of days, dose, and number of doses per day.

Usage

```
calc_stats(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  route = "oral",
  stats = c("AUC", "peak", "mean"),
  species = "Human",
  days = 28,
  daily.dose = 1,
  dose = NULL,
  doses.per.day = 1,
  output.units = "uM",
  concentration = "plasma",
  tissue = "plasma",
  model = "pbtk",
  default.to.human = FALSE,
  adjusted.Funbound.plasma = TRUE,
```

```
  regression = TRUE,
  restrictive.clearance = TRUE,
  suppress.messages = FALSE,
  ...
)
```

Arguments

chem.name	Name of desired chemical.
chem.cas	CAS number of desired chemical.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_pbtk function, overrides chem.name and chem.cas.
route	String specification of route of exposure for simulation: "oral", "iv", "inhalation", ...
stats	Desired values (either 'AUC', 'mean', 'peak', or a vector containing any combination).
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
days	Length of the simulation.
daily.dose	Total daily dose, mg/kg BW.
dose	Amount of a single dose at time zero, mg/kg BW.
doses.per.day	Number of doses per day.
output.units	Desired units (either "mg/L", "mg", "umol", or default "uM").
concentration	Desired concentration type, 'blood' or default 'plasma'.
tissue	Desired steady state tissue conentration.
model	Model used in calculation, 'pbtk' for the multiple compartment model,'3compartment' for the three compartment model, '3compartmentss' for the three compartment steady state model, and '1compartment' for one compartment model.
default.to.human	Substitutes missing animal values with human values if true (hepatic intrinsic clearance or fraction of unbound plasma).
adjusted.Funbound.plasma	Uses adjusted Funbound.plasma when set to TRUE along with partition coefficients calculated with this value.
regression	Whether or not to use the regressions in calculating partition coefficients.
restrictive.clearance	Protein binding not taken into account (set to 1) in liver clearance if FALSE.
suppress.messages	Whether to suppress output message.
...	Arguments passed to solve function.

Details

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

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

Value

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

Author(s)

Robert Pearce and John Wambaugh

---

calc_tkstats *Calculate toxicokinetic summary statistics.*

Description

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

Usage

```
calc_tkstats(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  route = "oral",
  stats = c("AUC", "peak", "mean"),
  species = "Human",
  days = 28,
  daily.dose = 1,
  dose = NULL,
  forcings = NULL,
  doses.per.day = 1,
  output.units = "uM",
  concentration = "plasma",
  tissue = "plasma",
  model = "pbtk",
  suppress.messages = FALSE,
  ...
)
```

Arguments

chem.name	Name of desired chemical.
chem.cas	CAS number of desired chemical.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_pbtk function, overrides chem.name and chem.cas.
route	String specification of route of exposure for simulation: "oral", "iv", "inhalation", ...
stats	Desired values (either 'AUC', 'mean', 'peak', or a vector containing any combination).
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
days	Length of the simulation.
daily.dose	Total daily dose, mg/kg BW.
dose	Amount of a single dose at time zero, mg/kg BW.
forcings	Manual input of 'forcings' data series argument for ode integrator, defaults is NULL. Then other input parameters (see exp.start.time, exp.conc, exp.duration, and period) provide the necessary information to assemble a forcings data series.
doses.per.day	Number of doses per day.
output.units	Desired units (either "mg/L", "mg", "umol", or default "uM").
concentration	Desired concentration type, 'blood' or default 'plasma'.
tissue	Desired steady state tissue conentration.
model	Model used in calculation, 'pbtk' for the multiple compartment model,'3compartment' for the three compartment model, '3compartmentss' for the three compartment steady state model, and '1compartment' for one compartment model.
suppress.messages	Whether to suppress output message.
...	Additional arguments passed to the solve_model

Details

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

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

Value

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

Author(s)

Robert Pearce and John Wambaugh

Examples

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


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

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

calc_tkstats(dtxsid="DTXSID0020442",days=1)

calc_tkstats(dtxsid="DTXSID0020442",days=10)

calc_tkstats(dtxsid="DTXSID0020442",days=100)
```

---

calc_total_clearance *Calculate the total plasma clearance.*

Description

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

Usage

```
calc_total_clearance(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  model = "3compartmentss",
  suppress.messages = FALSE,
  species = "Human",
  ...
)
```

Arguments

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

dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_steadystate function, overrides chem.name and chem.cas.
model	The model used to calculate total clearance (defaults to "3compartmentss")
suppress.messages	Whether or not the output message is suppressed.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
...	Additional parameters passed to parameterize function 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 using predict_partitioning_schmitt, then lumps them into a single compartment.

Usage

```
calc_vdist(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  suppress.messages = FALSE,
  adjusted.Funbound.plasma = TRUE,
  species = "Human",
  default.to.human = FALSE,
  ...
)
```

Arguments

chem.cas	Either the CAS number or the chemical name must be specified when Funbound.plasma is not given in parameter list.
chem.name	Either the chemical name or the CAS number must be specified when Funbound.plasma is not given in parameter list.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Parameters from parameterize_3comp, parameterize_pbtk or predict_partitioning_schmitt.
suppress.messages	Whether or not the output message is suppressed.
adjusted.Funbound.plasma	Uses Pearce et al. (2017) lipid binding adjustment for Funbound.plasma (which impacts partition coefficients) when set to TRUE (Default).
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
default.to.human	Substitutes missing animal values with human values if true.
...	Additional parameters passed to parameterize function if parameters is NULL.

Details

The effective volume of distribution is calculated by summing each tissues volume times it's partition coefficient relative to plasma. Plasma, and the paritioning into RBCs are also added to get the total volume of distribution in L/KG BW. Partition coefficients are calculated using Schmitt's (2008) method. When species is specified as rabbit, dog, or mouse, the function uses the appropriate physiological data(volumes and flows) but substitues human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Value

Volume of distribution	Units of L/ kg BW.

Author(s)

John Wambaugh and Robert Pearce

References

Schmitt W (2008). "General approach for the calculation of tissue to plasma partition coefficients." *Toxicology in vitro*, **22**(2), 457–467. doi:10.1016/j.tiv.2007.09.010.

Peyret T, Poulin P, Krishnan K (2010). "A unified algorithm for predicting partition coefficients for PBPK modeling of drugs and environmental chemicals." *Toxicology and applied pharmacology*, **249**(3), 197–207. doi:10.1016/j.taap.2010.09.010.

See Also

predict_partitioning_schmitt

tissue.data

physiology.data

Examples

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

# Create a list of parameters (that you can potentially change):
p <- parameterize_schmitt(chem.name="propranolol")
# Need to use those parameters to predict partition coefficients:
PCs <- predict_partitioning_schmitt(parameters = p)

# Lump the tissues into a single volume of distribution
calc_vdist(parameters=c(p,PCs))
# Should be the same as chemical by name:
calc_vdist(chem.name="propranolol")

# Different ways to give the arguments:
calc_vdist(chem.cas="80-05-7")
params <- parameterize_schmitt(chem.name="triclosan")
params <- c(params, predict_partitioning_schmitt(parameters = params))
calc_vdist(parameters=params)
params <- parameterize_3comp(chem.name="triclosan")
calc_vdist(parameters=params)
params <- parameterize_pbtk(chem.name="triclosan")
calc_vdist(parameters=params)
```

CAS.checksum *Test the check digit of a CAS number to confirm validity*

Description

Chemical abstracts services registry numbers (CAS-RN) include a final digit as a "checksum" to test for validity (that is, that the number has not been corrupted).

Usage

```
CAS.checksum(CAS.string)
```

Arguments

CAS.string	A character string of three numbers separated by two dashes

Details

The check digit (final number) is calculated by working from right to left, starting with the second to last digit of the CAS-RN. We multiply each digit by an increasing digit (1, 2, 3...) and sum as we work from right to left. The check digit should equal the final digit of the sum.

Value

logical (TRUE if final digit of CAS is consistent with other digits)

Author(s)

John Wambaugh

`cas_id_check` *CAS number format check function*

Description

This function checks whether the CAS/CARN chemical identifier follows the anticipated format of XXXXXXX-YY-Z (i.e. 2-7 digits, 2 digits, and 1 digit, respectively).

Usage

```
cas_id_check(cas)
```

Arguments

`cas`	A character string, or vector of character strings, indicating CAS/CASRN number.

Value

Logical output (TRUE or FALSE) indicating whether the character string(s) provided match the anticipated format for a CAS/CASRN chemical identifier.

check_model *Check for sufficient model parameters*

Description

This function halt model evaluation if not all the needed parameters (as specified in the modelinfo_[MODEL].r file) are available. The function uses get_cheminfo, so if the chemical has been checked against that function already then evaluation should proceed as expected. If you do not have the parameters you need and are using a non-human species try default.to.human = TRUE (there are many more values for human than any other species). If working in human, try first using load_dawson2021, load_sipes2017, or load_pradeep2020.

Usage

```
check_model(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  model = NULL,
  species = NULL,
  class.exclude = TRUE,
  physchem.exclude = TRUE,
  default.to.human = FALSE
)
```

Arguments

chem.name	Chemical name (spaces and capitalization ignored) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXSIDs
model	Model to be checked, modelinfo files specify the requrements of each model.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
class.exclude	Exclude chemical classes identified as outside of domain of applicability by relevant modelinfo_[MODEL] file (default TRUE).
physchem.exclude	Exclude chemicals on the basis of physico-chemical properties (currently only Henry's law constant) as specified by the relevant modelinfo_[MODEL] file (default TRUE).
default.to.human	Substitutes missing fraction of unbound plasma with human values if true.

Value

Stops code from running if all parameters needed for model are not available, otherwise does nothing.

Author(s)

john Wambaugh

See Also

get_cheminfo

---

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 (Fabsgut), 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

References

Wambaugh JF, Hughes MF, Ring CL, MacMillan DK, Ford J, Fennell TR, Black SR, Snyder RW, Sipes NS, Wetmore BA, others (2018). "Evaluating in vitro-in vivo extrapolation of toxicokinetics." *Toxicological Sciences*, **163**(1), 152–169. doi:10.1093/toxsci/kfy020.

`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

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

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

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`chem.invivo.PK.summary.data`

Summary of published toxicokinetic time course experiments

Description

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

Usage

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

Format

A data.frame containing 100 rows and 25 columns.

Author(s)

John Wambaugh

Source

Wambaugh et al. 2018 Toxicological Sciences, in press

References

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

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

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

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

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

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`chem.physical_and_invitro.data`

Physico-chemical properties and in vitro measurements for toxicokinetics

---

Description

This data set contains the necessary information to make basic, high-throughput toxicokinetic (HTTK) predictions for compounds, including Funbound.plasma, molecular weight (g/mol), logP, logMA (membrane affinity), intrinsic clearance(uL/min/10^6 cells), and pKa. These data have been compiled from multiple sources, and can be used to parameterize a variety of toxicokinetic models. See variable EPA.ref for information on the reference EPA.

Usage

```
chem.physical_and_invitro.data
```

Format

A data.frame containing 9411 rows and 54 columns.

Column Name	Description
Compound	The preferred name of the chemical compound
CAS	The preferred Chemical Abstracts Service Registry Number
CAS.Checksum	A logical indicating whether the CAS number is valid
DTXSID	DSSTox Structure ID (https://comptox.epa.gov/dashboard)
Formula	The proportions of atoms within the chemical compound
All.Compound.Names	All names of the chemical as they occured in the data
logHenry	The log10 Henry's law constant (Conc_air = 10^logH * Conc_liquid)
logHenry.Reference	Reference for Henry's law constant
logP	The log10 octanol:water partition coefficient (PC)
logP.Reference	Reference for logPow
logPwa	The log10 water:air PC
logPwa.Reference	Reference for logPwa
logMA	The log10 phospholipid:water PC or "Membrane affinity"
logMA.Reference	Reference for membrane affinity
logWSol	The log10 water solubility
logWSol.Reference	Reference for logWsol
MP	The chemical compound melting point
MP.Reference	Reference for melting point
MW	The chemical compound molecular weight
MW.Reference	Reference for molecular weight
pKa_Accept	The hydrogen acceptor equilibria concentrations
pKa_Accept.Reference	Reference for pKa_Accept
pKa_Donor	The hydrogen acceptor equilibria concentrations
pKa_Donor.Reference	Reference for pKa_Donor
All.Species	All species for which data were available
DTXSID.Reference	Reference for DTXSID
Formula.Reference	Reference for chemical formulat
[SPECIES].Clint	(Primary hepatocyte suspension) intrinsic hepatic clearance. *Entries with comma separat*
[SPECIES].Clint.pValue	Probability that there is no clearance observed. Values close to 1 indicate clearance is not
[SPECIES].Clint.pValue.Ref	Reference for Clint pValue
[SPECIES].Clint.Reference	Reference for Clint
[SPECIES].Caco2.Pab	Caco-2 Apical-to-Basal Membrane Permeability
[SPECIES].Caco2.Pab.Reference	Reference for Caco-2 Membrane Permeability
[SPECIES].Fabs	In vivo measured fraction of an oral dose of chemical absorbed from the gut lumen into tl
[SPECIES].Fabs.Reference	Reference for Fabs
[SPECIES].Fgut	In vivo measured fraction of an oral dose of chemical that passes gut metabolism and clea
[SPECIES].Fgut.Reference	Reference for Fgut
[SPECIES].Foral	In vivo measued fractional systemic bioavailability of an oral dose, modeled as he produc
[SPECIES].Foral.Reference	Reference for Foral
[SPECIES].Funbound.plasma	Chemical fraction unbound in presence of plasma proteins (fup). *Entries with comma sep*
[SPECIES].Funbound.plasma.Ref	Reference for Funbound.plasma
[SPECIES].Rblood2plasma	Chemical concentration blood to plasma ratio
[SPECIES].Rblood2plasma.Ref	Reference for Rblood2plasma
Chemical.Class	All classes to which the chemical has been assigned

Details

In some cases the rapid equilbrium dailysis method (Waters et al., 2008) fails to yield detectable concentrations for the free fraction of chemical. In those cases we assume the compound is highly bound (that is, Fup approaches zero). For some calculations (for example, steady-state plasma concentration) there is precendent (Rotroff et al., 2010) for using half the average limit of detection, that is 0.005. We do not recomend using other models where quantities like partition coefficients must be predicted using Fup. We also do not recomend including the value 0.005 in training sets for Fup predictive models.

Note that in some cases the **Funbound.plasma** and the **intrinsic clearance** are *provided as a series of numbers separated by commas*. These values are the result of Bayesian analysis and characterize a distribution: the first value is the median of the distribution, while the second and third values are the lower and upper 95th percentile (that is qunatile 2.5 and 97.5) respectively. For intrinsic clearance a fourth value indicating a p-value for a decrease is provided. Typically 4000 samples were used for the Bayesian analusis, such that a p-value of "0" is equivale to "<0.00025". See Wambaugh et al. (2019) for more details.

Any one chemical compound *may have multiple ionization equilibria* (see Strope et al., 2018) may both for donating or accepting a proton (and therefore changing charge state). If there are multiple equlibria of the same type (donor/accept])the are concatonated by commas.

All species-specific information is initially from experimental measurements. The functions `load_sipes2017`, `load_pradeep2020`, and `load_dawson2021` may be used to add in silico, structure-based predictions for many thousands of additional compounds to this table.

Author(s)

John Wambaugh

Source

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

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CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard)

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

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F. L. Wood, J. B. Houston and D. Hallifax 'Drug Metabolism and Disposition November 1, 2017, 45 (11) 1178-1188; DOI: https://doi.org/10.1124/dmd.117.077040

See Also

`get_physchem_param`

`get_invitroPK_param`

`add_chemtable`

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

Description

Predict GFR from serum creatinine, gender, and age.

Usage

```
ckd_epi_eq(scr, gender, reth, age_years, ckd_epi_race_coeff = FALSE)
```

Arguments

scr	Vector of serum creatinine values in mg/dL.
gender	Vector of genders (either 'Male' or 'Female').
reth	Vector of races/ethnicities. Not used unless ckd_epi_race_coeff is TRUE.
age_years	Vector of ages in years.
ckd_epi_race_coeff	Whether to use the "race coefficient" in the CKD-EPI equation. Default is FALSE.

Details

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

Value

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

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

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concentration_data_Linakis2020

Concentration data involved in Linakis 2020 vignette analysis.

Description

These rat and human TK concentration vs. time (CvT) data are drawn from the CvTdb (Sayre et el., 2020). Concentrations have all been converted to the units of uM. All data are from inhalation studies.

Usage

```
concentration_data_Linakis2020
```

Format

A data.frame containing 2142 rows and 16 columns.

Details

Abbreviations used for sampling matrix: BL : blood EEB : end-exhaled breath MEB : mixed exhaled breath VBL : venous blood ABL : arterial blood EB : unspecified exhaled breath sample (assumed to be EEB) PL: plasma +W with work/exercise

Column Name	Description
PREFERRED_NAME	Substance preferred name
DTXSID	Identifier for CompTox Chemical Dashboard
CASRN	Chemical abstracts service registration number
AVERAGE_MASS	Substance molecular weight g/mol
DOSE DOSE_U	Inhalation exposure concentration in parts per million
EXP_LENGTH	Duration of inhalation exposur
TIME	Measurment time
TIME_U	Time units for all times reported
CONC_SPECIES	Species for study
SAMPLING_MATRIX	Matrix analyzed
SOURCE_CVT	Data source identifier within CvTdb
ORIG_CONC_U	Original reported units for concentration
CONCENTRATION	Analyte concentration in uM units

Author(s)

Matt Linakis

Source

Matt Linakis

References

Linakis MW, Sayre RR, Pearce RG, Sfeir MA, Sipes NS, Pangburn HA, Gearhart JM, Wambaugh JF (2020). "Development and evaluation of a high-throughput inhalation model for organic chemicals." *Journal of exposure science & environmental epidemiology*, **30**(5), 866–877. doi:10.1038/s41370-0200238y. Sayre RR, Wambaugh JF, Grulke CM (2020). "Database of pharmacokinetic time-series data and parameters for 144 environmental chemicals." *Scientific data*, **7**(1), 122. doi:10.1038/s4159702004551.

`convert_solve_x` *convert_solve_x*

Description

This function is designed to convert compartment values estimated from one of the HTTK models (e.g. "1compartment) using the solve_model function. It takes the HTTK model output matrix, model name, desired output units, and compound information to perform the conversion default model units to user specified units.

Usage

```
convert_solve_x(
  model.output.mat,
  model = NULL,
  output.units = NULL,
  MW = NULL,
  vol = NULL,
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  monitor.vars = NULL,
  suppress.messages = FALSE,
  verbose = FALSE,
  ...
)
```

Arguments

model.output.mat	Matrix of results from HTTK solve_model function.
model	Specified model to use in simulation: "pbtk", "3compartment", "3compartmentss", "1compartment", "schmitt", ...
output.units	Output units of interest for the compiled components. Defaults to NULL, and will provide values in model units if unspecified.
MW	Molecular weight of substance of interest in g/mole
vol	Volume for the target tissue of interest in liters (L). NOTE: Volume should not be in units of per BW, i.e. "kg".
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
chem.name	Either the chemical name, CAS number, or the parameters must be specified.
dtxsid	EPA's DSSTox Structure ID . (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs.
parameters	A set of model parameters, especially a set that includes MW (molecular weight) for our conversions.
monitor.vars	A vector of character strings indicating the model component variables to retain in the conversion factor table (assuming suppress.messages == FALSE). It should also be noted this option does NOT exclude columns from the input matrix provided in the 'model.output.mat' parameter. (Default is NULL, i.e. conversion factors for all model components are included in the reporting matrix.)
suppress.messages	Whether or not the output messages are suppressed. (Default is FALSE, i.e. show messages.)
verbose	Whether or not to display the full conversion factor table. (Default is FALSE, i.e. only include rows where the conversion factor is 1.)

... Other parameters that can be passed to convert_units, e.g. temperature and compound state. See details in convert_units.

Details

The function can be used to convert all compartments to a single unit, only units for a single model compartment, or units for a set of model compartments.

More details on the unit conversion can be found in the documentation for convert_units.

Value

'new.ouput.matrix' A matrix with a column for time (in days), each compartment, and the area under the curve (AUC) and a row for each time point. The compartment and AUC columns are converted from model specified units to user specified units.

'output.units.vector' A vector of character strings providing the model compartments and their corresponding units after convert_solve_x.

Author(s)

Sarah E. Davidson

See Also

convert_units

Examples

```
output.mat <- solve_1comp(dtxsid = "DTXSID0020573",days=1)
new.output.mat <- convert_solve_x(output.units = "mg",
                                  model.output.mat = output.mat,
                                  model = "1compartment",
                                  dtxsid = "DTXSID0020573")
```

---

convert_units *convert_units*

Description

This function is designed to accept input units, output units, and the molecular weight (MW) of a substance of interest to then use a table lookup to return a scaling factor that can be readily applied for the intended conversion. It can also take chemical identifiers in the place of a specified molecular weight value to retrieve that value for its own use.

Usage

```
convert_units(
  input.units = NULL,
  output.units = NULL,
  MW = NULL,
  vol = NULL,
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  temp = 25,
  liquid.density = 1,
  state = "liquid"
)
```

Arguments

input.units	Assigned input units of interest
output.units	Desired output units
MW	Molecular weight of substance of interest in g/mole
vol	Volume for the target tissue of interest in liters (L). NOTE: Volume should not be in units of per BW, i.e. "kg".
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
chem.name	Either the chemical name, CAS number, or the parameters must be specified.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	A set of model parameters, especially a set that includes MW (molecular weight) for our conversions
temp	Temperature for conversions (default = 25 degreees C)
liquid.density	Density of the specified chemical in liquid state, numeric value, (default 1.0 g/mL).
state	Chemical state (gas or default liquid).

Details

If input or output units not contained in the table are queried, it gives a corresponding error message. It gives a warning message about the handling of 'ppmv,' as the function is only set up to convert between ppmv and mass-based units (like mg/m^3 or umol/L) in the context of ideal gases.

convert_units is not directly configured to accept and convert units based on BW, like mg/kg. For this purpose, see scale_dosing.

The function supports a limited set of most relevant units across toxicological models, currently including umol, uM, mg, mg/L, mg/m^3 or umol/L), and in the context of gases assumed to be ideal, ppmv.

Andersen and Clewell's Rules of PBPK Modeling:

1. Check Your Units
2. **Check Your Units**
3. Check Mass Balance

Author(s)

Mark Sfeir, John Wambaugh, and Sarah E. Davidson

Examples

```
# MW BPA is 228.29 g/mol
# 1 mg/L -> 1/228.29*1000 = 4.38 uM
convert_units("mg/L","uM",chem.cas="80-05-7")

# MW Diclofenac is 296.148 g/mol
# 1 uM -> 296.148/1000 =  0.296
convert_units("uM","mg/L",chem.name="diclofenac")

# ppmv only works for gasses:
try(convert_units("uM","ppmv",chem.name="styrene"))
convert_units("uM","ppmv",chem.name="styrene",state="gas")

# Compare with https://www3.epa.gov/ceampubl/learn2model/part-two/onsite/ia_unit_conversion.html
# 1 ug/L Toluene -> 0.263 ppmv
convert_units("ug/L","ppmv",chem.name="toluene",state="gas")
# 1 pppmv Toluene, 0.0038 mg/L
convert_units("ppmv","mg/L",chem.name="toluene",state="gas")

MW_pyrene <- get_physchem_param(param='MW', chem.name='pyrene')
conversion_factor <- convert_units(input.units='mg/L', output.units ='uM',
  MW=MW_pyrene)

calc_mc_oral_equiv(15, parameters=p)
```

`create_mc_samples` *Create a table of parameter values for Monte Carlo*

Description

This is the HTTK master function for creating a data table for use with Monte Carlo methods to simulate parameter uncertainty and variabilit. Each column of the output table corresponds to an HTTK model parameter and each row corresponds to a different random draw (for example, different individuals when considering biological variability). This function call three different key functions to simulate parameter parameter uncertainty and/or variability in one of three ways. First parameters can be varied in an uncorrelated manner using truncated normal distributions by the function `monte_carlo`. Then, physiological parameters can be varied in a correlated manner according to the Ring et al. (2017) (doi:10.1016/j.envint.2017.06.004) *httk-pop* approach by the function `httkpop_mc`. Next, both uncertainty and variability of in vitro HTTK parameters can be

simulated by the function invitro_mc as described by Wambaugh et al. (2019) (doi:10.1093/toxsci/kfz205). Finally, tissue-specific partition coefficients are predicted for each draw using the Schmitt (2008) (doi:10.1016/j.tiv.2007.09.010) method as calibrated to *in vivo* data by Pearce et al. (2017) (doi:10.1007/s1092801795487) and implemented in predict_partitioning_schmitt.

Usage

```
create_mc_samples(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  samples = 1000,
  species = "Human",
  suppress.messages = FALSE,
  model = "3compartmentss",
  httkpop = TRUE,
  invitrouv = TRUE,
  calcrb2p = TRUE,
  censored.params = list(),
  vary.params = list(),
  return.samples = FALSE,
  tissue = NULL,
  httkpop.dt = NULL,
  invitro.mc.arg.list = NULL,
  adjusted.Funbound.plasma = TRUE,
  adjusted.Clint = TRUE,
  httkpop.generate.arg.list = list(method = "direct resampling"),
  convert.httkpop.arg.list = NULL,
  propagate.invitrouv.arg.list = NULL,
  parameterize.args.list = NULL,
  Caco2.options = NULL
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Parameters from the appropriate parameterization function for the model indicated by argument model
samples	Number of samples generated in calculating quantiles.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human"). Species must be set to "Human" to run httkpop model.

`suppress.messages`
: Whether or not to suppress output message.

`model`
: Model used in calculation: 'pbtk' for the multiple compartment model,'3compartment' for the three compartment model, '3compartmentss' for the three compartment steady state model, and '1compartment' for one compartment model. This only applies when httkpop=TRUE and species="Human", otherwise '3compartmentss' is used.

`httkpop`
: Whether or not to use the Ring et al. (2017) "httkpop" population generator. Species must be 'Human'.

`invitrouv`
: Logical to indicate whether to include in vitro parameters such as intrinsic hepatic clearance rate and fraction unbound in plasma in uncertainty and variability analysis

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

`censored.params`
: The parameters listed in censored.params are sampled from a normal distribution that is censored for values less than the limit of detection (specified separately for each 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.

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

`tissue`
: Desired steady state tissue conentration.

`httkpop.dt`
: A data table generated by `httkpop_generate`. This defaults to NULL, in which case `httkpop_generate` is called to generate this table.

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

`adjusted.Funbound.plasma`
: Uses Pearce et al. (2017) lipid binding adjustment for Funbound.plasma when set to TRUE (Default).

`adjusted.Clint`
: Uses Kilford et al. (2008) hepatocyte incubation binding adjustment for Clint when set to TRUE (Default).

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

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

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

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

`Caco2.options`
: Arguments describing how to handle Caco2 absorption data that are passed to `invitro_mc` and the parameterize_[MODEL] functions. See `get_fbio` for further details.

Details

The Monte Carlo methods used here were recently updated and described by Breen et al. (2022).

We aim to make any function that uses chemical identifiers (name, CAS, DTXSID) also work if passed a complete vector of parameters (that is, a row from the table generated by this function). This allows the use of Monte Carlo to vary the parameters and therefore vary the function output. Depending on the type of parameters (for example, physiological vs. in vitro measurements) we vary the parameters in different ways with different functions.

Value

A data table where each column corresponds to parameters needed for the specified model and each row represents a different Monte Carlo sample of parameter values.

Author(s)

Caroline Ring, Robert Pearce, and John Wambaugh

References

Breen M, Wambaugh JF, Bernstein A, Sfeir M, Ring CL (2022). "Simulating toxicokinetic variability to identify susceptible and highly exposed populations." *Journal of Exposure Science & Environmental Epidemiology*, **32**(6), 855–863. doi:10.1038/s41370022004910.

Kilford PJ, Gertz M, Houston JB, 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), 1194–1197. doi:10.1124/dmd.108.020834.

Pearce RG, Setzer RW, Davis JL, Wambaugh JF (2017). "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." *Journal of pharmacokinetics and pharmacodynamics*, **44**, 549–565. doi:10.1007/s1092801795487.

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

Schmitt W (2008). "General approach for the calculation of tissue to plasma partition coefficients." *Toxicology in vitro*, **22**(2), 457–467. doi:10.1016/j.tiv.2007.09.010.

Wambaugh JF, Wetmore BA, Ring CL, Nicolas CI, Pearce RG, Honda GS, Dinallo R, Angus D,

Gilbert J, Sierra T, others (2019). "Assessing toxicokinetic uncertainty and variability in risk prioritization." *Toxicological Sciences*, **172**(2), 235–251. doi:10.1093/toxsci/kfz205.

Examples

```
# We can use the Monte Carlo functions by passing a table
# where each row represents a different Monte Carlo draw of parameters:
p <- create_mc_samples(chem.cas="80-05-7")

# Use data.table for steady-state plasma concentration (Css) Monte Carlo:
calc_mc_css(parameters=p)

# Using the same table gives the same answer:
calc_mc_css(parameters=p)

# Use Css for 1 mg/kg/day for simple reverse toxicokinetics
# in Vitro-In Vivo Extrapolation to convert 15 uM to mg/kg/day:
15/calc_mc_css(parameters=p, output.units="uM")

# Can do the same with calc_mc_oral_equiv:
calc_mc_oral_equiv(15, parameters=p)

#Generate a population using the virtual-individuals method,
#including 80 females and 20 males,
#including only ages 20-65,
#including only Mexican American and
#Non-Hispanic Black individuals,
#including only non-obese individuals
set.seed(42)
mypop <- 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'))
# Including a httkpop.dt argument will overwrite the number of sample and
# the httkpop on/off logical switch:
samps1 <- create_mc_samples(chem.name="bisphenola",
                            httkpop=FALSE,
                            httkpop.dt=mypop)
samps2 <- create_mc_samples(chem.name="bisphenola",
                            httkpop.dt=mypop)
# But we can turn httkpop off altogether if desired:
samps3 <- create_mc_samples(chem.name="bisphenola",
                            httkpop=FALSE)
```

dawson2021 *Dawson et al. 2021 data*

Description

This table includes QSAR (Random Forest) model predicted values for unbound fraction plasma protein (fup) and intrinsic hepatic clearance (clint) for a subset of chemicals in the Tox21 library (see https://www.epa.gov/chemical-research/toxicology-testing-21st-century-tox21).

Usage

```
dawson2021
```

Format

data.frame

Details

Predictions were made with a set of Random Forest QSAR models, as reported in Dawson et al. (2021).

Author(s)

Daniel E. Dawson

References

Dawson DE, Ingle BL, Phillips KA, Nichols JW, Wambaugh JF, Tornero-Velez R (2021). "Designing QSARs for Parameters of High-Throughput Toxicokinetic Models Using Open-Source Descriptors." *Environmental Science & Technology*, **55**(9), 6505-6517. doi:10.1021/acs.est.0c06117, PMID: 33856768, https://doi.org/10.1021/acs.est.0c06117.

See Also

load_dawson2021

dtxsid_id_check *DTXSID number format check function*

Description

This function checks whether the DTXSID chemical identifier follows the anticipated format of "DTXSID<uniqueID>".

Usage

```
dtxsid_id_check(dtxsid)
```

Arguments

dtxsid	A character string, or vector of character strings, indicating DTXSID number.

Value

Logical output (TRUE or FALSE) indicating whether the character string(s) provided match the anticipated format for a DTXSID chemical identifier.

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

Description

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

Usage

```
EPA.ref
```

Format

An object of class `character` of length 1.

Author(s)

John Wambaugh

Source

https://comptox.epa.gov/dashboard

`estimate_gfr` *Predict GFR.*

Description

Predict GFR using CKD-EPI equation (for adults) or BSA-based equation (for children).

Usage

```
estimate_gfr(gfrtmp.dt, gfr_resid_var = TRUE, ckd_epi_race_coeff = FALSE)
```

Arguments

`gfrtmp.dt`	A data.table with columns `gender`, `reth`, `age_years`, `age_months`, `BSA_adj`, `serum_creat`.
`gfr_resid_var`	Logical value indicating whether or not to include residual variability when generating GFR values. (Default is TRUE.)
`ckd_epi_race_coeff`	Logical value indicating whether or not to use the "race coefficient" from the CKD-EPI equation when estimating GFR values. (Default is FALSE.)

Details

Add residual variability based on reported residuals for each equation.

Value

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

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

`estimate_gfr_ped` *Predict GFR in children.*

Description

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

Usage

```
estimate_gfr_ped(BSA)
```

Arguments

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

Value

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

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

`estimate_hematocrit` *Generate hematocrit values for a virtual population*

Description

Predict hematocrit from age using smoothing splines and kernel density estimates of residual variability fitted to NHANES data, for a given combination of gender and NHANES race/ethnicity category.

Usage

```
estimate_hematocrit(gender, reth, age_years, age_months, nhanes_mec_svy)
```

Arguments

gender	Gender for which to generate hematocrit values ("Male" or "Female")
reth	NHANES race/ethnicity category for which to generate serum creatinine values ("Mexican American", "Non-Hispanic Black", "Non-Hispanic White", "Other", or "Other Hispanic")
age_years	Vector of ages in years for individuals for whom to generate hematocrit values (corresponding to age_months)
age_months	vector of ages in months for individuals for whom to generate hematocrit values (between 0-959 months)
nhanes_mec_svy	surveydesign object created from mecdt using svydesign (this is done in httkpop_generate)

Details

This function should usually not be called directly by the user. It is used by httkpop_generate() in "virtual-individuals" mode, after drawing gender, NHANES race/ethnicity category, and age from their NHANES proportions/distributions.

Value

A vector of numeric generated hematocrit values (blood percentage red blood cells by volume).

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

---

example.seem *SEEM Example Data We can grab SEEM daily intake rate predictions already in RData format from https://github.com/HumanExposure/SEEM3RPackage/tree/main/SEEM3/data Download the file Ring2018Preds.RData*

Description

We do not have the space to distribute all the SEEM predictions within this R package, but we can give you our "Intro to IVIVE" example chemicals

Usage

```
example.seem
```

Format

data.frame

References

Ring CL, Arnot JA, Bennett DH, Egeghy PP, Fantke P, Huang L, Isaacs KK, Jolliet O, Phillips KA, Price PS, others (2018). "Consensus modeling of median chemical intake for the US population based on predictions of exposure pathways." *Environmental science & technology*, **53**(2), 719–732. doi:10.1021/acs.est.8b04056.

`example.toxcast` *ToxCast Example Data The main page for the ToxCast data is here: https://www.epa.gov/comptox-tools/exploring-toxcast-data Most useful to us is a single file containing all the hits across all chemcials and assays: https://clowder.edap-cluster.com/datasets/6364026ee4b04f6bb1409eda?space=62bb560ee4b07abf29f88fef*

Description

As of November, 2022 the most recent version was 3.5 and was available as an .Rdata file (invitrodb_3_5_mc5.Rdata)

Usage

```
example.toxcast
```

Format

data.frame

Details

Unfortunately for this vignette there are too many ToxCast data to fit into a 5mb R package. So we will subset to just the shemicals for the "Intro to IVIVE" vignette and distribute only those data. In addition, out of 78 columns in the data, we will keep only eight.

`export_pbtk_jarnac` *Export model to jarnac.*

Description

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

Usage

```
export_pbtk_jarnac(
  chem.cas = NULL,
  chem.name = NULL,
  species = "Human",
  initial.amounts = list(Agutlumen = 0),
  folder = tempdir(),
  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.
`folder`	The folder on the file system containing the output file. Defaults to `tempdir`.
`filename`	The name of the jarnac file containing the model.
`digits`	Desired number of decimal places to round the parameters.

Details

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

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

Value

Text containing a Jarnac language version of the PBTK model.

Author(s)

Robert Pearce

Examples

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

`export_pbtk_sbml` *Export model to sbml.*

Description

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

Usage

```
export_pbtk_sbml(
  chem.cas = NULL,
  chem.name = NULL,
  species = "Human",
  initial.amounts = list(Agutlumen = 0),
  filename = "default.xml",
  folder = tempdir(),
  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.
`folder`	The folder on the file system containing the output file. Defaults to `tempdir`.
`digits`	Desired number of decimal places to round the parameters.

Details

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

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

Value

Text describing the PBTK model in SBML.

Author(s)

Robert Pearce

Examples

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

`fetalpcs` *Fetal Partition Coefficients*

Description

Partition coefficients were measured for tissues, including placenta, in vitro by Csanady et al. (2002) for Bisphenol A and Diadzen. Curley et al. (1969) measured the concentration of a variety of pesticides in the cord blood of newborns and in the tissues of infants that were stillborn.

Usage

```
fetalpcs
```

Format

data.frame

Details

Three of the chemicals studied by Curley et al. (1969) were modeled by Weijs et al. (2013) using the same partition coefficients for mother and fetus. The values used represented "prior knowledge" summarizing the available literature.

Source

Kapraun DF, Sfeir M, Pearce RG, Davidson-Fritz SE, Lumen A, Dallmann A, Judson RS, Wambaugh JF (2022). "Evaluation of a rapid, generic human gestational dose model." *Reproductive Toxicology*, **113**, 172–188. doi:10.1016/j.reprotox.2022.09.004.

References

Csanady G, Oberste-Frielinghaus H, Semder B, Baur C, Schneider K, Filser J (2002). "Distribution and unspecific protein binding of the xenoestrogens bisphenol A and daidzein." *Archives of toxicology*, **76**(5-6), 299–305. doi:10.1007/s0020400203395. Curley A, Copeland MF, Kimbrough RD (1969). "Chlorinated Hydrocarbon Insecticides in Organs of Stillborn and Blood of Newborn Babies." *Archives of Environmental Health: An International Journal*, **19**(5), 628–632. doi:10.1080/00039896.1969.10666901, PMID: 4187028, https://doi.org/10.1080/00039896.1969.10666901. Weijs L, Yang RS, Das K, Covaci A, Blust R (2013). "Application of Bayesian population physiologically based pharmacokinetic (PBPK) modeling and Markov chain Monte Carlo simulations to pesticide kinetics studies in protected marine mammals: DDT, DDE, and DDD in harbor porpoises." *Environmental science & technology*, **47**(9), 4365–4374. doi:10.1021/es400386a.

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

Description

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

Usage

```
Frank2018invivo
```

Format

A data.frame containing 14 rows and 16 columns.

Author(s)

Timothy J. Shafer

References

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

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

gen_age_height_weight *Generate demographic parameters for a virtual population*

Description

Generate gender, NHANES race/ethnicity category, ages, heights, and weights for a virtual population, based on NHANES data.

Usage

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

Arguments

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

nhanes_mec_svy surveydesign object created from mecdt using svydesign (this is done in httkpop_generate)

Details

This function should usually not be called directly by the user. It is used by httkpop_generate() in "virtual-individuals" mode.

Value

A data.table containing variables

gender Gender of each virtual individual

reth Race/ethnicity of each virtual individual

age_months Age in months of each virtual individual

age_years Age in years of each virtual individual

weight Body weight in kg of each virtual individual

height Height in cm of each virtual individual

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

importFrom survey svymean

---

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

Description

Predict height and weight from age using smoothing splines, and then add residual variability from a 2-D KDE, both fitted to NHANES data, for a given combination of gender and NHANES race/ethnicity category.

Usage

```
gen_height_weight(gender, reth, age_months, nhanes_mec_svy)
```

Arguments

gender	Gender for which to calculate height/weight ("Male" or "Female")
reth	NHANES race/ethnicity category for which to calculate height/weight ("Mexican American", "Non-Hispanic Black", "Non-Hispanic White", "Other", or "Other Hispanic")
age_months	vector of ages in months for individuals for whom to calculate height/weight (between 0-959 months)
nhanes_mec_svy	surveydesign object created from mecdt using svydesign (this is done in httkpop_generate)

Details

This function should usually not be called directly by the user. It is used by httkpop_generate() in "virtual-individuals" mode, after drawing gender, NHANES race/ethnicity category, and age from their NHANES proportions/distributions.

Value

A list containing two named elements, weight and height, each of which is a numeric vector. weight gives individual body weights in kg, and height gives individual heights in cm, corresponding to each item in the input age_months.

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

---

gen_serum_creatinine *Generate serum creatinine values for a virtual population.*

Description

Predict serum creatinine from age using smoothing splines and kernel density estimates of residual variability fitted to NHANES data,, for a given combination of gender and NHANES race/ethnicity category.

Usage

```
gen_serum_creatinine(gender, reth, age_years, age_months, nhanes_mec_svy)
```

Arguments

gender	Gender for which to generate serum creatinine values ("Male" or "Female")
reth	NHANES race/ethnicity category for which to generate serum creatinine values ("Mexican American", "Non-Hispanic Black", "Non-Hispanic White", "Other", or "Other Hispanic")
age_years	Vector of ages in years for individuals for whom to generate serum creatinine values (corresponding to age_months)
age_months	vector of ages in months for individuals for whom to generate serum creatinine values (between 0-959 months)
nhanes_mec_svy	surveydesign object created from mecdt using svydesign (this is done in httkpop_generate)

Details

This function should usually not be called directly by the user. It is used by `httkpop_generate()` in "virtual-individuals" mode, after drawing gender, NHANES race/ethnicity category, and age from their NHANES proportions/distributions.

Value

A vector of numeric generated serum creatinine values (mg/dL).

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

---

get_caco2 *Retrieve in vitro measured Caco-2 membrane permeabilit*

Description

This function checks for chemical-specific in vitro measurements of the Caco-2 membrane permeability in the chem.physical_and_invitro.data table. If no value is available argument `Caco2.Pab.default` is returned. Anywhere that the values is reported by three numbers separated by a comma (this also happens for plasma protein binding) the three values are: median, lower 95 percent confidence intervals, upper 95 percent confidence interval. Unless you are doing monte carlo work it makes sense to ignore the second and third values.

Usage

```
get_caco2(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  Caco2.Pab.default = 1.6,
  suppress.messages = FALSE
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) – the chemical must be identified by either CAS, name, or DTXSIDs
Caco2.Pab.default	sets the default value for Caco2.Pab if Caco2.Pab is unavailable.
suppress.messages	Whether or not the output message is suppressed.

Author(s)

John Wambaugh

---

get_cheminfo *Retrieve chemical information available from HTTK package*

Description

This function lists information on all the chemicals within HTTK for which there are sufficient data for the specified model and species. By default the function returns only CAS (that is, info="CAS"). The type of information available includes chemical identifiers ("Compound", "CAS", "DTXSID"), in vitro measurements ("Clint", "Clint.pvalue", "Funbound plasma", "Rblood2plasma"), and physico-chemical information ("Formula", "logMA", "logP", "MW", "pKa_Accept", "pKa_Donor"). The argument "info" can be a single type of information, "all" information, or a vector of specific types of information. The argument "model" defaults to "3compartmentss" and the argument "species" defaults to "human". Since different models have different requirements and not all chemicals have complete data, this function will return different numbers of chemicals depending on the model specified. If a chemical is not listed by get_cheminfo then either the in vitro or physico-chemical data needed are currently missing (but could potentially be added using add_chemtable.

Usage

```
get_cheminfo(
  info = "CAS",
  species = "Human",
  fup.lod.default = 0.005,
  model = "3compartmentss",
  default.to.human = FALSE,
  median.only = FALSE,
  fup.ci.cutoff = TRUE,
  clint.pvalue.threshold = 0.05,
  physchem.exclude = TRUE,
  class.exclude = TRUE,
  suppress.messages = FALSE
)
```

Arguments

info	A single character vector (or collection of character vectors) from "Compound", "CAS", "DTXSID, "logP", "pKa_Donor"," pKa_Accept", "MW", "Clint", "Clint.pValue", "Funbound.plasma","Structure_Formula", or "Substance_Type". info="all" gives all information for the model and species.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
fup.lod.default	Default value used for fraction of unbound plasma for chemicals where measured value was below the limit of detection. Default value is 0.0005.
model	Model used in calculation, 'pbtk' for the multiple compartment model, '1compartment' for the one compartment model, '3compartment' for three compartment model, '3compartmentss' for the three compartment model without partition coefficients, or 'schmitt' for chemicals with logP and fraction unbound (used in predict_partitioning_schmitt).
default.to.human	Substitutes missing values with human values if true.
median.only	Use median values only for fup and clint. Default is FALSE.
fup.ci.cutoff	Boolean eliminating uncertain fup estimates. If TRUE, fup values whose 95 spans 0.1 to 0.9 (or more) are eliminated. (Default value is TRUE.)
clint.pvalue.threshold	Hepatic clearance for chemicals where the in vitro clearance assay result has a p-values greater than the threshold are set to zero.
physchem.exclude	Exclude chemicals on the basis of physico-chemical properties (currently only Henry's law constant) as specified by the relevant modelinfo_[MODEL] file (default TRUE).
class.exclude	Exclude chemical classes identified as outside of domain of applicability by the relevant modelinfo_[MODEL] file (default TRUE).
suppress.messages	Whether or not the output messages are suppressed (default FALSE).

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.

In some cases the rapid equilibrium dialysis method (Waters et al., 2008) fails to yield detectable concentrations for the free fraction of chemical. In those cases we assume the compound is highly bound (that is, Fup approaches zero). For some calculations (for example, steady-state plasma concentration) there is precedent (Rotroff et al., 2010) for using half the average limit of detection, that is, 0.005 (this value is configurable via the argument fup.lod.default). We do not recommend using other models where quantities like partition coefficients must be predicted using Fup. We also do not recommend including the value 0.005 in training sets for Fup predictive models.

Note that in some cases the **Funbound.plasma** (fup) and the **intrinsic clearance** (clint) are *provided as a series of numbers separated by commas*. These values are the result of Bayesian analysis and characterize a distribution: the first value is the median of the distribution, while the second and third values are the lower and upper 95th percentile (that is quantile 2.5 and 97.5) respectively. For intrinsic clearance a fourth value indicating a p-value for a decrease is provided. Typically 4000 samples were used for the Bayesian analysis, such that a p-value of "0" is equivalent to "<0.00025". See Wambaugh et al. (2019) for more details. If argument median.only == TRUE then only the median is reported for parameters with Bayesian analysis distributions. If the 95 credible interval spans the range of 0.1 to 0.9 and fup.ci.cutoff is set to TRUE, i.e., the default setting, then the Fup is treated as too uncertain and the value NA is given.

Value

`vector/data.table`

Table (if info has multiple entries) or vector containing a column for each valid entry specified in the argument "info" and a row for each chemical with sufficient data for the model specified by argument "model":

Column	Description
Compound	The preferred name of the chemical compound
CAS	The preferred Chemical Abstracts Service Registry Number
DTXSID	DSSTox Structure ID (https://comptox.epa.gov/dashboard)
logP	The log10 octanol:water partition coefficient
MW	The chemical compound molecular weight
pKa_Accept	The hydrogen acceptor equilibria concentrations
pKa_Donor	The hydrogen donor equilibria concentrations
[SPECIES].Clint	(Primary hepatocyte suspension) intrinsic hepatic clearance. *Entries with comma separated v*
[SPECIES].Clint.pValue	Probability that there is no clearance observed. Values close to 1 indicate clearance is not stat
[SPECIES].Funbound.plasma	Chemical fraction unbound in presence of plasma proteins (fup). *Entries with comma separat*
[SPECIES].Rblood2plasma	Chemical concentration blood to plasma ratio

Author(s)

John Wambaugh, Robert Pearce, and Sarah E. Davidson

References

Rotroff DM, Wetmore BA, Dix DJ, Ferguson SS, Clewell HJ, Houck KA, LeCluyse EL, Andersen ME, Judson RS, Smith CM, others (2010). "Incorporating human dosimetry and exposure into high-throughput in vitro toxicity screening." *Toxicological Sciences*, **117**(2), 348–358. doi:10.1093/toxsci/kfq220.

Waters NJ, Jones R, Williams G, Sohal B (2008). "Validation of a rapid equilibrium dialysis approach for the measurement of plasma protein binding." *Journal of pharmaceutical sciences*, **97**(10), 4586–4595. doi:10.1002/jps.21317.

Wambaugh JF, Wetmore BA, Ring CL, Nicolas CI, Pearce RG, Honda GS, Dinallo R, Angus D, Gilbert J, Sierra T, others (2019). "Assessing toxicokinetic uncertainty and variability in risk prioritization." *Toxicological Sciences*, **172**(2), 235–251. doi:10.1093/toxsci/kfz205.

Examples

```
# 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)

# create a data.frame with all the Fup values, we ask for model="schmitt" since
```

```
# that model only needs fup, we ask for "median.only" because we don't care
# about uncertainty intervals here:
fup.tab <- get_cheminfo(info="all",median.only=TRUE,model="schmitt")
# calculate the median, making sure to convert to numeric values:
median(as.numeric(fup.tab$Human.Funbound.plasma),na.rm=TRUE)
# calculate the mean:
mean(as.numeric(fup.tab$Human.Funbound.plasma),na.rm=TRUE)
# count how many non-NA values we have (should be the same as the number of
# rows in the table but just in case we ask for non NA values:
sum(!is.na(fup.tab$Human.Funbound.plasma))
```

`get_chem_id` *Retrieve chemical identity from HTTK package*

Description

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

Usage

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

Arguments

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

Value

A list containing the following chemical identifiers:

`chem.cas`	CAS registry number
`chem.name`	Name
`dtxsid`	DTXSID

Author(s)

John Wambaugh and Robert Pearce

get_clint *Retrieve and parse intrinsic hepatic clearance*

Description

This function retrieves the chemical- and species-specific intinsic hepatic clearance (Cl_{int}, inits of uL/min/million hepatocytes) from chem.physical_and_invitro.data. If that parameter is described by a distribution (that is, a median, lower-, upper-95th percentile and p-value separated by commas) this function splits those quantiles into separate values. Most Cl_{int} values have an accompanying p-value indicating the probability that no decrease was observed. If the p-values exceeds a threhsold (default 0.05) the clearance is set to zero (no clearance). Some values extracted from the literature do not have a p-value.

Usage

```
get_clint(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
  default.to.human = FALSE,
  force.human.clint = FALSE,
  suppress.messages = FALSE,
  clint.pvalue.threshold = 0.05
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXSIDs
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
default.to.human	Substitutes missing hepatic clearance with human values if true.
force.human.clint	If a non-human species value (matching argument species) is available, it is ignored and the human intrinsic clearance is used
suppress.messages	Whether or not the output message is suppressed.
clint.pvalue.threshold	Hepatic clearance for chemicals where the in vitro clearance assay result has a p-values greater than the threshold are set to zero.

Value

list containing:

CLint.point	Point estimate (central tendency) of the intrinsic hepatic clearance
Clint.dist	Quantiles of a distribution (median, lower, upper 95th percentiles) and pvalue
Clint.pvalue	pvalue for whether disapperance of parent compound was observed

Author(s)

John Wambaugh

See Also

chem.physical_and_invitro.data

---

get_fbio *Retrieve or calculate fraction of chemical absorbed from the gut*

Description

This function checks for chemical-specific in vivo measurements of the fraction absorbed from the gut in the chem.physical_and_invitro.data table. If in vivo data are unavailable (or keepit100 == TRUE) we attempt to use in vitro Caco-2 membrane permeability to predict the fractions according to calc_fbio.oral.

Usage

```
get_fbio(
  parameters = NULL,
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
  Caco2.Pab.default = 1.6,
  Caco2.Fgut = TRUE,
  Caco2.Fabs = TRUE,
  overwrite.invivo = FALSE,
  keepit100 = FALSE,
  suppress.messages = FALSE,
  ...
)
```

Arguments

parameters	A list of the parameters (Caco2.Pab, Funbound.Plasma, Rblood2plasma, Clint, BW, Qsmallintestine, Fabs, Fgut) used in the calculation, either supplied by user or calculated in parameterize_steady_state.
chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) – the chemical must be identified by either CAS, name, or DTXSIDs
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
Caco2.Pab.default	sets the default value for Caco2.Pab if Caco2.Pab is unavailable.
Caco2.Fgut	= TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = Fgut.
Caco2.Fabs	= TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = Fabs.
overwrite.invivo	= TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available.
keepit100	TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings.
suppress.messages	Whether or not the output message is suppressed.
...	Additional parameters passed to parameterize function if parameters is NULL.

Author(s)

Greg Honda and John Wambaugh

See Also

calc_fbio.oral

---

get_fup *Retrieve and parse fraction unbound in plasma*

Description

This function retrieves the chemical- and species-specific fraction unbound in plasma (f_{up}) from chem.physical_and_invitro.data. If that parameter is described by a distribution (that is, a median, lower-, and upper-95th percentile separated by commas) this function splits those quantiles into separate values.

Usage

```
get_fup(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
  default.to.human = FALSE,
  force.human.fup = FALSE,
  suppress.messages = FALSE,
  minimum.Funbound.plasma = 1e-04
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXSIDs
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
default.to.human	Substitutes missing fraction of unbound plasma with human values if true.
force.human.fup	If a non-human species value (matching argument species) is available, it is ignored and the human fraction unbound is returned
suppress.messages	Whether or not the output message is suppressed.
minimum.Funbound.plasma	f_{up} is not allowed to drop below this value (default is 0.0001).

Value

list containing:

Funbound.plasma.point	Point estimate (central tendency) of the Unbound fraction in plasma
Funbound.plasma.dist	Quantiles of a distribution (median, lower and upper 95th percentiles) for the unbound fraction

Author(s)

John Wambaugh

See Also

chem.physical_and_invitro.data

`get_gfr_category` *Categorize kidney function by GFR.*

Description

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

Usage

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

Arguments

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

Details

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

Value

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

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

get_input_param_timeseries *Get timeseries containing the change of each of the input parameters.*

Description

The deSolve package uses timeseries as forcing functions. In lieu of hard- coding time evolution of parameters into a model, these timeseries may be used to change the value of parameters in time. The function get_input_parm_timeseries queries a virutal population and non-parametrically produces timeseries that preserve the percentile score of the given starting values.

Usage

```
get_input_param_timeseries(
  model,
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  initial.params = NULL,
  initial.percentiles = NULL,
  start.age = 360,
  days = 10,
  ref.params = NULL,
  bandwidth = 12,
  get.median.param.vals = FALSE
)
```

Arguments

model	The name of a model which can accept timeseries as forcing functions.
chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) – the chemical must be identified by either CAS, name, or DTXSIDs
initial.params	The values for each parameter at the beginning of the simulation. All compiled parameters should be present. The output of the parameterize_<model> function is appropriate for initial.params.
initial.percentiles	If initial.params are not provided, initial.percentiles will designate a starting value for each parameter according to the corresponding percentile within the NHANES population. Values should be between zero and one. If neither initial.params nor initial.percentiles are provided, the initial value for the parameter is taken to be the median of the population value.

`start.age` The age in months of the individual at the beginning of the simulation. Used for determining the percentile score of the initial parameter values when producing the timeseries determining parameter changes.

`days` The length of the simulation in days. Equivalent to the `days` parameter in `solve_model`.

`ref.params` Model parameters of a reference population used in determining timeseries. Recommended column binding ages in months (as `age_months`) to the output of `create_mc_samples`.

`bandwidth` Dictates the length of time centered around the present to use when calculating non-parametric regressions.

`get.median.param.vals`
Return, instead of the timeseries, the median values for the dynamic model parameters at the given start age.

Details

For each time-dependent model, there should be a function that determines the model parameter values for each individual in the NHANES dataset. The resulting value are used to form the non-parametric regression curve.

Value

A list of two-column matrices indexed by names of compiled parameters for the designated model. The first column contains a list of times (in days) and the second the total change in that parameter from the initial value.

Author(s)

Colin Thomson

See Also

`solve_pbtk_lifestage`

Examples

```
params <- parameterize_pbtk(chem.name = 'Bisphenol A')

pop.phys <- httkpop_generate(method = 'virtual individuals',
                             nsamp = 25000,
                             agelim_years = c(18, 79),
                             weight_category = c("Normal"))
pop.params <- create_mc_samples(chem.name = 'Bisphenol A',
                                model = 'pbtk',
                                httkpop.dt = pop.phys)
ref.params <- cbind(pop.params,
                    age_months = pop.phys$age_months)
ts <- get_input_param_timeseries(model = 'pbtk_lifestage',
                                 chem.name = 'Bisphenol A',
```

```
initial.params = params,
start.age = 600, # age fifty
days = 365,
ref.params = ref.params)
```

`get_invitroPK_param` *Retrieve species-specific in vitro data from chem.physical_and_invitro.data table*

Description

This function retrieves in vitro PK data (for example, intrinsic metabolic clearance or fraction unbound in plasma) for the the chemical specified by argument "chem.name", "dtxsid", or chem.cas from the table `chem.physical_and_invitro.data`. This function looks for species-specific values based on the argument "species".

Usage

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

Arguments

`param`	The desired parameters, a vector or single value.
`species`	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
`chem.name`	The chemical names that you want parameters for, a vector or single value
`chem.cas`	The chemical CAS numbers that you want parameters for, a vector or single value
`dtxsid`	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard)

Details

Note that this function works with a local version of the `chem.physical_and_invitro.data` table to allow users to add/modify chemical data (for example, adding new data via `add_chemtable` or loading in silico predictions distributed with httk via `load_sipes2017`, `load_pradeep2020`, `load_dawson2021`, or `load_honda2023`).

User can request via argument param (case-insensitive):

Parameter	Description
[SPECIES].Clint	(Primary hepatocyte suspension) intrinsic hepatic clearance. *Entries with comma separated va*
[SPECIES].Clint.pValue	Probability that there is no clearance observed. Values close to 1 indicate clearance is not stat
[SPECIES].Caco2.Pab	Caco-2 Apical-to-Basal Membrane Permeability
[SPECIES].Fabs	In vivo measured fraction of an oral dose of chemical absorbed from the gut lumen into the gu
[SPECIES].Fgut	In vivo measured fraction of an oral dose of chemical that passes gut metabolism and clearanc
[SPECIES].Foral	In vivo measued fractional systemic bioavailability of an oral dose, modeled as he product of
[SPECIES].Funbound.plasma	Chemical fraction unbound in presence of plasma proteins (fup). *Entries with comma separat*
[SPECIES].Rblood2plasma	Chemical concentration blood to plasma ratio

Value

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

Author(s)

John Wambaugh and Robert Pearce

See Also

chem.physical_and_invitro.data

get_invitroPK_param

add_chemtable

`get_lit_cheminfo` *Get literature Chemical Information.*

Description

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

Usage

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

Arguments

info	A single character vector (or collection of character vectors) from "Compound", "CAS", "MW", "Raw.Experimental.Percentage.Unbound", "Entered.Experimental.Percentage.Unbound", "Fub", "source_PPB", "Renal_Clearance", "Met_Stab", "Met_Stab_entered", "r2", "p.val", "Concentration..uM.", "Css_lower_5th_perc.mg.L.", "Css_median_perc.mg.L.", "Css_upper_95th_perc.mg.L.", "Css_lower_5th_perc.uM.","Css_median_perc.uM.","Css_upper_95th_p 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 BA, Wambaugh JF, Ferguson SS, Sochaski MA, Rotroff DM, Freeman K, Clewell III HJ, Dix DJ, Andersen ME, Houck KA, others (2012). "Integration of dosimetry, exposure, and high-throughput screening data in chemical toxicity assessment." *Toxicological Sciences*, **125**(1), 157–174. doi:10.1093/toxsci/kfr254.

Wetmore BA, Wambaugh JF, Ferguson SS, Li L, Clewell III HJ, Judson RS, Freeman K, Bao W, Sochaski MA, Chu T, others (2013). "Relative impact of incorporating pharmacokinetics on predicting in vivo hazard and mode of action from high-throughput in vitro toxicity assays." *toxicological sciences*, **132**(2), 327–346. doi:10.1093/toxsci/kft012.

Wetmore BA, Wambaugh JF, Allen B, Ferguson SS, Sochaski MA, Setzer RW, Houck KA, Strope CL, Cantwell K, Judson RS, others (2015). "Incorporating high-throughput exposure predictions with dosimetry-adjusted in vitro bioactivity to inform chemical toxicity testing." *Toxicological Sciences*, **148**(1), 121–136. doi:10.1093/toxsci/kfv171.

Examples

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

---

get_lit_css *Get literature Css*

Description

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

Usage

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

Arguments

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

Value

A numeric vector with the literature steady-state plasma concentration (1 mg/kg/day) for the requested quantiles

Author(s)

John Wambaugh

References

Wetmore BA, Wambaugh JF, Ferguson SS, Sochaski MA, Rotroff DM, Freeman K, Clewell III HJ, Dix DJ, Andersen ME, Houck KA, others (2012). "Integration of dosimetry, exposure, and high-throughput screening data in chemical toxicity assessment." *Toxicological Sciences*, **125**(1), 157–174. doi:10.1093/toxsci/kfr254.

Wetmore BA, Wambaugh JF, Ferguson SS, Li L, Clewell III HJ, Judson RS, Freeman K, Bao W, Sochaski MA, Chu T, others (2013). "Relative impact of incorporating pharmacokinetics on predicting in vivo hazard and mode of action from high-throughput in vitro toxicity assays." *toxicological sciences*, **132**(2), 327–346. doi:10.1093/toxsci/kft012.

Wetmore BA, Wambaugh JF, Allen B, Ferguson SS, Sochaski MA, Setzer RW, Houck KA, Strope CL, Cantwell K, Judson RS, others (2015). "Incorporating high-throughput exposure predictions with dosimetry-adjusted in vitro bioactivity to inform chemical toxicity testing." *Toxicological Sciences*, **148**(1), 121–136. doi:10.1093/toxsci/kfv171.

Examples

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

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

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

`get_lit_oral_equiv` *Get Literature Oral Equivalent Dose*

Description

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

Usage

```
get_lit_oral_equiv(
  conc,
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  suppress.messages = FALSE,
  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.
`dtxsid`	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
`suppress.messages`	Suppress output messages.
`which.quantile`	Which quantile from the SimCYP Monte Carlo simulation is requested. Can be a vector. Papers include 0.05, 0.5, and 0.95 for humans and 0.5 for rats.
`species`	Species desired (either "Rat" or default "Human").
`input.units`	Units of given concentration, default of uM but can also be mg/L.
`output.units`	Units of dose, default of 'mg' for mg/kg BW/ day or 'mol' for mol/ kg BW/ day.
`clearance.assay.conc`	Concentration of chemical used in measureing intrinsic clearance data, 1 or 10 uM.
`...`	Additional parameters passed to get_lit_css.

Value

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

Author(s)

John Wambaugh

References

Wetmore BA, Wambaugh JF, Ferguson SS, Sochaski MA, Rotroff DM, Freeman K, Clewell III HJ, Dix DJ, Andersen ME, Houck KA, others (2012). "Integration of dosimetry, exposure, and high-throughput screening data in chemical toxicity assessment." *Toxicological Sciences*, **125**(1), 157–174. doi:10.1093/toxsci/kfr254.

Wetmore BA, Wambaugh JF, Ferguson SS, Li L, Clewell III HJ, Judson RS, Freeman K, Bao W, Sochaski MA, Chu T, others (2013). "Relative impact of incorporating pharmacokinetics on predicting in vivo hazard and mode of action from high-throughput in vitro toxicity assays." *toxicological sciences*, **132**(2), 327–346. doi:10.1093/toxsci/kft012.

Wetmore BA, Wambaugh JF, Allen B, Ferguson SS, Sochaski MA, Setzer RW, Houck KA, Strope CL, Cantwell K, Judson RS, others (2015). "Incorporating high-throughput exposure predictions with dosimetry-adjusted in vitro bioactivity to inform chemical toxicity testing." *Toxicological Sciences*, **148**(1), 121–136. doi:10.1093/toxsci/kfv171.

Examples

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

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

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

---

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

Description

This function retrieves physico-chemical properties ("param") for the chemical specified by chem.name or chem.cas from the table chem.physical_and_invitro.data. This function is distinguished from get_invitroPK_param in that there are no species-specific values. Physically meaningful values for ionization equilibria are NA/none (that is, no ionization), a single value, or a series of values separated by commas. If logMA (log10 membrane affinity) is NA, we use calc_ma() to predict it later on in the model parameterization functions.

Usage

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

Arguments

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

Details

Note that this function works with a local version of the chem.physical_and_invitro.data table to allow users to add/modify chemical data (for example, adding new data via add_chemtable or loading in silico predictions distributed with httk via load_sipes2017, load_pradeep2020, load_dawson2021, or load_honda2023).

User can request the following via argument param (case-insensitive):

Parameter	Description	Units
MW	Molecular weight	g/mole
pKa_Donor	Hydrogen donor ionization equilibria (acidic pKa)	pH
pKa_Accept	Hyrdogen acceptor ionization equilibria (basic pKa	pH
logMA	log10 Membrane Affinity	unitless
logP	log10 Octanol:Water Partition Coefficient (hydrophobicity)	unitless
logPwa	log10 Water:Air Partition Coefficient	unitless
logHenry	log10 Henry's Law Constant	atm-m3/mole
logWSol	log10 Water Solubility	moles/L: Water solubility at 25C
MP	Melting point	deg C

Value

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

Author(s)

John Wambaugh and Robert Pearce

See Also

chem.physical_and_invitro.data

get_invitroPK_param

add_chemtable

Examples

```
get_physchem_param(param = 'logP', chem.cas = '80-05-7')
get_physchem_param(param = c('logP','MW'), chem.cas = c('80-05-7','81-81-2'))
# This function should be case-insensitive:
try(get_physchem_param(chem.cas="80-05-7","LogP"))
# Asking for a parameter we "don't" have produces an error:
try(get_physchem_param(chem.cas="80-05-7","MA"))
get_physchem_param(chem.cas="80-05-7","logMA")
# Ionization equilibria can be NA/none, a single value, or a series of values
# separated by commas:
get_physchem_param(chem.cas="80-05-7","pKa_Donor")
get_physchem_param(chem.cas="80-05-7","pKa_Accept")
get_physchem_param(chem.cas="71751-41-2","pKa_Donor")
get_physchem_param(chem.cas="71751-41-2","pKa_Accept")
# If logMA (log10 membrane affinity) is NA, we use calc_ma() to predict it
# in the parameterization functions:
get_physchem_param(chem.cas="71751-41-2","logMA")
parameterize_steadystate(chem.cas="71751-41-2")
```

---

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

Description

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

Usage

```
get_rblood2plasma(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  species = "Human",
  default.to.human = FALSE
)
```

Arguments

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

Details

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

Value

A numeric value for the steady-state ratio of chemical concentration in blood to plasma

Author(s)

Robert Pearce

Examples

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

---

get_weight_class *Assign weight class (underweight, normal, overweight, obese)*

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').

Details

According to the U.S. Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/disability-and-health/conditions/obesity.html), adult weight classes are defined using body mass index (BMI) as follows:

Underweight BMI less than 18.5

Normal BMI between 18.5 and 25

Overweight BMI between 25 and 30

Obese BMI greater than 30

For children ages 2 years and older, weight classes are defined using percentiles of sex-specific BMI for age, as follows (Barlow et al., 2007):

Underweight Below 5th percentile BMI for age

Normal 5th-85th percentile BMI for age

Overweight 85th-95th percentile BMI for age

Obese Above 95th percentile BMI for age

For children birth to age 2, weight classes are defined using percentiles of sex-specific weight-for-length (Grummer-Strawn et al., 2009). Weight above the 97.7th percentile, or below the 2.3rd percentile, of weight-for-length is considered potentially indicative of adverse health conditions. Here, weight below the 2.3rd percentile is categorized as "Underweight" and weight above the 97.7th percentile is categorized as "Obese."

Value

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

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics. 2007;120 Suppl 4. doi:10.1542/peds.2007-2329C

Grummer-Strawn LM, Reinold C, Krebs NF. Use of World Health Organization and CDC growth charts for children Aged 0-59 months in the United States. Morb Mortal Wkly Rep. 2009;59(RR-9). https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5909a1.htm

`get_wetmore_cheminfo` *Get literature Chemical Information. (deprecated).*

Description

This function is included for backward compatibility. It calls `get_lit_cheminfo` which provides the information specified in "info=" for all chemicals with data from the Wetmore et al. (2012) and (2013) publications and other literature.

Usage

```
get_wetmore_cheminfo(
  info = "CAS",
  species = "Human",
  suppress.messages = FALSE
)
```

Arguments

`info`	A single character vector (or collection of character vectors) from "Compound", "CAS", "MW", "Raw.Experimental.Percentage.Unbound", "Entered.Experimental.Percentage.Unbound", "Fub", "source_PPB", "Renal_Clearance", "Met_Stab", "Met_Stab_entered", "r2", "p.val", "Concentration..uM.", "Css_lower_5th_perc.mg.L.", "Css_median_perc.mg.L.", "Css_upper_95th_perc.mg.L.", "Css_lower_5th_perc.uM.","Css_median_perc.uM.","Css_upper_95th_p and "Species".
`species`	Species desired (either "Rat" or default "Human").
`suppress.messages`	Whether or not the output message is suppressed.

Value

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

Author(s)

John Wambaugh

References

Wetmore BA, Wambaugh JF, Ferguson SS, Sochaski MA, Rotroff DM, Freeman K, Clewell III HJ, Dix DJ, Andersen ME, Houck KA, others (2012). "Integration of dosimetry, exposure, and high-throughput screening data in chemical toxicity assessment." *Toxicological Sciences*, **125**(1), 157–174. doi:10.1093/toxsci/kfr254.

Wetmore BA, Wambaugh JF, Ferguson SS, Li L, Clewell III HJ, Judson RS, Freeman K, Bao W, Sochaski MA, Chu T, others (2013). "Relative impact of incorporating pharmacokinetics on predicting in vivo hazard and mode of action from high-throughput in vitro toxicity assays." *toxicological sciences*, **132**(2), 327–346. doi:10.1093/toxsci/kft012.

Wetmore BA, Wambaugh JF, Allen B, Ferguson SS, Sochaski MA, Setzer RW, Houck KA, Strope CL, Cantwell K, Judson RS, others (2015). "Incorporating high-throughput exposure predictions with dosimetry-adjusted in vitro bioactivity to inform chemical toxicity testing." *Toxicological Sciences*, **148**(1), 121–136. doi:10.1093/toxsci/kfv171.

Examples

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

`get_wetmore_css` *Get literature Css (deprecated).*

Description

This function is included for backward compatibility. It calls `get_lit_css` which retrieves a steady-state plasma concentration as a result of infusion dosing from the Wetmore et al. (2012) and (2013) publications and other literature.

Usage

```
get_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 = FALSE
)
```

Arguments

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

Value

A numeric vector with the literature steady-state plasma concentration (1 mg/kg/day) for the requested quantiles

Author(s)

John Wambaugh

References

Wetmore BA, Wambaugh JF, Ferguson SS, Sochaski MA, Rotroff DM, Freeman K, Clewell III HJ, Dix DJ, Andersen ME, Houck KA, others (2012). "Integration of dosimetry, exposure, and high-throughput screening data in chemical toxicity assessment." *Toxicological Sciences*, **125**(1), 157–174. doi:10.1093/toxsci/kfr254.

Wetmore BA, Wambaugh JF, Ferguson SS, Li L, Clewell III HJ, Judson RS, Freeman K, Bao W, Sochaski MA, Chu T, others (2013). "Relative impact of incorporating pharmacokinetics on predicting in vivo hazard and mode of action from high-throughput in vitro toxicity assays." *toxicological sciences*, **132**(2), 327–346. doi:10.1093/toxsci/kft012.

Wetmore BA, Wambaugh JF, Allen B, Ferguson SS, Sochaski MA, Setzer RW, Houck KA, Strope CL, Cantwell K, Judson RS, others (2015). "Incorporating high-throughput exposure predictions with dosimetry-adjusted in vitro bioactivity to inform chemical toxicity testing." *Toxicological Sciences*, **148**(1), 121–136. doi:10.1093/toxsci/kfv171.

Examples

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

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

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

---

get_wetmore_oral_equiv

Get Literature Oral Equivalent Dose (deprecated).

Description

This function is included for backward compatibility. It calls `get_lit_oral_equiv` which converts a chemical plasma concetration to an oral equivalent dose using the values from the Wetmore et al. (2012) and (2013) publications and other literature.

Usage

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

Arguments

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

Value

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

Author(s)

John Wambaugh

References

Wetmore BA, Wambaugh JF, Ferguson SS, Sochaski MA, Rotroff DM, Freeman K, Clewell III HJ, Dix DJ, Andersen ME, Houck KA, others (2012). "Integration of dosimetry, exposure, and high-throughput screening data in chemical toxicity assessment." *Toxicological Sciences*, **125**(1), 157–174. doi:10.1093/toxsci/kfr254.

Wetmore BA, Wambaugh JF, Ferguson SS, Li L, Clewell III HJ, Judson RS, Freeman K, Bao W, Sochaski MA, Chu T, others (2013). "Relative impact of incorporating pharmacokinetics on predicting in vivo hazard and mode of action from high-throughput in vitro toxicity assays." *toxicological sciences*, **132**(2), 327–346. doi:10.1093/toxsci/kft012.

Wetmore BA, Wambaugh JF, Allen B, Ferguson SS, Sochaski MA, Setzer RW, Houck KA, Strope CL, Cantwell K, Judson RS, others (2015). "Incorporating high-throughput exposure predictions with dosimetry-adjusted in vitro bioactivity to inform chemical toxicity testing." *Toxicological Sciences*, **148**(1), 121–136. doi:10.1093/toxsci/kfv171.

Examples

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

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

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

---

hct_h *KDE bandwidths for residual variability in hematocrit*

Description

Bandwidths used for a one-dimensional kernel density estimation of the distribution of residual errors around smoothing spline fits of hematocrit vs. age for NHANES respondents in each of ten combinations of sex and race/ethnicity categories.

Usage

```
hct_h
```

Format

A named list with 10 elements, each a numeric value. Each list element corresponds to, and is named for, one combination of NHANES sex categories (Male and Female) and NHANES race/ethnicity categories (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other).

Details

Each matrix is the standard deviation for a normal distribution: this is the bandwidth to be used for a kernel density estimation (KDE) (using a normal kernel) of the distribution of residual errors around smoothing spline fits of hematocrit vs. age for NHANES respondents in the specified sex and race/ethnicity category. Optimal bandwidths were pre-calculated by doing the smoothing spline fits, getting the residuals, then calling `kde` on the residuals (which calls `hpi` to compute the plug-in bandwidth).

Used by HTTK-Pop only in "virtual individuals" mode (i.e. `httkpop_generate` with `method = "v"`), in `estimate_hematocrit`.

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

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

Description

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

Usage

```
hematocrit_infants(age_months)
```

Arguments

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

Details

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

Value

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

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

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

Description

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

Usage

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

Arguments

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

Details

Only four sets of IVIVE assumptions that performed well in Honda et al. (2019) are currently included: "Honda1" through "Honda4". The use of max (peak) concentration can not be currently be calculated with `calc_analytic_css`. The httk default settings correspond to "Honda3":

	In Vivo Conc.	Metabolic Clearance	Bioactive Chemical Conc. *In Vivo*	TK Statistic Used*	Bioactive
Honda1	Veinous (Plasma)	Restrictive	Free	Mean Conc. In Vivo	
Honda2	Veinous	Restrictive	Free	Mean Conc. In Vivo	
Honda3	Veinous	Restrictive	Total	Mean Conc. In Vivo	
Honda4	Target Tissue	Non-restrictive	Total	Mean Conc. In Vivo	

"Honda1" uses plasma concentration, restrictive clearance, and treats the unbound invivo concentration as bioactive. For IVIVE, any input nominal concentration in vitro should be converted to cfree.invitro using armitage_eval, otherwise performance will be the same as "Honda2".

Value

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

Author(s)

Greg Honda and John Wambaugh

References

Honda GS, Pearce RG, Pham LL, Setzer RW, Wetmore BA, Sipes NS, Gilbert J, Franz B, Thomas RS, Wambaugh JF (2019). "Using the concordance of in vitro and in vivo data to evaluate extrapolation assumptions." *PloS one*, **14**(5), e0217564. doi:10.1371/journal.pone.0217564.

Examples

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

---

honda2023.data *Measured Caco-2 Apical-Basal Permeability Data*

Description

In vitro Caco-2 membrane permeabilities characterize how readily absobed/transported a chemical is. These measurements are all for the apical-to-basal Caco-2 orientation. These data were either measured by EPA or collected by other others, as indicated by the column 'Data Origin'. Anywhere that the values is reported by three numbers separated by a comma (this also happens for plasma protein binding) the three values are: median, lower 95 percent confidence intervals, upper 95 percent confidence interval. Unless you are doing monte carlo work it makes sense to ignore the second and third values.

Usage

```
honda2023.data
```

Format

An object of class data.frame with 634 rows and 5 columns.

Details

Column Name	Description	Units
DTXSID	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard)	
Pab	Apical-to-basal Caco-2 permeability	10^-6 cr
Data Origin	The reference which collected/generated the measurement	
Test	Whether (1) or not (0) the data was withheld from model building to be used in the QSPR test set	
CAS	Chemical Abstracts Service Registry Number	

References

Obringer C, Manwaring J, Goebel C, Hewitt NJ, Rothe H (2016). "Suitability of the in vitro Caco-2 assay to predict the oral absorption of aromatic amine hair dyes." *Toxicology in Vitro*, **32**, 1–7. doi:10.1016/j.tiv.2015.11.007.

Lanevskij K, Didziapetris R (2019). "Physicochemical QSAR analysis of passive permeability across Caco-2 monolayers." *Journal of Pharmaceutical Sciences*, **108**(1), 78–86. doi:10.1016/j.xphs.2018.10.006.

Gaulton A, Bellis LJ, Bento AP, Chambers J, Davies M, Hersey A, Light Y, McGlinchey S, Michalovich D, Al-Lazikani B, others (2012). "ChEMBL: a large-scale bioactivity database for drug discovery." *Nucleic Acids Research*, **40**(D1), D1100–D1107. doi:10.1093/nar/gkr777.

Honda GS, Kenyon EM, Davidson-Fritz S, Dinallo R, El Masri H, Korol-Bexell E, Li L, Angus D, Pearce RG, Sayre RR, others (2025). "Impact of gut permeability on estimation of oral bioavailability for chemicals in commerce and the environment." *ALTEX-Alternatives to animal experimentation*, **42**(1), 56–74. doi:10.14573/altex.2403271.

---

honda2023.qspr *Predicted Caco-2 Apical-Basal Permeabilities*

Description

Honda et al. (2023) describes the construction of a machine-learning quantitative structure-property relationship (QSPR)model for in vitro Caco-2 membrane permeabilites. That model was used to make chemical-specific predictions provided in this table.

Usage

```
honda2023.qspr
```

Format

An object of class `data.frame` with 14033 rows and 5 columns.

Details

Column Name	Description
DTXSID	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard)
Pab.Class.Pred	Predicted Pab rate of slow (1), moderate (2), or fast (3)
Pab.Pred.AD	Whether (1) or not (0) the chemical is anticipated to be withing the QSPR domain of applicability
CAS	Chemical Abstracts Service Registry Number
Pab.Quant.Pred	Median and 95-percent interval for values within the predicted class's training data moderate (2), or fast (3)

References

Honda GS, Kenyon EM, Davidson-Fritz S, Dinallo R, El Masri H, Korol-Bexell E, Li L, Angus D, Pearce RG, Sayre RR, others (2025). "Impact of gut permeability on estimation of oral bioavailability for chemicals in commerce and the environment." *ALTEX-Alternatives to animal experimentation*, **42**(1), 56–74. doi:10.14573/altex.2403271.

See Also

load_honda2023

`howgate` *Howgate 2006*

Description

This data set is only used in Vignette 5.

Usage

```
howgate
```

Format

A data.table containing 24 rows and 11 columns.

Author(s)

Caroline Ring

References

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

`httk.performance` *Historical Performance of R Package httk*

Description

This table records the historical performance and other metrics of the R package "httk" as profiled with the function `benchmark_httk`. There is a row for each version and a column for each benchmark or metric. This table is used to generate graphs comparing the current version to past performance in order to help identify unintended degradtion of package capabilities.

Usage

```
httk.performance
```

Format

An object of class `data.frame` with 28 rows and 18 columns.

Details

Column Name	Description
Version	The release of httk (major.minor.patch)
N.steadystate	The number of chemicals for which Css can be predicted for the steady-state model
calc_analytic.units	The ratio of the output of `calc_analytic_css` in mg/L to uM multiplied by 1000/MW (should be 1)
calc_mc.units	The ratio of the output of `calc_mc_css` in mg/L to uM multiplied by 1000/MW (should be 1)
solve_pbtk.units	The ratio of a Cplasma value from `solve_pbtk` in mg/L to uM multiplied by 1000/MW (should be 1)
RMSLE.Wetmore	Root mean squared log10 error between Css predictions from httk and published values from Wetmor
N.Wetmore	Number of chemicals used in RMSLE evaluation
RMSLE.noMC	RMSLE between 95th percentile Css prediction and median prediction
N.noMC	Number of chemicals used in RMSLE evaluation
RMSLE.InVivoCss	RMSLE for predictions of in vivo measured Css
N.InVivoCss	Number of chemicals used in RMSLE evaluation
RMSLE.InVivoAUC	RMSLE for predictions of in vivo measured AUCs
N.InVivoAUC	Number of chemicals used in RMSLE evaluation
RMSLE.InVivoCmax	RMSLE for predictions of in vivo measured Cmax
N.InVivoCmax	Number of chemicals used in RMSLE evaluation
RMSLE.TissuePC	RMSLE for predicted tissue:plasma partition coefficients
N.TissuePC	Number of chemicals used in RMSLE evaluation
Notes	Why benchmarks/metrics may have changed

References

Davidson-Fritz SE, Ring CL, Evans MV, Schacht CM, Chang X, Breen M, Honda GS, Kenyon E, Linakis MW, Meade A, others (2025). "Enabling Transparent Toxicokinetic Modeling for Public Health Risk Assessment." *PLOS ONE*, **20**(4), 1-40. doi:10.1371/journal.pone.0321321.

See Also

benchmark_httk

---

httkpop *httkpop: Virtual population generator for HTTK.*

Description

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

Details

To simulate inter-individual variability in the TK model, a MC approach is used: the model parameters are sampled from known or assumed distributions, and the model is evaluated for each sampled set of parameters. To simulate variability across subpopulations, the MC approach needs to capture the parameter correlation structure. For example, kidney function changes with age (Levey et al., 2009), thus the distribution of GFR is likely different in 6-year-olds than in 65-yearolds. To directly measure the parameter correlation structure, all parameters need to be measured in each individual in a representative sample population. Such direct measurements are extremely limited. However, the correlation structure of the physiological parameters can be inferred from their known individual correlations with demographic and anthropometric quantities for which direct population measurements do exist. These quantities are sex, race/ethnicity, age, height, and weight (Howgate et al., 2006; Jamei et al., 2009a; Johnson et al., 2006; McNally et al., 2014; Price et al., 2003). Direct measurements of these quantities in a large, representative sample of the U.S. population are publicly available from NHANES. NHANES also includes laboratory measurements, including both serum creatinine, which can be used to estimate GFR (Levey et al., 2009), and hematocrit. For conciseness, sex, race/ethnicity, age, height, weight, serum creatinine, and hematocrit will be called the NHANES quantities.

HTTK-Pop's correlated MC approach begins by sampling from the joint distribution of the NHANES quantities to simulate a population. Then, for each individual in the simulated population, HTTKePop predicts the physiological parameters from the NHANES quantities using regression equations from the literature (Barter et al., 2007; Baxter-Jones et al., 2011; Bosgra et al., 2012; Koo et al., 2000; Levey et al., 2009; Looker et al., 2013; McNally et al., 2014; Ogiu et al., 1997; Price et al., 2003; Schwartz and Work, 2009; Webber and Barr 2012). Correlations among the physiological parameters are induced by their mutual dependence on the correlated NHANES quantities. Finally, residual variability is added to the predicted physiological parameters using estimates of residual marginal variance (i.e., variance not explained by the regressions on the NHANES quantities) (McNally et al., 2014).

Data were combined from the three most recent publicly-available NHANES cycles: 2007-2008, 2009-2010, and 2011-2012. For each cycle, some NHANES quantities - height, weight, serum creatinine, and hematocrit - were measured only in a subset of respondents. Only these subsets were included in HTTKePop. The pooled subsets from the three cycles contained 29,353 unique respondents. Some respondents were excluded from analysis: those with age recorded as 80 years (because all NHANES respondents 80 years and older were marked as "80"); those with missing height, weight or hematocrit data; and those aged 12 years or older with missing serum creatinine data. These criteria excluded 4807 respondents, leaving 24,546 unique respondents. Each

NHANES respondent was assigned a cycle-specific sample weight, which can be interpreted as the number of individuals in the total U.S. population represented by each NHANES respondent in each cycle (Johnson et al., 2013). Because data from three cycles were combined, the sample weights were rescaled (divided by the number of cycles being combined, as recommended in NHANES data analysis documentation) (Johnson et al., 2013). To handle the complex NHANES sampling structure, the R survey package was used to analyze the NHANES data (Lumley, 2004).

To allow generation of virtual populations specified by weight class, we coded a categorical variable for each NHANES respondent. The categories Underweight, Normal, Overweight, or Obese were assigned based on weight, age, and height/length (Grummer-Strawn et al., 2010; Kuczmarski et al., 2002; Ogden et al., 2014; WHO, 2006, 2010). We implemented two population simulation methods within HTTK-Pop: the direct-resampling method and the virtual-individuals method. The direct-resampling method simulated a population by sampling NHANES respondents with replacement, with probabilities proportional to the sample weights. Each individual in the resulting simulated population was an NHANES respondent, identified by a unique NHANES sequence number. By contrast, the second method generates "virtual individuals" - sets of NHANES quantities that obey the approximate joint distribution of the NHANES quantities (calculated using weighted smoothing functions and kernel density estimators), but do not necessarily correspond to any particular NHANES respondent. The direct-resampling method removed the possibility of generating unrealistic combinations of the NHANES quantities; the virtual-individuals method allowed the use of interpolation to simulate subpopulations represented by only a small number of NHANES respondents.

For either method, HTTK-Pop takes optional specifications about the population to be simulated and then samples from the appropriate conditional joint distribution of the NHANES quantities.

Once HTTK-Pop has simulated a population characterized by the NHANES quantities, the physiological parameters of the TK model are predicted from the NHANES quantities using regression equations from the literature. Liver mass was predicted for individuals over age 18 using allometric scaling with height from Reference Man (Valentin, 2002), and for individuals under 18 using regression relationships with height and weight published by Ogiu et al. (1997). Residual marginal variability was added for each individual as in PopGen (McNally et al., 2014). Similarly, hepatic portal vein blood flows (in L/h) are predicted as fixed fractions of a cardiac output allometrically scaled with height from Reference Man (Valentin, 2002), and residual marginal variability is added for each individual (McNally et al., 2014). Glomerular filtration rate (GFR) (in L/h/1.73 m2 body surface area) is predicted from age, race, sex, and serum creatinine using the CKD-EPI equation, for individuals over age 18 (Levey et al., 2009). For individuals under age 18, GFR is estimated from body surface area (BSA) (Johnson et al., 2006); BSA is predicted using Mosteller's formula (Verbraecken et al., 2006) for adults and Haycock's formula (Haycock et al., 1978) for children. Hepatocellularity (in millions of cells per gram of liver tissue) is predicted from age using an equation developed by Barter et al. (2007). Hematocrit is estimated from NHANES data for individuals 1 year and older. For individuals younger than 1 year, for whom NHANES did not measure hematocrit directly, hematocrit was predicted from age in months, using published reference ranges (Lubin, 1987).

In addition to the HTTK physiological parameters, the HTTK models include chemical-specific parameters representing the fraction of chemical unbound in plasma (Fup) and intrinsic clearance (CLint). Because these parameters represent interactions of the chemical with the body, their values will vary between individuals. To simulate this variability, Fub and CLint were included in MC simulations, by sampling from estimated or assumed distributions for the parameters defining them.

Variability in hematocrit was simulated either using NHANES data (for individuals ages 1 and

older) or using age-based reference ranges (for individuals under age 1). Fup was treated as a random variable obeying a distribution censored below the average limit of quantification (LOQ) of the in vitro assay. Specifically, Fup was assumed to obey a normal distribution truncated below at 0 and above at 1, centered at the Fup value measured in vitro, with a 30 the average LOQ (0.01), Fup was instead drawn from a uniform distribution between 0 and 0.01. Fup was assumed to be independent of all other parameters. This censored normal distribution was chosen to match that used in Wambaugh et al. (2015).

Variability in hepatocellularity (106 cells/g liver) and Mliver (kg) were simulated. The remaining source of variability in CLint,h is variability in CLint, which was simulated using a Gaussian mixture distribution to represent the population proportions of poor metabolizers (PMs) and non-PMs of each substance. The true prevalence of PMs is isozyme-specific (Ma et al., 2002; Yasuda et al., 2008); however, isozyme- specific metabolism data were not available for the majority of chemicals considered. We therefore made a simplifying assumption that 5 slower than average. With 95 a normal distribution truncated below at zero, centered at the value measured in vitro, with a 30 CLint was drawn from a PM distribution: a truncated normal distribution centered on one-tenth of the in vitro value with 30 Both CLint itself and the probability of being a PM were assumed to be independent of all other parameters. The truncated normal nonePM distribution was chosen because it has been used (with 100 in previous work (Rotroff et al., 2010; Wambaugh et al., 2015; Wetmore et al., 2014; Wetmore et al., 2015; Wetmore et al., 2012); the PM distribution was chosen to comport with the nonePM distribution.

Main function to generate a population

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

Using HTTK-Pop with HTTK

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

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

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

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httkpop_biotophys_default

Convert HTTK-Pop-generated parameters to HTTK physiological parameters

Description

Convert HTTK-Pop-generated parameters to HTTK physiological parameters

Usage

```
httkpop_biotophys_default(indiv_dt)
```

Arguments

indiv_dt	The data.table object returned by `httkpop_generate()`

Value

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

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

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"),
  gfr_resid_var = TRUE,
  ckd_epi_race_coeff = FALSE,
  nhanes_mec_svy
)
```

Arguments

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

ckd_epi_race_coeff
: Logical value indicating whether or not to use the "race coefficient" from the CKD-EPI equation when estimating GFR values. (Default is FALSE.)

nhanes_mec_svy
: surveydesign object created from mecdt using svydesign (this is done in httkpop_generate)

Value

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

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

---

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,
  gfr_resid_var,
  ckd_epi_race_coeff,
  nhanes_mec_svy
)
```

Arguments

nsamp	The desired number of individuals in the virtual population. nsamp need not be provided if gendernum is provided.
gendernum	Optional: A named list giving the numbers of male and female individuals to include in the population, e.g. list(Male=100,Female=100). Default is NULL, meaning both males and females are included, in their proportions in the NHANES data. If both nsamp and gendernum are provided, they must agree (i.e., nsamp must be the sum of gendernum).
agelim_months	Optional: A two-element numeric vector giving the minimum and maximum ages (in months) to include in the population. Default is c(0, 959), equivalent to the default agelim_years. If agelim_months is provided and agelim_years is not, agelim_months will override the default values of agelim_years.
agelim_years	Optional: A two-element numeric vector giving the minimum and maximum ages (in years) to include in the population. Default is c(0,79). If agelim_years is provided and agelim_months is not, agelim_years will override the default value of agelim_months.
reths	Optional: a character vector giving the races/ethnicities to include in the population. Default is c('Mexican American','Other Hispanic','Non-Hispanic White','Non-Hispanic Black','Other'), to include all races and ethnicities in their proportions in the NHANES data. User-supplied vector must contain one or more of these strings.
weight_category	Optional: The weight categories to include in the population. Default is c('Underweight', 'Normal', 'Overweight','Obese'). User-supplied vector must contain one or more of these strings.
gfr_resid_var	Logical value indicating whether or not to include residual variability when generating GFR values. (Default is TRUE, passed from 'httkpop_direct_resample'.)
ckd_epi_race_coeff	Logical value indicating whether or not to use the "race coefficient" from the CKD-EPI equation when estimating GFR values. (Default is FALSE, passed from 'httkpop_direct_resample'.)
nhanes_mec_svy	surveydesign object created from mecdt using svydesign (this is done in httkpop_generate)

Value

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

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

httkpop_generate *Generate a virtual population for PBTK*

Description

Generate a virtual population characterized by demographic, anthropometric, and physiological parameters relevant to PBTK.

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"),
  gfr_resid_var = TRUE,
  ckd_epi_race_coeff = FALSE
)
```

Arguments

method	The population-generation method to use. Either "virtual individuals" or "direct resampling." Short names may be used: "d" or "dr" for "direct resampling", and "v" or "vi" for "virtual individuals".
nsamp	The desired number of individuals in the virtual population. nsamp need not be provided if gendernum is provided.
gendernum	Optional: A named list giving the numbers of male and female individuals to include in the population, e.g. list(Male=100,Female=100). Default is NULL, meaning both males and females are included, in their proportions in the NHANES data. If both nsamp and gendernum are provided, they must agree (i.e., nsamp must be the sum of gendernum).
agelim_years	Optional: A two-element numeric vector giving the minimum and maximum ages (in years) to include in the population. Default is c(0,79). If only a single value is provided, both minimum and maximum ages will be set to that value; e.g. agelim_years=3 is equivalent to agelim_years=c(3,3). If agelim_years is provided and agelim_months is not, agelim_years will override the default value of agelim_months.
agelim_months	Optional: A two-element numeric vector giving the minimum and maximum ages (in months) to include in the population. Default is c(0, 959), equivalent to the default agelim_years. If only a single value is provided, both minimum and maximum ages will be set to that value; e.g. agelim_months=36 is equivalent to

agelim_months=c(36,36). If agelim_months is provided and agelim_years is not, agelim_months will override the default values of agelim_years.

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

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

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

gfr_resid_var
: TRUE to add residual variability to GFR predicted from serum creatinine; FALSE to not add residual variability

ckd_epi_race_coeff
: TRUE to use the CKD-EPI equation as originally published (with a coefficient changing predicted GFR for individuals identified as "Non-Hispanic Black"); FALSE to set this coefficient to 1.

Details

Demographic and anthropometric (body measures) variables, along with serum creatinine and hematocrit, are generated from survey data from the Centers for Disease Control's National Health and Nutrition Examination Survey (NHANES). Those data are stored in the object nhanes_mec_svy (a survey.design object, see package survey). With method = "d", these variables will be sampled with replacement directly from NHANES data. Each NHANES respondent's likelihood of being sampled is given by their sample weight. With method = "v", these variables will be sampled from distributions fitted to NHANES data. Tissue masses and flows are generated based on demographic, body measures, and serum creatinine values, using regression equations from the literature and/or allometric scaling based on height. Extensive details about how each of these parameters are generated are available in the supplemental material of Ring et al. (2017) (see References for full citation).

Value

A data.table where each row represents an individual, and each column represents a demographic, anthropometric, or physiological parameter. Details of the parameters returned and their units are in the following tables.

Demographic variables

Name	Defini
seqn	NHANES unique identifier (only included if method = "direct resampli
gender	Sex: "Male" or "Fem
reth	Race/ethnicity: "Non-Hispanic Black", "Non-Hispanic white", "Mexican American", "Other Hispanic", or "Otl
age_years	Age (0-79 y

age_months	Age (0-959 mon

Body measures and laboratory measurements

Name	Definition	Units
height	Height	cm
weight	Body weight	kg
serum_creat	Serum creatinine	mg/dL
hematocrit	Hematocrit (percentage by volume of red blood cells in blood)	%

Tissue masses

Name	
Blood_mass	M
Brain_mass	M
Gonads_mass	Mas
Heart_mass	M
Kidneys_mass	Mas
Large_intestine_mass	Mass of la
Liver_mass	M
Lung_mass	M
Muscle_mass	Mass of ske
Pancreas_mass	Mass
Skeleton_mass	Mass of skeleton (including bone, red and yellow marrow, cartilage, periarti
Skin_mass	M
Small_intestine_mass	Mass of sm
Spleen_mass	Ma
Stomach_mass	Mass of sto
Other_mass	Mass of GI tract contents (1.4% of body weight) and tissues not otherwise enumerated (3.3% of bo
org_mass_sum	Sum of the above tissue masses. A check to ensure this is less than b
Adipose_mass	Mass of adipose tissue. Assigned as weight - org

Tissue flows

Name	Definition
Adipose_flow	Blood flow to adipose tissue
Brain_flow	Blood flow to brain tissue
CO	Cardiac output
Gonads_flow	Blood flow to gonads tissue
Heart_flow	Blood flow to heart tissue

Kidneys_flow	Blood flow to kidneys tissue (not for glomerular filtration!)
Large_intestine_flow	Blood flow to large intestine tissue
Liver_flow	Blood flow to liver tissue
Lung_flow	Blood flow to lung tissue
Muscle_flow	Blood flow to skeletal muscle tissue
Pancreas_flow	Blood flow to pancreas tissue
Skeleton_flow	Blood flow to skeleton
Skin_flow	Blood flow to skin
Small_intestine_flow	Blood flow to small intestine
Spleen_flow	Blood flow to spleen
Stomach_flow	Blood flow to stomach
org_flow_check	Sum of blood flows as a fraction of cardiac output (CO). A check to make sure this is less than 1.

Adjusted variables

Name	
weight_adj	
BSA_adj	
million.cells.per.gliver	
gfr_est	Glomerular filtration rate (GFR) estimated using either the CKD-EPI equatio
bmi_adj	Bo
weight_class	Weight category based on bmi_adj: "Underweight" (BMI < 18.5), "Normal" (18.5 < BMI < 2
gfr_class	Kidney function category based on GFR: "Normal" (GFR >=60 mL/min/1.73 m^2), "Kidr

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

Examples

```
#Simply generate a virtual population of 100 individuals,
 #using the direct-resampling method
 set.seed(42)
httkpop_generate(method='direct resampling', nsamp=100)

#Generate a population using the virtual-individuals method,
#including 80 females and 20 males,
#including only ages 20-65,
```

```
#including only Mexican American and
#Non-Hispanic Black individuals,
#including only non-obese individuals
set.seed(42)
mypop <- 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'))
# Including a httkpop.dt argument will overwrite the number of sample and
# the httkpop on/off logical switch:
samps1 <- create_mc_samples(chem.name="bisphenola",
                            httkpop=FALSE,
                            httkpop.dt=mypop)
samps2 <- create_mc_samples(chem.name="bisphenola",
                            httkpop.dt=mypop)
samps3 <- create_mc_samples(chem.name="bisphenola",
                            httkpop=FALSE)
# Now run calc_mc_oral equiv on the same pop for two different chemcials:
calc_mc_oral_equiv(conc=10,
                   chem.name="bisphenola",
                   httkpop.dt=mypop,
                   return.samples=TRUE)
calc_mc_oral_equiv(conc=2,
                   chem.name="triclosan",
                   httkpop.dt=mypop,
                   return.samples=TRUE)
```

`httkpop_mc` *httk-pop: Correlated human physiological parameter Monte Carlo*

Description

This is the core function for httk-pop correlated human physiological variability simulation as described by Ring et al. (2017) (doi:10.1016/j.envint.2017.06.004). This functions takes the data table of population biometrics (one individual per row) generated by `httkpop_generate`, and converts it to the corresponding table of HTTK model parameters for a specified HTTK model.

Usage

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

Arguments

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

Details

The Monte Carlo methods used here were recently updated and described by Breen et al. (submitted).

Value

A data.table with a row for each individual in the sample and a column for each parater in the model.

Author(s)

Caroline Ring and John Wambaugh

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

Breen M, Wambaugh JF, Bernstein A, Sfeir M, Ring CL (2022). "Simulating toxicokinetic variability to identify susceptible and highly exposed populations." *Journal of Exposure Science & Environmental Epidemiology*, **32**(6), 855–863. doi:10.1038/s41370022004910.

Rowland M, Benet LZ, Graham GG (1973). "Clearance concepts in pharmacokinetics." *Journal of pharmacokinetics and biopharmaceutics*, **1**(2), 123–136. doi:10.1007/BF01059626.

Examples

```
set.seed(42)
indiv_examp <- httkpop_generate(method="d", nsamp=10)

httk_param <- httkpop_mc(httkpop.dt=indiv_examp,
                         samples=10,
                         model="1compartment")
```

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

Description

Generate a virtual population by the virtual individuals method.

Usage

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

Arguments

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

reths	Optional: a character vector giving the races/ethnicities to include in the population. Default is c('Mexican American','Other Hispanic','Non-Hispanic White','Non-Hispanic Black','Other'), to include all races and ethnicities in their proportions in the NHANES data. User-supplied vector must contain one or more of these strings.
gfr_resid_var	Logical value indicating whether or not to include residual variability when generating GFR values. (Default is TRUE.)
ckd_epi_race_coeff	Logical value indicating whether or not to use the "race coefficient" from the CKD-EPI equation when estimating GFR values. (Default is FALSE.)
nhanes_mec_svy	surveydesign object created from mecdt using svydesign (this is done in httkpop_generate, which calls this function)

Value

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

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

---

httk_chem_subset *HTTK data chemical subsetting function*

Description

This function is meant to take any 'httk' data and subset it based on a list of chemicals provided. Main functionality is for speeding up the 'load_sipes2017', 'load_pradeep2020', 'load_dawson2021', 'load_honda2023', and similar phys-chem data files. However, it should be generalizable to any dataset with CAS/CASRN or DTXSID chemical identifiers.

Usage

```
httk_chem_subset(data, chem_include)
```

Arguments

data	Data frame, with chemical data, to be subset.
chem_include	(*character vector*) A character vector containing CAS/CASRN or DTXSID chemical identifiers to include in the data subset.

Value

A subset data set containing only the data rows for chemicals identified as those that should be included.

`hw_H` *KDE bandwidth for residual variability in height/weight*

Description

Bandwidths used for a two-dimensional kernel density estimation of the joint distribution of residual errors around smoothing spline fits of height vs. age and weight vs. age for NHANES respondents in each of ten combinations of sex and race/ethnicity categories.

Usage

```
hw_H
```

Format

A named list with 10 elements, each a matrix with 2 rows and 2 columns. Each list element corresponds to, and is named for, one combination of NHANES sex categories (Male and Female) and NHANES race/ethnicity categories (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other).

Details

Each matrix is a variance-covariance matrix for a two-dimensional normal distribution: this is the bandwidth to be used for a two-dimensional kernel density estimation (KDE) (using a two-dimensional normal kernel) of the joint distribution of residual errors around smoothing spline fits of height vs. age and weight vs. age for NHANES respondents in the specified sex and race/ethnicity category. Optimal bandwidths were pre-calculated by doing the smoothing spline fits, getting the residuals, then calling `kde` on the residuals (which calls `Hpi` to compute the plug-in bandwidth).

Used by HTTK-Pop only in "virtual individuals" mode (i.e. `httkpop_generate` with `method = "v"`), in `gen_height_weight`.

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

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

Description

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

Usage

```
in.list(chem.cas = NULL, which.list = "ToxCast")
```

Arguments

`chem.cas`	The Chemical Abstracts Service Resgistry Number (CAS-RN) corresponding to the chemical of interest.
`which.list`	A character string that can take the following values: "ToxCast", "Tox21", "ExpoCast", "NHANES", ""NHANES.serum.parent", "NHANES.serum.analyte","NHANES.blood.parent","NHANES.blood.analyte","NHANES.urine.parent","NHANES.urine.analyte"

Details

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

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

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

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

Value

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

Author(s)

John Wambaugh

References

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

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

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

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

See Also

is.httk for determining inclusion in httk project

Examples

```
httk.table <- get_cheminfo(info=c("CAS","Compound"))
httk.table[,"Rat"] <- ""
httk.table[,"NHANES"] <- ""
httk.table[,"Tox21"] <- ""
httk.table[,"ToxCast"] <- ""
httk.table[,"ExpoCast"] <- ""
httk.table[,"PBTK"] <- ""
# To make this example run quickly, this loop is only over the first five
# chemicals. To build a table with all available chemicals use:
# for (this.cas in httk.table$CAS)
for (this.cas in httk.table$CAS[1:5])
{
  this.index <- httk.table$CAS==this.cas
  if (is.nhanes(this.cas)) httk.table[this.index,"NHANES"] <- "Y"
  if (is.tox21(this.cas)) httk.table[this.index,"Tox21"] <- "Y"
  if (is.toxcast(this.cas)) httk.table[this.index,"ToxCast"] <- "Y"
  if (is.expocast(this.cas)) httk.table[this.index,"ExpoCast"] <- "Y"
  if (is.httk(this.cas,model="PBTK")) httk.table[this.index,"PBTK"] <- "Y"
  if (is.httk(this.cas,species="rat")) httk.table[this.index,"Rat"] <- "Y"
}
```

`invitro_mc` *Monte Carlo for in vitro toxicokinetic parameters including uncertainty and variability.*

Description

Given a CAS in the HTTK data set, a virtual population from HTTK-Pop, some user specifications on the assumed distributions of Funbound.plasma and Clint, draw "individual" values of Funbound.plasma and Clint from those distributions. The methodology for this function was developed and described by Wambaugh et al. (2019) (doi:10.1093/toxsci/kfz205).

Usage

```
invitro_mc(
  parameters.dt = NULL,
  samples,
  fup.meas.mc = TRUE,
  fup.pop.mc = TRUE,
  clint.meas.mc = TRUE,
  clint.pop.mc = TRUE,
  fup.meas.cv = 0.4,
  clint.meas.cv = 0.3,
  fup.pop.cv = 0.3,
  clint.pop.cv = 0.3,
  caco2.meas.sd = 0.3,
  caco2.pop.sd = 0.3,
  Caco2.Fgut = TRUE,
  Caco2.Fabs = TRUE,
  keepit100 = FALSE,
  poormetab = TRUE,
  fup.lod = 0.01,
  fup.censored.dist = FALSE,
  adjusted.Funbound.plasma = TRUE,
  adjusted.Clint = TRUE,
  clint.pvalue.threshold = 0.05,
  minimum.Funbound.plasma = 1e-04
)
```

Arguments

parameters.dt	A data table of physiological and chemical-specific parameters
samples	The number of samples to draw.
fup.meas.mc	Logical – should we perform measurment (uncertainty) Monte Carlo for Funbound.plasma values (Default TRUE). If FALSE, the user may choose to provide columns for "unadjusted.Funbound.plasma" or "fup.mean" from their own methods.
fup.pop.mc	Logical – should we perform population (variability) Monte Carlo for Funbound.plasma values (Default TRUE)
clint.meas.mc	Logical – should we perform measurment (uncertainty) Monte Carlo for Clint values (Default TRUE)
clint.pop.mc	Logical – should we perform population (variability) Monte Carlo for Clint values (Default TRUE)
fup.meas.cv	Coefficient of variation of distribution of measured Funbound.plasma values.

clint.meas.cv Coefficient of variation of distribution of measured Clint values.

fup.pop.cv Coefficient of variation of distribution of population Funbound.plasma values.

clint.pop.cv Coefficient of variation of distribution of population Clint values.

caco2.meas.sd Standard deviation of the measured oral absorption - numeric value (Default 0.3).

caco2.pop.sd Standard deviation of the population level oral absorption - numeric value (Default 0.3).

Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = Fgut.

Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = Fabs.

keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings.

poormetab Logical. Whether to include poor metabolizers in the Clint distribution or not.

fup.lod The average limit of detection for Funbound.plasma, below which distribution will be censored if fup.censored.dist is TRUE. Default 0.01.

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

adjusted.Funbound.plasma
Uses the Pearce et al. (2017) lipid binding adjustment for Funbound.plasma when set to TRUE (Default).

adjusted.Clint Uses Kilford et al. (2008) hepatocyte incubation binding adjustment for Clint when set to TRUE (Default).

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

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

parameters A list of chemical-specific model parameters containing at least Funbound.plasma, Clint, and Fhep.assay.correction.

Details

The Monte Carlo methods used here were recently updated and described by Breen et al. (2022).

Value

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

Author(s)

Caroline Ring and John Wambaugh

References

Breen M, Wambaugh JF, Bernstein A, Sfeir M, Ring CL (2022). "Simulating toxicokinetic variability to identify susceptible and highly exposed populations." *Journal of Exposure Science & Environmental Epidemiology*, **32**(6), 855–863. doi:10.1038/s41370022004910.

Kilford PJ, Gertz M, Houston JB, 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), 1194–1197. doi:10.1124/dmd.108.020834.

Pearce RG, Setzer RW, Davis JL, Wambaugh JF (2017). "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." *Journal of pharmacokinetics and pharmacodynamics*, **44**, 549–565. doi:10.1007/s1092801795487.

Wambaugh JF, Wetmore BA, Ring CL, Nicolas CI, Pearce RG, Honda GS, Dinallo R, Angus D, Gilbert J, Sierra T, others (2019). "Assessing toxicokinetic uncertainty and variability in risk prioritization." *Toxicological Sciences*, **172**(2), 235–251. doi:10.1093/toxsci/kfz205.

Examples

```
#Simply generate a virtual population of 100 individuals,
#using the direct-resampling method
set.seed(42)

# Pull mean chemical=specific values:
chem.props <- parameterize_pbtk(chem.name="bisphenolb")

# Convert to data.table with one row per sample:
parameters.dt <- monte_carlo(chem.props,samples=100)

# Use httk-pop to generate a population:
pop <- httkpop_generate(method='direct resampling', nsamp=100)

# Overwrite parameters specified by httk-pop:
parameters.dt[,names(pop):=pop]

# Vary in vitro parameters:
parameters.dt <- invitro_mc(parameters.dt,samples=100)
```

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

Description

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

Usage

```
is.httk(chem.cas, species = "Human", model = "3compartmentss")
```

Arguments

chem.cas	The Chemical Abstracts Service Resgistry Number (CAS-RN) corresponding to the chemical of interest.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
model	Model used in calculation, 'pbtk' for the multiple compartment model, '1compartment' for the one compartment model, '3compartment' for three compartment model, '3compartmentss' for the three compartment model without partition coefficients, or 'schmitt' for chemicals with logP and fraction unbound (used in predict_partitioning_schmitt).

Details

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

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

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

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

Value

logical	A Boolean (1/0) value that is TRUE if the chemical is included in the httk project with a given modeling scheme (PBTK) and a given species

Author(s)

John Wambaugh

References

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

Judson, R. S., Houck, K. A., Kavlock, R. J., Knudsen, T. B., Martin, M. T., Mortensen, H. M., Reif, D. M., Rotroff, D. M., Shah, I., Richard, A. M. and Dix, D. J. (2010). In Vitro Screening of

Environmental Chemicals for Targeted Testing Prioritization: The ToxCast Project. Environmental Health Perspectives 118(4), 485-492.

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

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

See Also

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

Examples

```
httk.table <- get_cheminfo(info=c("CAS","Compound"))
httk.table[,"Rat"] <- ""
httk.table[,"NHANES"] <- ""
httk.table[,"Tox21"] <- ""
httk.table[,"ToxCast"] <- ""
httk.table[,"ExpoCast"] <- ""
httk.table[,"PBTK"] <- ""
# To make this example run quickly, this loop is only over the first five
# chemicals. To build a table with all available chemicals use:
# for (this.cas in httk.table$CAS)
for (this.cas in httk.table$CAS[1:5])
{
  this.index <- httk.table$CAS==this.cas
  if (is.nhanes(this.cas)) httk.table[this.index,"NHANES"] <- "Y"
  if (is.tox21(this.cas)) httk.table[this.index,"Tox21"] <- "Y"
  if (is.toxcast(this.cas)) httk.table[this.index,"ToxCast"] <- "Y"
  if (is.expocast(this.cas)) httk.table[this.index,"ExpoCast"] <- "Y"
  if (is.httk(this.cas,model="PBTK")) httk.table[this.index,"PBTK"] <- "Y"
  if (is.httk(this.cas,species="rat")) httk.table[this.index,"Rat"] <- "Y"
}
```

---

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

Description

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

Usage

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

Arguments

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

Value

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

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

`johnson` *Johnson 2006*

Description

This data set is only used in Vignette 5.

Usage

```
johnson
```

Format

A data.table containing 60 rows and 11 columns.

Author(s)

Caroline Ring

References

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

kapraun2019 *Kapraun et al. 2019 data*

Description

A list object containing time-varying parameters for the human maternal-fetal HTTK model. List elements contain scalar coefficients for the polynomial, logistic, Gompertz, and other functions of time describing blood flow rates, tissue volumes, hematocrits, and other anatomical/physiological quantities that change in the human mother and her fetus during pregnancy and gestation.

Usage

```
kapraun2019
```

Format

list

Author(s)

Dustin F. Kapraun

Source

Kapraun DF, Sfeir M, Pearce RG, Davidson-Fritz SE, Lumen A, Dallmann A, Judson RS, Wambaugh JF (2022). "Evaluation of a rapid, generic human gestational dose model." *Reproductive Toxicology*, **113**, 172–188. doi:10.1016/j.reprotox.2022.09.004.

References

Kapraun DF, Wambaugh JF, Setzer RW, Judson RS (2019). "Empirical models for anatomical and physiological changes in a human mother and fetus during pregnancy and gestation." *PLOS ONE*, **14**(5), 1-56. doi:10.1371/journal.pone.0215906.

kidney_mass_children *Predict kidney mass for children*

Description

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

Usage

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

Arguments

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

Value

A vector of kidney masses in kg.

Author(s)

Caroline Ring

References

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

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

---

list_models *List all available HTTK models*

Description

List all available HTTK models

Usage

```
list_models()
```

Value

Prints a list of available HTTK models to the screen.

Author(s)

John Wambaugh

liver_mass_children *Predict liver mass for children*

Description

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

Usage

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

Arguments

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

Value

A vector of liver masses in kg.

Author(s)

Caroline Ring

References

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

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

load_dawson2021 *Load CLint and Fup QSPR predictions from Dawson et al. 2021.*

Description

This function returns an updated version of chem.physical_and_invitro.data that includes Clint and Fup predictions from the Random Forest quantitative structure-property relationship (QSPR) models developed and presented in Dawson et al. 2021, included in table dawson2021.

Usage

```
load_dawson2021(
  overwrite = FALSE,
  exclude_oad = TRUE,
  chem_include = NULL,
  target.env = .GlobalEnv
)
```

Arguments

overwrite	Only matters if load.image=FALSE. If overwrite=TRUE then existing data in chem.physical_and_invitro.data will be replaced by any predictions in Dawson et al. (2021) 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.
exclude_oad	Include the chemicals only within the applicability domain. If exclude_oad=TRUE (DEFAULT) chemicals outside the applicability domain do not have their predicted values loaded.
chem_include	A vector of CAS numbers indicating only the chemicals to be included in the loading process. If set to 'NULL' all applicable chemicals are loaded. (Default is 'NULL'.)
target.env	The environment where the new chem.physical_and_invitro.data is loaded. Defaults to global environment.

Details

Because Clint and Fup are the only measurements required for many HTTK models, changing the number of chemicals for which a value is available will change the number of chemicals which are listed with the get_cheminfo command. Use the command reset_httk to return to the initial (measured only) chem.physical_and_invitro.data (for all parameters).

Value

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

Author(s)

Sarah E. Davidson

References

Dawson DE, Ingle BL, Phillips KA, Nichols JW, Wambaugh JF, Tornero-Velez R (2021). "Designing QSARs for Parameters of High-Throughput Toxicokinetic Models Using Open-Source Descriptors." *Environmental Science & Technology*, **55**(9), 6505-6517. doi:10.1021/acs.est.0c06117, PMID: 33856768, https://doi.org/10.1021/acs.est.0c06117.

See Also

reset_httk

get_cheminfo

Examples

```
# Count how many chemicals for which HTTK is available without the QSPR:
num.chems <- length(get_cheminfo())
print(num.chems)

# For chemicals with Dawson et al. (2021) Clint and Fup QSPR predictions,
# add them to our chemical information wherever measured values are
# unavailable:
load_dawson2021()
# For chemicals with Dawson et al. (2021) QSPR predictions, add them to
# our chemical information -- overwriting measured values where we had them:
load_dawson2021(overwrite=TRUE)

# Let's see how many chemicals we have now with the Dawson et al. (2021)
# predictions loaded:
length(get_cheminfo())

# Now let us reset the chemical data to the initial version:
reset_httk()

# We should be back to our original number:
num.chems == length(get_cheminfo())

# Demonstrate loading data for specific chemicals:
#
# Find chemicals with a clint and no fup:
subset(chem.physical_and_invitro.data,!is.na(Human.Clint) & Human.Funbound.plasma==0)$CAS
chem1 <- "32598-13-3"
chem2 <- "2971-36-0"
# Take a look at what parameterize_steadystate gives (working from a default fup of 0.005):
a1 <- parameterize_steadystate(chem.cas=chem1)
a2 <- parameterize_steadystate(chem.cas=chem2)

# load Dawson for this chemical:
load_dawson2021(chem_include=chem1)
# Check values, only fup for the first chemical should change:
a3 <- parameterize_steadystate(chem.cas=chem1)
a4 <- parameterize_steadystate(chem.cas=chem2)
# All tests should be true:
a1[["Clint"]] == a3[["Clint"]]
a1[["Funbound.plasma"]] != a3[["Funbound.plasma"]]
a2[["Clint"]] == a4[["Clint"]]
a2[["Funbound.plasma"]] == a4[["Funbound.plasma"]]

# load Dawson for this chemical, but allow it to overwrite the clint:
load_dawson2021(chem_include=chem1, overwrite=TRUE)
```

```
# Check values, both clint and fup for the first chemical should change:
a5 <- parameterize_steadystate(chem.cas=chem1)
a6 <- parameterize_steadystate(chem.cas=chem2)
# All tests should be true:
a1[["Clint"]] != a5[["Clint"]]
a1[["Funbound.plasma"]] != a5[["Funbound.plasma"]]
a2[["Clint"]] == a6[["Clint"]]
a2[["Funbound.plasma"]] == a6[["Funbound.plasma"]]

# Load Dawson for all chemicals, fup should change for second chemical:
load_dawson2021()
a7 <- parameterize_steadystate(chem.cas=chem1)
a8 <- parameterize_steadystate(chem.cas=chem2)
# All tests should be true:
a1[["Clint"]] != a7[["Clint"]]
a1[["Funbound.plasma"]] != a7[["Funbound.plasma"]]
a2[["Clint"]] == a8[["Clint"]]
a2[["Funbound.plasma"]] != a8[["Funbound.plasma"]]

# load Dawson for this chemical, but allow it to overwrite all clints:
load_dawson2021(overwrite=TRUE)
# Both clint and fup should now be changed for second chemical:
a9 <- parameterize_steadystate(chem.cas=chem1)
a10 <- parameterize_steadystate(chem.cas=chem2)
# All tests should be true:
a1[["Clint"]] != a9[["Clint"]]
a1[["Funbound.plasma"]] != a9[["Funbound.plasma"]]
a2[["Clint"]] != a10[["Clint"]]
a2[["Funbound.plasma"]] != a10[["Funbound.plasma"]]
```

`load_honda2023` *Load Caco2 QSPR predictions from Honda et al. 2023*

Description

This function returns an updated version of `chem.physical_and_invitro.data` that includes Caco2 Pab predictions from the Random Forest quantitative structure-property relationship (QSPR) models developed and presented in Honda et al. 2023, included in table `honda2023.qspr`.

Usage

```
load_honda2023(
  overwrite = FALSE,
  exclude_oad = TRUE,
  chem_include = NULL,
  target.env = .GlobalEnv
)
```

Arguments

overwrite	Only matters if load.image=FALSE. If overwrite=TRUE then existing data in chem.physical_and_invitro.data will be replaced by any prediction in Honda et al. (2023) that is for the same chemical and property. If overwrite=FALSE (DEFAULT) then new data for the same chemical and property are ignored.
exclude_oad	Include the chemicals only within the applicability domain. If exclude_oad=TRUE (DEFAULT) chemicals outside the applicability domain do not have their predicted values loaded.
chem_include	A vector of CAS numbers indicating only the chemicals to be included in the loading process. If set to 'NULL' all applicable chemicals are loaded. (Default is 'NULL'.)
target.env	The environment where the new chem.physical_and_invitro.data is loaded. Defaults to global environment.

Details

Note that because Pab is not required for most HTTK models, changing the number of chemicals for which a value is available will not change the number of chemicals which are listed with the get_cheminfo command. Use the command reset_httk to return to the initial (measured only) chem.physical_and_invitro.data (for all parameters).

Value

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

Author(s)

John Wambaugh

See Also

reset_httk

get_cheminfo

Examples

```
# For chemicals with Honda et al. (2023) Caco2 Pab QSPR predictions,
# add them to our chemical information wherever measured values are
# unavailable:
load_honda2023()

# Or, for chemicals with Honda et al. (2023) QSPR predictions, add them to
# our chemical information but overwrite measured values where we had them:
load_honda2023(overwrite=TRUE)

# Now let us reset the chemical data to the initial version:
reset_httk()
```

load_pradeep2020 *Load CLint and Fup QSPR predictions predictions from Pradeep et al. 2020.*

Description

This function returns an updated version of chem.physical_and_invitro.data that includes quantitative structure-property relationship (QSPR) predictions from Support Vector Machine and Random Forest models developed and presented in Pradeep et al. 2020, included in pradeep2020.

Usage

```
load_pradeep2020(
  overwrite = FALSE,
  chem_include = NULL,
  target.env = .GlobalEnv
)
```

Arguments

overwrite	Only matters if load.image=FALSE. If overwrite=TRUE then existing data in chem.physical_and_invitro.data will be replaced by any predictions in Pradeep et al. (2020) 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.
chem_include	A vector of CAS numbers indicating only the chemicals to be included in the loading process. If set to 'NULL' all applicable chemicals are loaded. (Default is 'NULL'.)
target.env	The environment where the new chem.physical_and_invitro.data is loaded. Defaults to global environment.

Details

Because Clint and Fup are the only measurements required for many HTTK models, changing the number of chemicals for which a value is available will change the number of chemicals which are listed with the get_cheminfo command. Use the command reset_httk to return to the initial (measured only) chem.physical_and_invitro.data (for all parameters).

Value

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

Author(s)

Sarah E. Davidson

References

Pradeep P, Patlewicz G, Pearce R, Wambaugh J, Wetmore B, Judson R (2020). "Using chemical structure information to develop predictive models for in vitro toxicokinetic parameters to inform high-throughput risk-assessment." *Computational Toxicology*, **16**, 100136. ISSN 2468-1113, doi:10.1016/j.comtox.2020.100136.

See Also

reset_httk

get_cheminfo

Examples

```
# Count how many chemicals for which HTTK is available without the QSPR:
num.chems <- length(get_cheminfo())
print(num.chems)

# For chemicals with Pradeep et al. (2020) Clint and Fup QSPR predictions,
# add them to our chemical information wherever measured values are
# unavailable:
load_pradeep2020()

# Or, for chemicals with Pradeep et al. (2020) QSPR predictions, add them to
# our chemical information but overwrite measured values where we had them:
load_pradeep2020(overwrite=TRUE)

# Let's see how many chemicals we have now with the Pradeep et al. (2020)
# predictions data loaded:
length(get_cheminfo())

# Now let us reset the chemical data to the initial version:
reset_httk()

# We should be back to our original number:
num.chems == length(get_cheminfo())

# Demonstrate loading data for specific chemicals:
#
# Find chemicals with a clint and no fup:
subset(chem.physical_and_invitro.data,!is.na(Human.Clint) & Human.Funbound.plasma==0)$CAS
chem1 <- "101-05-3"
chem2 <- "2971-36-0"
# Take a look at what parameterize_steadystate gives (working from a default fup of 0.005):
a1 <- parameterize_steadystate(chem.cas=chem1)
a2 <- parameterize_steadystate(chem.cas=chem2)

# load Pradeep for this chemical:
load_pradeep2020(chem_include=chem1)
# Check values, only fup for the first chemical should change:
a3 <- parameterize_steadystate(chem.cas=chem1)
```

```
a4 <- parameterize_steadystate(chem.cas=chem2)
# All tests should be true:
a1[["Clint"]] == a3[["Clint"]]
a1[["Funbound.plasma"]] != a3[["Funbound.plasma"]]
a2[["Clint"]] == a4[["Clint"]]
a2[["Funbound.plasma"]] == a4[["Funbound.plasma"]]

# load Pradeep for this chemical, but allow it to overwrite the clint:
load_pradeep2020(chem_include=chem1, overwrite=TRUE)
# Check values, both clint and fup for the first chemical should change:
a5 <- parameterize_steadystate(chem.cas=chem1)
a6 <- parameterize_steadystate(chem.cas=chem2)
# All tests should be true:
a1[["Clint"]] != a5[["Clint"]]
a1[["Funbound.plasma"]] != a5[["Funbound.plasma"]]
a2[["Clint"]] == a6[["Clint"]]
a2[["Funbound.plasma"]] == a6[["Funbound.plasma"]]

# Load Pradeep for all chemicals, fup should change for second chemical:
load_pradeep2020()
a7 <- parameterize_steadystate(chem.cas=chem1)
a8 <- parameterize_steadystate(chem.cas=chem2)
# All tests should be true:
a1[["Clint"]] != a7[["Clint"]]
a1[["Funbound.plasma"]] != a7[["Funbound.plasma"]]
a2[["Clint"]] == a8[["Clint"]]
a2[["Funbound.plasma"]] != a8[["Funbound.plasma"]]

# load Pradeep for this chemical, but allow it to overwrite all clints:
load_pradeep2020(overwrite=TRUE)
# Both clint and fup should now be changed for second chemical:
a9 <- parameterize_steadystate(chem.cas=chem1)
a10 <- parameterize_steadystate(chem.cas=chem2)
# All tests should be true:
a1[["Clint"]] != a9[["Clint"]]
a1[["Funbound.plasma"]] != a9[["Funbound.plasma"]]
a2[["Clint"]] != a10[["Clint"]]
a2[["Funbound.plasma"]] != a10[["Funbound.plasma"]]
```

---

load_sipes2017 *Load CLint and Fup QSPR predictions from Sipes et al 2017.*

Description

This function returns an updated version of chem.physical_and_invitro.data that includes quantitative structure-property relationship (QSPR) predictions from Simulations Plus' ADMET predictor as used in Sipes et al. 2017, included in sipes2017.

Usage

```
load_sipes2017(overwrite = FALSE, chem_include = NULL, target.env = .GlobalEnv)
```

Arguments

overwrite	Only matters if load.image=FALSE. If overwrite=TRUE then existing data in chem.physical_and_invitro.data will be replaced by any predictions in Sipes et al. (2017) that is for the same chemical and property. If overwrite=FALSE (DEFAULT) then new data for the same chemical and property are ignored. Funbound.plasma values of 0 (below limit of detection) are overwritten either way.
chem_include	A vector of CAS numbers indicating only the chemicals to be included in the loading process. If set to 'NULL' all applicable chemicals are loaded. (Default is 'NULL'.)
target.env	The environment where the new chem.physical_and_invitro.data is loaded. Defaults to global environment.

Details

Because Clint and Fup are the only measurements required for many HTTK models, changing the number of chemicals for which a value is available will change the number of chemicals which are listed with the get_cheminfo command. Use the command reset_httk to return to the initial (measured only) chem.physical_and_invitro.data (for all parameters).

Value

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

Author(s)

Robert Pearce and John Wambaugh

References

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

See Also

reset_httk

get_cheminfo

Examples

```
# Count how many chemicals for which HTTK is available without the QSPR:
num.chems <- length(get_cheminfo())
print(num.chems)
```

```
# For chemicals with Sipes et al. (2017) Clint and Fup QSPR predictions,
# add them to our chemical information wherever measured values are
# unavailable:
load_sipes2017()

# Here's a chemical we didn't have before (this one is a good test since the
# logP is nearly 10 and it probably wouldn't work in vitro):
calc_css(chem.cas="26040-51-7")

# Let's see how many chemicals we have now with the Sipes et al. (2017)
# predictions data loaded:
length(get_cheminfo())

# Now let us reset the chemical data to the initial version:
reset_httk()

# We should be back to our original number:
num.chems == length(get_cheminfo())

# Demonstrate loading data for specific chemicals:
#
# Find chemicals with a clint and no fup:
subset(chem.physical_and_invitro.data,!is.na(Human.Clint) & Human.Funbound.plasma==0)$CAS
chem1 <- "101-05-3"
chem2 <- "2971-36-0"
# Take a look at what parameterize_steadystate gives (working from a default fup of 0.005):
a1 <- parameterize_steadystate(chem.cas=chem1)
a2 <- parameterize_steadystate(chem.cas=chem2)

# load Sipes for this chemical:
load_sipes2017(chem_include=chem1)
# Check values, only fup for the first chemical should change:
a3 <- parameterize_steadystate(chem.cas=chem1)
a4 <- parameterize_steadystate(chem.cas=chem2)
# All tests should be true:
a1[["Clint"]] == a3[["Clint"]]
a1[["Funbound.plasma"]] != a3[["Funbound.plasma"]]
a2[["Clint"]] == a4[["Clint"]]
a2[["Funbound.plasma"]] == a4[["Funbound.plasma"]]

# load Sipes for this chemical, but allow it to overwrite the clint:
load_sipes2017(chem_include=chem1, overwrite=TRUE)
# Check values, both clint and fup for the first chemical should change:
a5 <- parameterize_steadystate(chem.cas=chem1)
a6 <- parameterize_steadystate(chem.cas=chem2)
# All tests should be true:
a1[["Clint"]] != a5[["Clint"]]
a1[["Funbound.plasma"]] != a5[["Funbound.plasma"]]
a2[["Clint"]] == a6[["Clint"]]
a2[["Funbound.plasma"]] == a6[["Funbound.plasma"]]

# Load Sipes for all chemicals, fup should change for second chemical:
load_sipes2017()
```

```
a7 <- parameterize_steadystate(chem.cas=chem1)
a8 <- parameterize_steadystate(chem.cas=chem2)
# All tests should be true:
a1[["Clint"]] != a7[["Clint"]]
a1[["Funbound.plasma"]] != a7[["Funbound.plasma"]]
a2[["Clint"]] == a8[["Clint"]]
a2[["Funbound.plasma"]] != a8[["Funbound.plasma"]]

# load Sipes for this chemical, but allow it to overwrite all clints:
load_sipes2017(overwrite=TRUE)
# Both clint and fup should now be changed for second chemical:
a9 <- parameterize_steadystate(chem.cas=chem1)
a10 <- parameterize_steadystate(chem.cas=chem2)
# All tests should be true:
a1[["Clint"]] != a9[["Clint"]]
a1[["Funbound.plasma"]] != a9[["Funbound.plasma"]]
a2[["Clint"]] != a10[["Clint"]]
a2[["Funbound.plasma"]] != a10[["Funbound.plasma"]]
```

`lump_tissues` *Lump tissue parameters into model compartments*

Description

This function takes the tissue:plasma partition coefficients from `predict_partitioning_schmitt` along with the tissue-specific volumes and flows and aggregates (or "lumps") them according to the needed scheme of toxicokinetic model tissue comparments.

`predict_partitioning_schmitt` makes tissue-specific predictions drawing from those tissues described in `tissue.data`. Since different physiologically-based toxicokinetic (PBTK) models use diffeent schemes for rganizing the tissues of the body into differing compartments (for example, "rapidly perfused tissues"), this function lumps tissues into compartments as specified by the argument 'tissuelist'. Aggregate flows, volumes, and partition coefficients are provided for the lumped tissue compartments. Flows and volumes are summed while partition coefficients is calculated using averaging weighted by species-specific tissue volumes.

The name of each entry in 'tissuelist' is its own compartment. The modelinfo_MODEL.R file corresponding to the model specified by argument 'model' includes both a 'tissuelist' describing to the model's compartmentallumping schme as well as a vector of 'tissuenames' specifying all tissues to be lumped into those compartments.

Alternatively the 'tissuelist' and 'tissuenames' can also be manually specified for alternate lumping schemes not necessarily related to a pre-made httk model. For example, tissuelist<-list(Rapid=c("Brain","Kidney")).

The tissues contained in 'tissuenames' that are unused in 'tissuelist' are aggregated into a single compartment termed "rest".

NOTE: The partition coefficients of lumped compartments vary according to individual and species differences since the volumes of the consitutent tissues may vary.

Usage

```
lump_tissues(
  Ktissue2pu.in,
  parameters = NULL,
  tissuelist = NULL,
  species = "Human",
  tissue.vols = NULL,
  tissue.flows = NULL,
  tissuenames = NULL,
  model = "pbtk",
  suppress.messages = FALSE
)
```

Arguments

Ktissue2pu.in	List of partition coefficients from predict_partitioning_schmitt. The tissues named in this list are lumped into the compartments specified by tissuelist unless they are not present the specified model's associated alltissues.
parameters	A list of physiological parameters including flows and volumes for tissues named in Ktissue2pu.in
tissuelist	Manually specifies compartment names and tissues, which override the standard compartment names and tissues that are usually specified in a model's associated modelinfo file. Remaining tissues in the model's associated alltissues listing are lumped in the rest of the body.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
tissue.vols	A list of volumes for tissues in tissuelist.
tissue.flows	A list of flows for tissues in tissuelist.
tissuenames	A list of tissue names in tissuenames.
model	Specify which model (and therefore which tissues) are being considered.
suppress.messages	Whether or not the output message is suppressed.

Value

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

Author(s)

John Wambaugh and Robert Pearce

References

Pearce RG, Setzer RW, Davis JL, Wambaugh JF (2017). "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." *Journal of pharmacokinetics and pharmacodynamics*, **44**, 549–565. doi:10.1007/s1092801795487.

See Also

predict_partitioning_schmitt

tissue.data

Examples

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

---

lung_mass_children *Predict lung mass for children*

Description

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

Usage

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

Arguments

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

Value

A vector of lung masses in kg.

Author(s)

Caroline Ring

References

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

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

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

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

Description

Reference tissue masses, flows, and residual variance distributions from Tables 1, 4, and 5 of McNally et al. 2014.

Usage

```
mcnally_dt
```

Format

A data.table with variables:

`tissue` Body tissue

`gender` Gender: Male or Female

`mass_ref` Reference mass in kg, from Reference Man

`mass_cv` Coefficient of variation for mass

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

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

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

`height_ref` Reference heights (by gender)

`CO_ref` Reference cardiac output by gender

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

Author(s)

Caroline Ring

Source

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

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

`mecdt` *Pre-processed NHANES data.*

Description

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

Usage

```
mecdt
```

Format

A data.table with 23620 rows and 12 variables.

seqn NHANES unique identifier for individual respondents.

sddsrvyr NHANES two-year cycle: one of "NHANES 2013-2014", "NHANES 2015-2016", "NHANES 2017-2018".

riagendr Gender: "Male" or "Female"

ridreth1 Race/ethnicity category: one of "Mexican American", "Non-Hispanic White", "Non-Hispanic Black", "Other", "Other Hispanic".

ridexagm Age in months at the time of examination (if not recorded by NHANES, it was imputed based on age at the time of screening)

ridexagy Age in years at the time of examination (if not recorded by NHANES, it was imputed based on age at the time of screening)

bmxwt Weight in kg

lbxscr Serum creatinine, mg/dL

lbxhct Hematocrit, percent by volume of blood composed of red blood cells

`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.

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

Author(s)

Caroline Ring

Source

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

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

---

metabolism_data_Linakis2020

Metabolism data involved in Linakis 2020 vignette analysis.

Description

Metabolism data involved in Linakis 2020 vignette analysis.

Usage

```
metabolism_data_Linakis2020
```

Format

A data.frame containing x rows and y columns.

Author(s)

Matt Linakis

Source

Matt Linakis

References

Linakis MW, Sayre RR, Pearce RG, Sfeir MA, Sipes NS, Pangburn HA, Gearhart JM, Wambaugh JF (2020). "Development and evaluation of a high-throughput inhalation model for organic chemicals." *Journal of exposure science & environmental epidemiology*, **30**(5), 866–877. doi:10.1038/s41370-0200238y.

monte_carlo *Monte Carlo for toxicokinetic model parameters*

Description

This function performs basic, uncorrelated Monte Carlo to simulate uncertainty and/or variability for parameters of toxicokinetic models. Parameters can be varied according to either a normal distribution that is truncated at zero (using argument `cv.params`) or from a normal distribution that is censored for values less than the limit of detection (`censored.params`). Coefficient of variation (cv) and limit of of detectin can be specified separately for each parameter.

Usage

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

Arguments

`parameters`	These parameters that are also listed in either cv.params or censored.params are sampled using Monte Carlo.
`cv.params`	The parameters listed in cv.params are sampled from a normal distribution that is truncated at zero. This argument should be a list of coefficients of variation (cv) for the normal distribution. Each entry in the list is named for a parameter in "parameters". New values are sampled with mean equal to the value in "parameters" and standard deviation equal to the mean times the cv.
`censored.params`	The parameters listed in censored.params are sampled from a normal distribution that is censored for values less than the limit of detection (specified separately for each parameter). This argument should be a list of sub-lists. Each sublist is named for a parameter in "params" and contains two elements: "cv" (coefficient of variation) and "LOD" (limit of detection), below which parameter values are censored. New values are sampled with mean equal to the value in "params" and standard deviation equal to the mean times the cv. Censored values are sampled on a uniform distribution between 0 and the limit of detection.
`samples`	This argument is the number of samples to be generated for calculating quantiles.
`suppress.messages`	Whether or not the output message is suppressed.

Value

A data.table with a row for each individual in the sample and a column for each parater in the model.

Author(s)

John Wambaugh

References

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

Examples

```
#Example based on Pearce et al. (2017):

# Set up means:
params <- parameterize_pbtk(chem.name="zoxamide")
# Nothing changes:
monte_carlo(params)

vary.params <- NULL
for (this.param in names(params)[!(names(params) %in%
  c("Funbound.plasma", "pKa_Donor", "pKa_Accept" )) &
  !is.na(as.numeric(params))]) vary.params[this.param] <- 0.2
# Most everything varies with CV of 0.2:
monte_carlo(
  parameters=params,
  cv.params = vary.params)

censored.params <- list(Funbound.plasma = list(cv = 0.2, lod = 0.01))
# Fup is censored below 0.01:
monte_carlo(
  parameters=params,
  cv.params = vary.params,
  censored.params = censored.params)
```

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

Description

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

Usage

```
Obach2008
```

Format

A data.frame containing 670 rows and 8 columns.

References

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

`onlyp` *NHANES Exposure Data*

Description

This data set is only used in Vignette 6.

Usage

```
onlyp
```

Format

A data.table containing 1060 rows and 5 columns.

Author(s)

Caroline Ring

References

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

`pancreas_mass_children` *Predict pancreas mass for children*

Description

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

Usage

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

Arguments

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

Value

A vector of pancreas masses in kg.

Author(s)

Caroline Ring

References

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

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

`parameterize_1comp` *Parameters for a one compartment (empirical) toxicokinetic model*

Description

This function initializes the parameters needed in the function solve_1comp. Volume of distribution is estimated by using a modified Schmitt (2008) method to predict tissue particition coefficients (Pearce et al., 2017) and then lumping the compartments weighted by tissue volume:

Usage

```
parameterize_1comp(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
  default.to.human = FALSE,
  adjusted.Funbound.plasma = TRUE,
  adjusted.Clint = TRUE,
  regression = TRUE,
  restrictive.clearance = TRUE,
  well.stirred.correction = TRUE,
  suppress.messages = FALSE,
  clint.pvalue.threshold = 0.05,
  minimum.Funbound.plasma = 1e-04,
  class.exclude = TRUE,
  physchem.exclude = TRUE,
  Caco2.options = list(),
  ...
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) – the chemical must be identified by either CAS, name, or DTXSIDs
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
default.to.human	Substitutes missing rat values with human values if true.
adjusted.Funbound.plasma	Uses Pearce et al. (2017) lipid binding adjustment for Funbound.plasma (which impacts volume of distribution) when set to TRUE (Default).
adjusted.Clint	Uses Kilford et al. (2008) hepatocyte incubation binding adjustment for Clint when set to TRUE (Default).
regression	Whether or not to use the regressions in calculating partition coefficients in volume of distribution calculation.
restrictive.clearance	In calculating elimination rate and hepatic bioavailability, protein binding is not taken into account (set to 1) in liver clearance if FALSE.
well.stirred.correction	Uses correction in calculation of hepatic clearance for well-stirred model if TRUE. This assumes clearance relative to amount unbound in whole blood instead of plasma, but converted to use with plasma concentration.
suppress.messages	Whether or not to suppress messages.
clint.pvalue.threshold	Hepatic clearance for chemicals where the in vitro clearance assay result has a p-value greater than the threshold are set to zero.
minimum.Funbound.plasma	Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).
class.exclude	Exclude chemical classes identified as outside of domain of applicability by relevant modelinfo_[MODEL] file (default TRUE).
physchem.exclude	Exclude chemicals on the basis of physico-chemical properties (currently only Henry's law constant) as specified by the relevant modelinfo_[MODEL] file (default TRUE).
Caco2.options	A list of options to use when working with Caco2 apical to basolateral data Caco2.Pab, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = Fabs. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = Fgut. overwrite.invivo = TRUE overwrites Fabs and Fgut

in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See get_fbio for further details.

... Additional arguments, not currently used.

Details

$V_{d,steady-state} = \Sigma_{i \in tissues} K_i V_i + V_{plasma}$

where K_i is the tissue:unbound plasma concentration partition coefficient for tissue i.

Because this model does not simulate exhalation, inhalation, and other processes relevant to volatile chemicals, this model is by default restricted to chemicals with a logHenry's Law Constant less than that of Acetone, a known volatile chemical. That is, chemicals with logHLC > -4.5 (Log10 atm-m3/mole) are excluded. Volatility is not purely determined by the Henry's Law Constant, therefore this chemical exclusion may be turned off with the argument "physchem.exclude = FALSE". Similarly, per- and polyfluoroalkyl substances (PFAS) are excluded by default because the transporters that often drive PFAS toxicokinetics are not included in this model. However, PFAS chemicals can be included with the argument "class.exclude = FALSE".

Value

`Vdist` Volume of distribution, units of L/kg BW.

`Fabsgut` Fraction of the oral dose absorbed and surviving gut metabolism, 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.

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

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

`kelim` Elimination rate, units of 1/h.

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

`kgutabs` Rate chemical is absorbed, 1/h.

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

`MW` Molecular Weight, g/mol.

`Rblood2plasma` The ratio of the concentration of the chemical in the blood to the concentration in the plasma. Not used in calculations but included for the conversion of plasma outputs.

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

`BW` Body Weight, kg.

Author(s)

John Wambaugh and Robert Pearce

References

Pearce RG, Setzer RW, Strope CL, Wambaugh JF, Sipes NS (2017). "Httk: R package for high-throughput toxicokinetics." *Journal of Statistical Software*, **79**(4), 1. doi:10.18637/jss.v079.i04.

Schmitt W (2008). "General approach for the calculation of tissue to plasma partition coefficients." *Toxicology in vitro*, **22**(2), 457–467. doi:10.1016/j.tiv.2007.09.010.

Pearce RG, Setzer RW, Davis JL, Wambaugh JF (2017). "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." *Journal of pharmacokinetics and pharmacodynamics*, **44**, 549–565. doi:10.1007/s1092801795487.

Kilford PJ, Gertz M, Houston JB, 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), 1194–1197. doi:10.1124/dmd.108.020834.

See Also

solve_1comp

calc_analytic_css_1comp

calc_vdist

parameterize_steadystate

apply_clint_adjustment

tissue.data

physiology.data

Examples

```
 parameters1 <- parameterize_1comp(chem.name='Bisphenol-A',species='Rat')
 parameters2 <- parameterize_1comp(chem.cas='80-05-7',
                                   restrictive.clearance=FALSE,
                                   species='rabbit',
                                   default.to.human=TRUE)
# The following will not work because Diquat dibromide monohydrate's
# Henry's Law Constant (-3.912) is higher than that of Acetone (~-4.5):
try(parameters3 <- parameterize_1comp(chem.cas = "6385-62-2"))
# However, we can turn off checking for phys-chem properties, since we know
# that  Diquat dibromide monohydrate is not too volatile:
parameters3 <- parameterize_1comp(chem.cas = "6385-62-2",
                                   physchem.exclude = FALSE)
out <- solve_1comp(parameters=parameters1, days=1)
```

parameterize_1tri_pbtk *Parameterize_1tri_PBTK*

Description

This function initializes the parameters needed in the functions solve_1tri_pbtk by calling parameterize_pbtk and adding additional parameters.

Usage

```
parameterize_1tri_pbtk(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
  return.kapraun2019 = TRUE,
  suppress.messages = FALSE,
  ...
)
```

Arguments

chem.cas	Either the chemical name or the CAS number must be specified.
chem.name	Either the chemical name or the CAS number must be specified.
dtxsid	EPA's DSSTox Structure ID (http://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human"). Currently only a human model is supported.
return.kapraun2019	If TRUE (default), empirical parameters from Kapraun et al. (2019) necessary for defining the model are provided. This is a subset of the httk::kapraun2019 list object with additional parameters.
suppress.messages	Whether or not the output message is suppressed.
...	Arguments passed to parameterize_pbtk.

Details

Because this model does not simulate exhalation, inhalation, and other processes relevant to volatile chemicals, this model is by default restricted to chemicals with a logHenry's Law Constant less than that of Acetone, a known volatile chemical. That is, chemicals with logHLC > -4.5 (Log10 atm-m3/mole) are excluded. Volatility is not purely determined by the Henry's Law Constant, therefore this chemical exclusion may be turned off with the argument "physchem.exclude = FALSE". Similarly, per- and polyfluoroalkyl substances (PFAS) are excluded by default because the transporters that often drive PFAS toxicokinetics are not included in this model. However, PFAS chemicals can be included with the argument "class.exclude = FALSE".

Value

`pre_pregnant_BW`
: Body Weight before pregnancy, kg.

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

`Fabsgut`
: 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.

`Kadipose2pu`
: Ratio of concentration of chemical in adipose tissue to unbound concentration in plasma.

`Kconceptus2pu_initial`
: Ratio of concentration of chemical in "conceptus" compartment to unbound concentration in plasma at time 0.

`Kconceptus2pu_final`
: Ratio of concentration of chemical in "conceptus" compartment to unbound concentration in plasma at 13 weeks.

`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.

`Kthyroid2pu`
: Ratio of concentration of chemical in thyroid tissue to unbound concentration in plasma.

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

`MW`
: Molecular Weight, g/mol.

`pH_Plasma_mat`
: pH of the maternal plasma.

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

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

Vkidneyc	Volume of the kidneys per kg body weight, L/kg BW.
Vliverc	Volume of the liver per kg body weight, L/kg BW.
Vlungc	Volume of the lungs per kg body weight, L/kg BW.
Vthyroidc	Volume of the thyroid per kg body weight, L/kg BW.

Author(s)

Kimberly Truong, Mark Sfeir, Dustin Kapraun, John Wambaugh

References

Kilford PJ, Gertz M, Houston JB, 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), 1194–1197. doi:10.1124/dmd.108.020834.

Kapraun DF, Wambaugh JF, Setzer RW, Judson RS (2019). "Empirical models for anatomical and physiological changes in a human mother and fetus during pregnancy and gestation." *PLOS ONE*, **14**(5), 1-56. doi:10.1371/journal.pone.0215906.

Kapraun DF, Sfeir M, Pearce RG, Davidson-Fritz SE, Lumen A, Dallmann A, Judson RS, Wambaugh JF (2022). "Evaluation of a rapid, generic human gestational dose model." *Reproductive Toxicology*, **113**, 172–188. doi:10.1016/j.reprotox.2022.09.004.

Truong KT, Wambaugh JF, Kapraun DF, Davidson-Fritz SE, Eytcheson S, Judson RS, Paul Friedman K (2025). "Interpretation of thyroid-relevant bioactivity data for comparison to in vivo exposures: A prioritization approach for putative chemical inhibitors of in vitro deiodinase activity." *Toxicology*. doi:10.1016/j.tox.2025.154157.

See Also

solve_1tri_pbtk

parameterize_pbtk

predict_partitioning_schmitt

apply_clint_adjustment

tissue.data

physiology.data

kapraun2019

Examples

```
parameters <- parameterize_1tri_pbtk(dtxsid = "DTXSID7020182")

parameters <- parameterize_1tri_pbtk(chem.name='Bisphenol-A')
```

parameterize_3comp *Parameters for a three-compartment toxicokinetic model (dynamic)*

Description

This function generates the chemical- and species-specific parameters needed for model '3compartment', for example solve_3comp. A call is masde to parameterize_pbtk to use Schmitt (2008)'s method as modified by Pearce et al. (2017) to predict partition coefficients based on descriptions in tissue.data. Organ volumes and flows are retrieved from table physiology.data.

Usage

```
parameterize_3comp(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
  default.to.human = FALSE,
  class.exclude = TRUE,
  physchem.exclude = TRUE,
  force.human.clint.fup = FALSE,
  clint.pvalue.threshold = 0.05,
  adjusted.Funbound.plasma = TRUE,
  adjusted.Clint = TRUE,
  regression = TRUE,
  suppress.messages = FALSE,
  restrictive.clearance = TRUE,
  minimum.Funbound.plasma = 1e-04,
  Caco2.options = NULL,
  ...
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) – the chemical must be identified by either CAS, name, or DTXSIDs
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
default.to.human	Substitutes missing animal values with human values if true.
class.exclude	Exclude chemical classes identified as outside of domain of applicability by relevant modelinfo_[MODEL] file (default TRUE).

`physchem.exclude`
: Exclude chemicals on the basis of physico-chemical properties (currently only Henry's law constant) as specified by the relevant modelinfo_[MODEL] file (default TRUE).

`force.human.clint.fup`
: Forces use of human values for hepatic intrinsic clearance and fraction of unbound plasma if true.

`clint.pvalue.threshold`
: Hepatic clearances with clearance assays having p-values greater than the threshold are set to zero.

`adjusted.Funbound.plasma`
: Uses Pearce et al. (2017) lipid binding adjustment for Funbound.plasma (which impacts partition coefficients) when set to TRUE (Default).

`adjusted.Clint`
: Uses Kilford et al. (2008) hepatocyte incubation binding adjustment for Clint when set to TRUE (Default).

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

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

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

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

`Caco2.options`
: A list of options to use when working with Caco2 apical to basolateral data `Caco2.Pab`, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = `Fabs`. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = `Fgut`. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See `get_fbio` for further details.

`...`
: Additional arguments, not currently used.

Details

Because this model does not simulate exhalation, inhalation, and other processes relevant to volatile chemicals, this model is by default restricted to chemicals with a logHenry's Law Constant less than that of Acetone, a known volatile chemical. That is, chemicals with logHLC > -4.5 (Log10 atm-m3/mole) are excluded. Volatility is not purely determined by the Henry's Law Constant, therefore this chemical exclusion may be turned off with the argument "physchem.exclude = FALSE". Similarly, per- and polyfluoroalkyl substances (PFAS) are excluded by default because the transporters that often drive PFAS toxicokinetics are not included in this model. However, PFAS chemicals can be included with the argument "class.exclude = FALSE".

Value

BW	Body Weight, kg.
Clmetabolismc	Hepatic Clearance, L/h/kg BW.
Fabsgut	Fraction of the oral dose absorbed, i.e. the fraction of the dose that enters the gutlumen.
Funbound.plasma	Fraction of plasma that is not bound.
Fhep.assay.correction	The fraction of chemical unbound in hepatocyte assay using the method of Kilford et al. (2008)
hematocrit	Percent volume of red blood cells in the blood.
Kgut2pu	Ratio of concentration of chemical in gut tissue to unbound concentration in plasma.
Kliver2pu	Ratio of concentration of chemical in liver tissue to unbound concentration in plasma.
Krbc2pu	Ratio of concentration of chemical in red blood cells to unbound concentration in plasma.
Krest2pu	Ratio of concentration of chemical in rest of body tissue to unbound concentration in plasma.
million.cells.per.gliver	Millions cells per gram of liver tissue.
MW	Molecular Weight, g/mol.
Qcardiacc	Cardiac Output, L/h/kg BW^3/4.
Qgfrc	Glomerular Filtration Rate, L/h/kg BW^3/4, volume of fluid filtered from kidney and excreted.
Qgutf	Fraction of cardiac output flowing to the gut.
Qliverf	Fraction of cardiac output flowing to the liver.
Rblood2plasma	The ratio of the concentration of the chemical in the blood to the concentration in the plasma.
Vgutc	Volume of the gut per kg body weight, L/kg BW.
Vliverc	Volume of the liver per kg body weight, L/kg BW.
Vrestc	Volume of the rest of the body per kg body weight, L/kg BW.

Author(s)

Robert Pearce and John Wambaugh

References

Pearce RG, Setzer RW, Strope CL, Wambaugh JF, Sipes NS (2017). "Httk: R package for high-throughput toxicokinetics." *Journal of Statistical Software*, **79**(4), 1. doi:10.18637/jss.v079.i04.

Schmitt W (2008). "General approach for the calculation of tissue to plasma partition coefficients." *Toxicology in vitro*, **22**(2), 457–467. doi:10.1016/j.tiv.2007.09.010.

Pearce RG, Setzer RW, Davis JL, Wambaugh JF (2017). "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." *Journal of pharmacokinetics and pharmacodynamics*, **44**, 549–565. doi:10.1007/s1092801795487.

Kilford PJ, Gertz M, Houston JB, 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), 1194–1197. doi:10.1124/dmd.108.020834.

Wambaugh JF, Schacht CM, Ring CL (2025). "A Simple Physiologically Based Toxicokinetic Model for Multi-Route In Vitro–In Vivo Extrapolation." *Environmental Science & Technology Letters*, **12**(3), 261–268. doi:10.1021/acs.estlett.4c00967.

See Also

solve_3comp

calc_analytic_css_3comp

parameterize_pbtk

apply_clint_adjustment

tissue.data

physiology.data

Examples

```
parameters1 <- parameterize_3comp(chem.name='Bisphenol-A',species='Rat')

parameters2 <- parameterize_3comp(chem.cas='80-05-7',
                                  species='rabbit',default.to.human=TRUE)
# The following will not work because Diquat dibromide monohydrate's
# Henry's Law Constant (-3.912) is higher than that of Acetone (~-4.5):
try(parameters3 <- parameterize_3comp(chem.cas = "6385-62-2"))
# However, we can turn off checking for phys-chem properties, since we know
# that  Diquat dibromide monohydrate is not too volatile:
parameters3 <- parameterize_3comp(chem.cas = "6385-62-2",
                                  physchem.exclude = FALSE)
out <- solve_3comp(parameters=parameters1, plots=TRUE)
```

---

parameterize_3comp2 *Parameters for a three-compartment toxicokinetic model (dynamic)*

Description

This function generates the chemical- and species-specific parameters needed for model '3compartment', for example solve_3comp. A call is masde to parameterize_pbtk to use Schmitt (2008)'s method as modified by Pearce et al. (2017) to predict partition coefficients based on descriptions in tissue.data. Organ volumes and flows are retrieved from table physiology.data.

Usage

```
parameterize_3comp2(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
  default.to.human = FALSE,
  physchem.exclude = TRUE,
  class.exclude = TRUE,
  force.human.clint.fup = FALSE,
  clint.pvalue.threshold = 0.05,
  adjusted.Funbound.plasma = TRUE,
  adjusted.Clint = TRUE,
  regression = TRUE,
  suppress.messages = FALSE,
  restrictive.clearance = TRUE,
  minimum.Funbound.plasma = 1e-04,
  Caco2.options = NULL,
  ...
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) – the chemical must be identified by either CAS, name, or DTXSIDs
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
default.to.human	Substitutes missing animal values with human values if true.
physchem.exclude	Exclude chemicals on the basis of physico-chemical properties (currently only Henry's law constant) as specified by the relevant modelinfo_[MODEL] file (default TRUE).
class.exclude	Exclude chemical classes identified as outside of domain of applicability by relevant modelinfo_[MODEL] file (default TRUE).
force.human.clint.fup	Forces use of human values for hepatic intrinsic clearance and fraction of unbound plasma if true.
clint.pvalue.threshold	Hepatic clearances with clearance assays having p-values greater than the threshold are set to zero.
adjusted.Funbound.plasma	Uses Pearce et al. (2017) lipid binding adjustment for Funbound.plasma (which impacts partition coefficients) when set to TRUE (Default).

`adjusted.Clint` Uses Kilford et al. (2008) hepatocyte incubation binding adjustment for Clint when set to TRUE (Default).

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

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

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

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

`Caco2.options` A list of options to use when working with Caco2 apical to basolateral data `Caco2.Pab`, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = `Fabs`. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = `Fgut`. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See `get_fbio` for further details.

`...` Additional arguments are passed to `parameterize_pbtk`

Details

Per- and polyfluoroalkyl substances (PFAS) are excluded by default because the transporters that often drive PFAS toxicokinetics are not included in this model. However, PFAS chemicals can be included with the argument "class.exclude = FALSE".

Value

`BW` Body Weight, kg.

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

`Fabsgut` 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)

John Wambaugh

References

Pearce RG, Setzer RW, Strope CL, Wambaugh JF, Sipes NS (2017). "Httk: R package for high-throughput toxicokinetics." *Journal of Statistical Software*, **79**(4), 1. doi:10.18637/jss.v079.i04.

Schmitt W (2008). "General approach for the calculation of tissue to plasma partition coefficients." *Toxicology in vitro*, **22**(2), 457–467. doi:10.1016/j.tiv.2007.09.010.

Pearce RG, Setzer RW, Davis JL, Wambaugh JF (2017). "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." *Journal of pharmacokinetics and pharmacodynamics*, **44**, 549–565. doi:10.1007/s1092801795487.

Kilford PJ, Gertz M, Houston JB, 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), 1194–1197. doi:10.1124/dmd.108.020834.

Wambaugh JF, Schacht CM, Ring CL (2025). "A Simple Physiologically Based Toxicokinetic Model for Multi-Route In Vitro–In Vivo Extrapolation." *Environmental Science & Technology Letters*, **12**(3), 261–268. doi:10.1021/acs.estlett.4c00967.

See Also

solve_3comp

calc_analytic_css_3comp

parameterize_pbtk

apply_clint_adjustment

tissue.data

physiology.data

Examples

```
parameters <- parameterize_3comp2(chem.name='Bisphenol-A',species='Rat')

parameters <- parameterize_3comp2(chem.cas='80-05-7',
                                  species='rabbit',default.to.human=TRUE)
out <- solve_3comp2(parameters=parameters,plots=TRUE)
```

---

parameterize_fetal_pbtk

Parameterize_fetal_PBTK

Description

This function initializes the parameters needed in the functions solve_fetal_pbtk by calling parameterize_pbtk and adding additional parameters.

Usage

```
parameterize_fetal_pbtk(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
  fetal_fup_adjustment = TRUE,
  return.kapraun2019 = TRUE,
  suppress.messages = FALSE,
  ...
)
```

Arguments

chem.cas	Either the chemical name or the CAS number must be specified.
chem.name	Either the chemical name or the CAS number must be specified.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
species	Included for compatibility with other functions, but the model will not run for non-human species (default "Human").
fetal_fup_adjustment	Logical indicator of whether to use an adjusted estimate for fetal fup based on the fetal:maternal plasma protein binding ratios presented in McNamara and Alcorn's 2002 study "Protein Binding Predictions in Infants." Defaults to TRUE.

return.kapraun2019
: If TRUE (default) the empirical parameters for the Kapraun et al. (2019) maternal-fetal growth parameters are provided.

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

...
: Arguments passed to parameterize_pbtk.

Details

Because this model does not simulate exhalation, inhalation, and other processes relevant to volatile chemicals, this model is by default restricted to chemicals with a logHenry's Law Constant less than that of Acetone, a known volatile chemical. That is, chemicals with logHLC > -4.5 (Log10 atm-m3/mole) are excluded. Volatility is not purely determined by the Henry's Law Constant, therefore this chemical exclusion may be turned off with the argument "physchem.exclude = FALSE". Similarly, per- and polyfluoroalkyl substances (PFAS) are excluded by default because the transporters that often drive PFAS toxicokinetics are not included in this model. However, PFAS chemicals can be included with the argument "class.exclude = FALSE".

Value

pre_pregnant_BW
: Body Weight before pregnancy, kg.

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

Fabsgut
: 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.

Kadipose2pu
: Ratio of concentration of chemical in adipose tissue to unbound concentration in plasma.

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.

Kthyroid2pu	Ratio of concentration of chemical in thyroid tissue to unbound concentration in plasma.
Kfgut2pu	Ratio of concentration of chemical in fetal gut tissue to unbound concentration in plasma.
Kfkidney2pu	Ratio of concentration of chemical in fetal kidney tissue to unbound concentration in plasma.
Kfliver2pu	Ratio of concentration of chemical in fetal liver tissue to unbound concentration in plasma.
Kflung2pu	Ratio of concentration of chemical in fetal lung tissue to unbound concentration in plasma.
Kfrest2pu	Ratio of concentration of chemical in fetal rest of body tissue to unbound concentration in plasma.
Kfbrain2pu	Ratio of concentration of chemical in fetal brain tissue to unbound concentration in plasma.
Kfthyroid2pu	Ratio of concentration of chemical in fetal thyroid tissue to unbound concentration in plasma.
Kplacenta2pu	Ratio of concentration of chemical in placental tissue to unbound concentration in maternal plasma.
Kfplacenta2pu	Ratio of concentration of chemical in placental tissue to unbound concentration in fetal plasma.
million.cells.per.gliver	Millions cells per gram of liver tissue.
MW	Molecular Weight, g/mol.
pH_Plasma_mat	pH of the maternal plasma.
Qgfr	Glomerular Filtration Rate, L/h/kg BW^3/4, volume of fluid filtered from kidney and excreted.
Rblood2plasma	The ratio of the concentration of the chemical in the blood to the concentration in the plasma from available_rblood2plasma.
Vgutc	Volume of the gut per kg body weight, L/kg BW.
Vkidneyc	Volume of the kidneys per kg body weight, L/kg BW.
Vliverc	Volume of the liver per kg body weight, L/kg BW.
Vlungc	Volume of the lungs per kg body weight, L/kg BW.
Vthyroidc	Volume of the thyroid per kg body weight, L/kg BW.

Author(s)

Robert Pearce, Mark Sfeir, John Wambaugh, and Dustin Kapraun

Mark Sfeir, Dustin Kapraun, John Wambaugh

References

Kilford PJ, Gertz M, Houston JB, 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), 1194–1197. doi:10.1124/dmd.108.020834.

McNamara PJ, Alcorn J (2002). "Protein binding predictions in infants." *Aaps Pharmsci*, **4**, 19–26. doi:10.1208/ps040104.

Kapraun DF, Wambaugh JF, Setzer RW, Judson RS (2019). "Empirical models for anatomical and physiological changes in a human mother and fetus during pregnancy and gestation." *PLOS ONE*, **14**(5), 1-56. doi:10.1371/journal.pone.0215906.

Kapraun DF, Sfeir M, Pearce RG, Davidson-Fritz SE, Lumen A, Dallmann A, Judson RS, Wambaugh JF (2022). "Evaluation of a rapid, generic human gestational dose model." *Reproductive Toxicology*, **113**, 172–188. doi:10.1016/j.reprotox.2022.09.004.

See Also

solve_fetal_pbtk

parameterize_pbtk

predict_partitioning_schmitt

apply_clint_adjustment

tissue.data

physiology.data

kapraun2019

Examples

```
 parameters1 <- parameterize_fetal_pbtk(chem.cas='80-05-7')

 parameters2 <- parameterize_fetal_pbtk(chem.name='Bisphenol-A',species='Rat')

# The following will not work because Diquat dibromide monohydrate's
# Henry's Law Constant (-3.912) is higher than that of Acetone (~-4.5):
try(parameters3 <- parameterize_fetal_pbtk(chem.cas = "6385-62-2"))
# However, we can turn off checking for phys-chem properties, since we know
# that  Diquat dibromide monohydrate is not too volatile:
parameters3 <- parameterize_fetal_pbtk(chem.cas = "6385-62-2",
                                       physchem.exclude = FALSE)
```

parameterize_gas_pbtk *Parameters for a generic gas inhalation physiologically-based toxicokinetic model*

Description

This function initializes the parameters needed for the model 'gas_pbtk', for example solve_gas_pbtk. Chemical- and species-specific model parameters are generated. These include tissue:plasma partition coefficients via Schmitt (2008)'s method as modified by Pearce et al. (2017). Organ volumes and flows are retrieved from table physiology.data). This model was first described by Linakis et al. (2020).

Usage

```
parameterize_gas_pbtk(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
  default.to.human = FALSE,
  tissuelist = list(liver = c("liver"), kidney = c("kidney"), lung = c("lung"), gut =
    c("gut")),
  force.human.clint.fup = FALSE,
  clint.pvalue.threshold = 0.05,
  adjusted.Funbound.plasma = TRUE,
  adjusted.Clint = TRUE,
  regression = TRUE,
  vmax = 0,
  km = 1,
  exercise = FALSE,
  fR = 12,
  VT = 0.75,
  VD = 0.15,
  suppress.messages = FALSE,
  minimum.Funbound.plasma = 1e-04,
  Caco2.options = list(),
  class.exclude = TRUE,
  physchem.exclude = TRUE,
  restrictive.clearance = FALSE,
  ...
)
```

Arguments

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

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

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

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

`tissuelist` Specifies compartment names and tissues groupings. Remaining tissues in tissue.data are lumped in the rest of the body. However, solve_pbtk only works with the default parameters.

`force.human.clint.fup` Forces use of human values for hepatic intrinsic clearance and fraction of unbound plasma if true.

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

`adjusted.Funbound.plasma` Uses Pearce et al. (2017) lipid binding adjustment for Funbound.plasma (which impacts partition coefficients) when set to TRUE (Default).

`adjusted.Clint` Uses Kilford et al. (2008) hepatocyte incubation binding adjustment for Clint when set to TRUE (Default).

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

`vmax` Michaelis-Menten vmax value in reactions/min

`km` Michaelis-Menten concentration of half-maximal reaction velocity in desired output concentration units.

`exercise` Logical indicator of whether to simulate an exercise-induced heightened respiration rate

`fR` Respiratory frequency (breaths/minute), used especially to adjust breathing rate in the case of exercise. This parameter, along with VT and VD (below) gives another option for calculating Qalv (Alveolar ventilation) in case pulmonary ventilation rate is not known

`VT` Tidal volume (L), to be modulated especially as part of simulating the state of exercise

`VD` Anatomical dead space (L), to be modulated especially as part of simulating the state of exercise

`suppress.messages` Whether or not the output messages are suppressed.

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

`Caco2.options` A list of options to use when working with Caco2 apical to basolateral data `Caco2.Pab`, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise

fabs.oral = Fabs. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = Fgut. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See get_fbio for further details.

class.exclude
: Exclude chemical classes identified as outside of domain of applicability by relevant modelinfo_[MODEL] file (default TRUE).

physchem.exclude
: Exclude chemicals on the basis of physico-chemical properties (currently only Henry's law constant) as specified by the relevant modelinfo_[MODEL] file (default TRUE).

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

...
: Other parameters

Details

Per- and polyfluoroalkyl substances (PFAS) are excluded by default because the transporters that often drive PFAS toxicokinetics are not included in this model. However, PFAS chemicals can be included with the argument "class.exclude = FALSE".

Value

BW
: Body Weight, kg.

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

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

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

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

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

Funbound.plasma
: Fraction of chemical unbound to plasma.

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

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

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

Kblood2air
: Ratio of concentration of chemical in blood to air

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

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

Kkidney2pu	Ratio of concentration of chemical in kidney tissue to unbound concentration in plasma.
Kliver2pu	Ratio of concentration of chemical in liver tissue to unbound concentration in plasma.
Klung2pu	Ratio of concentration of chemical in lung tissue to unbound concentration in plasma.
km	Michaelis-Menten concentration of half-maximal activity
Kmuc2air	Mucus to air partition coefficient
Krbc2pu	Ratio of concentration of chemical in red blood cells to unbound concentration in plasma.
Krest2pu	Ratio of concentration of chemical in rest of body tissue to unbound concentration in plasma.
kUrtc	Unscaled upper respiratory tract uptake parameter (L/h/kg^0.75)
liver.density	Density of liver in g/mL
MA	phospholipid:water distribution coefficient, membrane affinity
million.cells.per.gliver	Millions cells per gram of liver tissue.
MW	Molecular Weight, g/mol.
pKa_Accept	compound H association equilibrium constant(s)
pKa_Donor	compound H dissociation equilibirum constant(s)
Pow	octanol:water partition coefficient (not log transformed)
Qalvc	Unscaled alveolar ventilation rate (L/h/kg^0.75)
Qcardiacc	Cardiac Output, L/h/kg BW^3/4.
Qgfrc	Glomerular Filtration Rate, L/h/kg BW^0.75, volume of fluid filtered from kidney and excreted.
Qgutf	Fraction of cardiac output flowing to the gut.
Qkidneyf	Fraction of cardiac output flowing to the kidneys.
Qliverf	Fraction of cardiac output flowing to the liver.
Qlungf	Fraction of cardiac output flowing to lung tissue.
Qrestf	Fraction of blood flow to rest of body
Rblood2plasma	The ratio of the concentration of the chemical in the blood to the concentration in the plasma from available_rblood2plasma.
Vartc	Volume of the arteries per kg body weight, L/kg BW.
Vgutc	Volume of the gut per kg body weight, L/kg BW.
Vkidneyc	Volume of the kidneys per kg body weight, L/kg BW.
Vliverc	Volume of the liver per kg body weight, L/kg BW.
Vlungc	Volume of the lungs per kg body weight, L/kg BW.
vmax	Michaelis-Menten maximum reaction velocity (1/min)
Vmucc	Unscaled mucosal volume (L/kg BW^0.75
Vrestc	Volume of the rest of the body per kg body weight, L/kg BW.
Vvenc	Volume of the veins per kg body weight, L/kg BW.

Author(s)

Matt Linakis, Robert Pearce, John Wambaugh

References

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Pearce RG, Setzer RW, Davis JL, Wambaugh JF (2017). "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." *Journal of pharmacokinetics and pharmacodynamics*, **44**, 549–565. doi:10.1007/s1092801795487.

Kilford PJ, Gertz M, Houston JB, 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), 1194–1197. doi:10.1124/dmd.108.020834.

See Also

solve_gas_pbtk

apply_clint_adjustment

predict_partitioning_schmitt

available_rblood2plasma

calc_kair

tissue.data

physiology.data

get_clint

get_fup

get_physchem_param

Examples

```
parameters <- parameterize_gas_pbtk(chem.cas='129-00-0')


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

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

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

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

```
                    tissuelist=compartments)
```

---

parameterize_pbtk *Parameters for a generic physiologically-based toxicokinetic model*

Description

Generate a chemical- and species-specific set of PBPK model parameters. Parameters include tissue:plasma partition coefficients, organ volumes, and flows for the tissue lumping scheme specified by argument tissuelist. Tissure:(fraction unbound in) plasma partitition coefficients are predicted via Schmitt (2008)'s method as modified by Pearce et al. (2017) using predict_partitioning_schmitt. Organ volumes and flows are retrieved from table physiology.data. Tissues must be described in table tissue.data.

Usage

```
parameterize_pbtk(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
  default.to.human = FALSE,
 tissuelist = list(liver = c("liver"), kidney = c("kidney"), lung = c("lung"), gut =
    c("gut")),
  force.human.clint.fup = FALSE,
  clint.pvalue.threshold = 0.05,
  adjusted.Funbound.plasma = TRUE,
  adjusted.Clint = TRUE,
  regression = TRUE,
  suppress.messages = FALSE,
  restrictive.clearance = TRUE,
  minimum.Funbound.plasma = 1e-04,
  class.exclude = TRUE,
  physchem.exclude = TRUE,
  million.cells.per.gliver = 110,
  liver.density = 1.05,
  kgutabs = NA,
  Caco2.options = NULL,
  ...
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – the chemical must be identified by either CAS, name, or DTXISD

`chem.name` Chemical name (spaces and capitalization ignored) – the chemical must be identified by either CAS, name, or DTXISD

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

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

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

`tissuelist` Specifies compartment names and tissues groupings. Remaining tissues in tissue.data are lumped in the rest of the body. However, `solve_pbtk` only works with the default parameters.

`force.human.clint.fup` Forces use of human values for hepatic intrinsic clearance and fraction of unbound plasma if true.

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

`adjusted.Funbound.plasma` Uses Pearce et al. (2017) lipid binding adjustment for Funbound.plasma (which impacts partition coefficients) when set to TRUE (Default).

`adjusted.Clint` Uses Kilford et al. (2008) hepatocyte incubation binding adjustment for Clint when set to TRUE (Default).

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

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

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

`minimum.Funbound.plasma` f_{up} is not allowed to drop below this value (default is 0.0001).

`class.exclude` Exclude chemical classes identified as outside of domain of applicability by relevant modelinfo_[MODEL] file (default TRUE).

`physchem.exclude` Exclude chemicals on the basis of physico-chemical properties (currently only Henry's law constant) as specified by the relevant modelinfo_[MODEL] file (default TRUE).

`million.cells.per.gliver` Hepatocellularity (defaults to 110 10^6 cells/g-liver, from Carlile et al. (1997))

`liver.density` Liver density (defaults to 1.05 g/mL from International Commission on Radiological Protection (1975))

`kgutabs` Oral absorption rate from gut (determined from Peff)

`Caco2.options` A list of options to use when working with Caco2 apical to basolateral data `Caco2.Pab`, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE).

Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = Fabs. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = Fgut. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See get_fbio for further details.

... Additional arguments, not currently used.

Details

By default, this function initializes the parameters needed in the functions solve_pbtk, calc_css, and others using the httk default generic PBTK model (for oral and intravenous dosing only).

The default PBTK model includes an explicit first pass of the chemical through the liver before it becomes available to systemic blood. We model systemic oral bioavailability as $F_{bio} = F_{abs} * F_{gut} * F_{hep}$. Only if F_{bio} has been measured in vivo and is found in table chem.physical_and_invitro.data then we set $F_{abs} * F_{gut}$ to the measured value divided by F_{hep} where F_{hep} is estimated from in vitro TK data using calc_hep_bioavailability. If Caco2 membrane permeability data or predictions are available F_{abs} is estimated using calc_fabs.oral. Intrinsic hepatic metabolism is used to very roughly estimate F_{gut} using calc_fgut.oral.

Because this model does not simulate exhalation, inhalation, and other processes relevant to volatile chemicals, this model is by default restricted to chemicals with a logHenry's Law Constant less than that of Acetone, a known volatile chemical. That is, chemicals with logHLC > -4.5 (Log10 atm-m3/mole) are excluded. Volatility is not purely determined by the Henry's Law Constant, therefore this chemical exclusion may be turned off with the argument "physchem.exclude = FALSE". Similarly, per- and polyfluoroalkyl substances (PFAS) are excluded by default because the transporters that often drive PFAS toxicokinetics are not included in this model. However, PFAS chemicals can be included with the argument "class.exclude = FALSE".

Value

BW Body Weight, kg.

Clmetabolismc Hepatic Clearance, L/h/kg BW.

Fabsgut Fraction of the oral dose absorbed, i.e. the fraction of the dose that enters the gutlumen.

Funbound.plasma
Fraction of plasma that is not bound.

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

hematocrit Percent volume of red blood cells in the blood.

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

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

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

Kliver2pu	Ratio of concentration of chemical in liver tissue to unbound concentration in plasma.
Klung2pu	Ratio of concentration of chemical in lung tissue to unbound concentration in plasma.
Krbc2pu	Ratio of concentration of chemical in red blood cells to unbound concentration in plasma.
Krest2pu	Ratio of concentration of chemical in rest of body tissue to unbound concentration in plasma.
million.cells.per.gliver	Millions cells per gram of liver tissue.
MW	Molecular Weight, g/mol.
Qcardiacc	Cardiac Output, L/h/kg BW^3/4.
Qgfrc	Glomerular Filtration Rate, L/h/kg BW^3/4, volume of fluid filtered from kidney and excreted.
Qgutf	Fraction of cardiac output flowing to the gut.
Qkidneyf	Fraction of cardiac output flowing to the kidneys.
Qliverf	Fraction of cardiac output flowing to the liver.
Rblood2plasma	The ratio of the concentration of the chemical in the blood to the concentration in the plasma from available_rblood2plasma.
Vartc	Volume of the arteries per kg body weight, L/kg BW.
Vgutc	Volume of the gut per kg body weight, L/kg BW.
Vkidneyc	Volume of the kidneys per kg body weight, L/kg BW.
Vliverc	Volume of the liver per kg body weight, L/kg BW.
Vlungc	Volume of the lungs per kg body weight, L/kg BW.
Vrestc	Volume of the rest of the body per kg body weight, L/kg BW.
Vvenc	Volume of the veins per kg body weight, L/kg BW.

Author(s)

John Wambaugh and Robert Pearce

References

Pearce RG, Setzer RW, Strope CL, Wambaugh JF, Sipes NS (2017). "Httk: R package for high-throughput toxicokinetics." *Journal of Statistical Software*, **79**(4), 1. doi:10.18637/jss.v079.i04.

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Pearce RG, Setzer RW, Davis JL, Wambaugh JF (2017). "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." *Journal of pharmacokinetics and pharmacodynamics*, **44**, 549–565. doi:10.1007/s1092801795487.

Kilford PJ, Gertz M, Houston JB, 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), 1194–1197. doi:10.1124/dmd.108.020834.

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See Also

solve_pbtk

calc_analytic_css_pbtk

predict_partitioning_schmitt

apply_clint_adjustment

tissue.data

physiology.data

Examples

```
parameters1 <- parameterize_pbtk(chem.cas='80-05-7')


parameters2 <- parameterize_pbtk(chem.name='Bisphenol-A',species='Rat')

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

# The following will not work because Diquat dibromide monohydrate's
# Henry's Law Constant (-3.912) is higher than that of Acetone (~-4.5):
try(parameters3 <- parameterize_pbtk(chem.cas = "6385-62-2"))
# However, we can turn off checking for phys-chem properties, since we know
# that  Diquat dibromide monohydrate is not too volatile:
parameters3 <- parameterize_pbtk(chem.cas = "6385-62-2",
                                 physchem.exclude = FALSE)
```

---

parameterize_schmitt *Parameters for Schmitt's (2008) Tissue Partition Coefficient Method*

Description

This function provides the necessary parameters to run predict_partitioning_schmitt, excluding the data in table tissue.data. The model is based on the Schmitt (2008) (doi:10.1016/j.tiv.2007.09.010) method for predicting tissue:plasma partition coefficients as modified by Pearce et al. (2017) (doi:10.1007/s1092801795487). The modifications include approaches adapted from Peyret et al. (2010) (doi:10.1016/j.taap.2010.09.010).

Usage

```
parameterize_schmitt(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  parameters = NULL,
  species = "Human",
  default.to.human = FALSE,
  force.human.fup = FALSE,
  adjusted.Funbound.plasma = TRUE,
  suppress.messages = FALSE,
  class.exclude = TRUE,
  minimum.Funbound.plasma = 1e-04
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) – if parameters is not specified then the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemcial and physiological description parameters needed to run the Schmitt et al. (2008) model
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
default.to.human	Substitutes missing fraction of unbound plasma with human values if true.
force.human.fup	Returns human fraction of unbound plasma in calculation for rats if true. When species is specified as rabbit, dog, or mouse, the human unbound fraction is substituted.
adjusted.Funbound.plasma	Uses Pearce et al. (2017) lipid binding adjustment for Funbound.plasma (which impacts partition coefficients) when set to TRUE (Default).
suppress.messages	Whether or not the output message is suppressed.
class.exclude	Exclude chemical classes identified as outside of domain of applicability by relevant modelinfo_[MODEL] file (default TRUE).
minimum.Funbound.plasma	Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).

Value

`Funbound.plasma`
: Unbound fraction in plasma, adjusted for lipid binding according to Pearce et al. (2017)

`unadjusted.Funbound.plasma`
: measured unbound fraction in plasma (0.005 if below limit of detection)

`Pow`
: octanol: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 and John Wambaugh

References

Pearce RG, Setzer RW, Strope CL, Wambaugh JF, Sipes NS (2017). "Httk: R package for high-throughput toxicokinetics." *Journal of Statistical Software*, **79**(4), 1. doi:10.18637/jss.v079.i04.

Schmitt W (2008). "General approach for the calculation of tissue to plasma partition coefficients." *Toxicology in vitro*, **22**(2), 457–467. doi:10.1016/j.tiv.2007.09.010.

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Pearce RG, Setzer RW, Davis JL, Wambaugh JF (2017). "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." *Journal of pharmacokinetics and pharmacodynamics*, **44**, 549–565. doi:10.1007/s1092801795487.

Peyret T, Poulin P, Krishnan K (2010). "A unified algorithm for predicting partition coefficients for PBPK modeling of drugs and environmental chemicals." *Toxicology and applied pharmacology*, **249**(3), 197–207. doi:10.1016/j.taap.2010.09.010.

See Also

`predict_partitioning_schmitt`

`tissue.data`

`calc_ma`

`apply_fup_adjustment`

Examples

```
library(httk)

# Create a list of parameters (that you can potentially change):
p <- parameterize_schmitt(chem.name="bisphenola")

# Predict the partition coefficients using a list of parameters:
PCs <- predict_partitioning_schmitt(parameters = p)

# Lump the tissues into the compartments for model "pbtk":
lump_tissues(PCs)

# Lump the tissues into a single volume of distribution
calc_vdist(parameters=c(p, PCs))
```

---

parameterize_steadystate

Parameters for a three-compartment toxicokinetic model at steady-state

---

Description

This function initializes the parameters needed in the functions calc_mc_css, calc_mc_oral_equiv, and calc_analytic_css for the three compartment steady state model ('3compartmentss') as used in Rotroff et al. (2010), Wetmore et al. (2012), Wetmore et al. (2015), and elsewhere. By assuming that enough time has passed to reach steady-state, we eliminate the need for tissue-specific parititon coefficients because we assume all tissues have come to equilibrium with the unbound concentration in plasma. However, we still use chemical properties to predict the blood:plasma ratio for estimating first-pass hepatic metabolism for oral exposures.

Usage

```
parameterize_steadystate(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
  clint.pvalue.threshold = 0.05,
  default.to.human = FALSE,
  class.exclude = TRUE,
  physchem.exclude = TRUE,
  force.human.clint.fup = FALSE,
  adjusted.Funbound.plasma = TRUE,
  adjusted.Clint = TRUE,
  restrictive.clearance = TRUE,
  fup.lod.default = 0.005,
  suppress.messages = FALSE,
```

```
  minimum.Funbound.plasma = 1e-04,
  Caco2.options = NULL,
  ...
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) – the chemical must be identified by either CAS, name, or DTXSIDs
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
clint.pvalue.threshold	Hepatic clearances with clearance assays having p-values greater than the threshold are set to zero.
default.to.human	Substitutes missing species-specific values with human values if TRUE (default is FALSE).
class.exclude	Exclude chemical classes identified as outside of domain of applicability by relevant modelinfo_[MODEL] file (default TRUE).
physchem.exclude	Exclude chemicals on the basis of physico-chemical properties (currently only Henry's law constant) as specified by the relevant modelinfo_[MODEL] file (default TRUE).
force.human.clint.fup	Uses human hepatic intrinsic clearance and fraction of unbound plasma in calculation of partition coefficients for rats if true.
adjusted.Funbound.plasma	Uses Pearce et al. (2017) lipid binding adjustment for Funbound.plasma (which impacts partition coefficients) when set to TRUE (Default).
adjusted.Clint	Uses Kilford et al. (2008) hepatocyte incubation binding adjustment for Clint when set to TRUE (Default).
restrictive.clearance	In calculating hepatic.bioavailability, protein binding is not taken into account (set to 1) in liver clearance if FALSE.
fup.lod.default	Default value used for fraction of unbound plasma for chemicals where measured value was below the limit of detection. Default value is 0.0005.
suppress.messages	Whether or not the output message is suppressed.
minimum.Funbound.plasma	Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).

`Caco2.options` A list of options to use when working with Caco2 apical to basolateral data `Caco2.Pab`, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = `Fabs`. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = `Fgut`. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See `get_fbio` for further details.

`...` Other parameters

Details

We model systemic oral bioavailability as $F_{bio} = F_{abs} * F_{gut} * F_{hep}$. F_{hep} is estimated from in vitro TK data using `calc_hep_bioavailability`. If F_{bio} has been measured in vivo and is found in table `chem.physical_and_invitro.data` then we set $F_{abs} * F_{git}$ to the measured value divided by F_{hep} Otherwise, if Caco2 membrane permeability data or predictions are available F_{abs} is estimated using `calc_fabs.oral`. Intrinsic hepatic metabolism is used to very roughly estimate F_{gut} using `calc_fgut.oral`.

Because this model does not simulate exhalation, inhalation, and other processes relevant to volatile chemicals, this model is by default restricted to chemicals with a logHenry's Law Constant less than that of Acetone, a known volatile chemical. That is, chemicals with logHLC > -4.5 (Log10 atm-m3/mole) are excluded. Volatility is not purely determined by the Henry's Law Constant, therefore this chemical exclusion may be turned off with the argument "physchem.exclude = FALSE". Similarly, per- and polyfluoroalkyl substances (PFAS) are excluded by default because the transporters that often drive PFAS toxicokinetics are not included in this model. However, PFAS chemicals can be included with the argument "class.exclude = FALSE".

Value

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

`Fabsgut` Fraction of the oral dose absorbed and surviving gut metabolism, that is, the fraction of the dose that enters the gutlumen.

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

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

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

`BW` Body Weight, kg

`MW` Molecular Weight, g/mol

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

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

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

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

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

Author(s)

John Wambaugh and Greg Honda

References

Pearce RG, Setzer RW, Strope CL, Wambaugh JF, Sipes NS (2017). "Httk: R package for high-throughput toxicokinetics." *Journal of Statistical Software*, **79**(4), 1. doi:10.18637/jss.v079.i04.

Kilford PJ, Gertz M, Houston JB, 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), 1194–1197. doi:10.1124/dmd.108.020834.

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Rotroff DM, Wetmore BA, Dix DJ, Ferguson SS, Clewell HJ, Houck KA, LeCluyse EL, Andersen ME, Judson RS, Smith CM, others (2010). "Incorporating human dosimetry and exposure into high-throughput in vitro toxicity screening." *Toxicological Sciences*, **117**(2), 348–358. doi:10.1093/toxsci/kfq220.

Wetmore BA, Wambaugh JF, Ferguson SS, Sochaski MA, Rotroff DM, Freeman K, Clewell III HJ, Dix DJ, Andersen ME, Houck KA, others (2012). "Integration of dosimetry, exposure, and high-throughput screening data in chemical toxicity assessment." *Toxicological Sciences*, **125**(1), 157–174. doi:10.1093/toxsci/kfr254.

Wetmore BA, Wambaugh JF, Allen B, Ferguson SS, Sochaski MA, Setzer RW, Houck KA, Strope CL, Cantwell K, Judson RS, others (2015). "Incorporating high-throughput exposure predictions with dosimetry-adjusted in vitro bioactivity to inform chemical toxicity testing." *Toxicological Sciences*, **148**(1), 121–136. doi:10.1093/toxsci/kfv171.

See Also

`calc_analytic_css_3compss`

`apply_clint_adjustment`

`tissue.data`

`physiology.data`

Examples

```
parameters1 <- parameterize_steadystate(chem.name='Bisphenol-A',species='Rat')

parameters2 <- parameterize_steadystate(chem.cas='80-05-7')
```

```
# The following will not work because Diquat dibromide monohydrate's
# Henry's Law Constant (-3.912) is higher than that of Acetone (~-4.5):
try(parameters3 <- parameterize_steadystate(chem.cas = "6385-62-2"))

# However, we can turn off checking for phys-chem properties, since we know
# that  Diquat dibromide monohydrate is not too volatile:
parameters3 <- parameterize_steadystate(chem.cas = "6385-62-2",
                                  physchem.exclude = FALSE)
```

`parameterize_sumclearances` *Parameters for a three-compartment model at steady-state with exhalation*

Description

This function initializes the parameters needed in the functions `calc_mc_css`, `calc_mc_oral_equiv`, and `calc_analytic_css` for the three compartment steady state model ('3compartmentss') as used in Rotroff et al. (2010), Wetmore et al. (2012), Wetmore et al. (2015), and elsewhere. By assuming that enough time has passed to reach steady-state, we eliminate the need for tissue-specific parititon coefficients because we assume all tissues have come to equilibrium with the unbound concentration in plasma. However, we still use chemical properties to predict the blood:plasma ratio for estimating first-pass hepatic metabolism for oral exposures.

Usage

```
parameterize_sumclearances(
  chem.cas = NULL,
  chem.name = NULL,
  dtxsid = NULL,
  species = "Human",
  clint.pvalue.threshold = 0.05,
  default.to.human = FALSE,
  physchem.exclude = TRUE,
  class.exclude = TRUE,
  force.human.clint.fup = FALSE,
  adjusted.Funbound.plasma = TRUE,
  adjusted.Clint = TRUE,
  restrictive.clearance = TRUE,
  fup.lod.default = 0.005,
  suppress.messages = FALSE,
  minimum.Funbound.plasma = 1e-04,
  Caco2.options = NULL,
  ...
)
```

Arguments

chem.cas	Chemical Abstract Services Registry Number (CAS-RN) – the chemical must be identified by either CAS, name, or DTXISD
chem.name	Chemical name (spaces and capitalization ignored) – the chemical must be identified by either CAS, name, or DTXISD
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) – the chemical must be identified by either CAS, name, or DTXSIDs
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
clint.pvalue.threshold	Hepatic clearances with clearance assays having p-values greater than the threshold are set to zero.
default.to.human	Substitutes missing species-specific values with human values if TRUE (default is FALSE).
physchem.exclude	Exclude chemicals on the basis of physico-chemical properties (currently only Henry's law constant) as specified by the relevant modelinfo_[MODEL] file (default TRUE).
class.exclude	Exclude chemical classes identified as outside of domain of applicability by relevant modelinfo_[MODEL] file (default TRUE).
force.human.clint.fup	Uses human hepatic intrinsic clearance and fraction of unbound plasma in calculation of partition coefficients for rats if true.
adjusted.Funbound.plasma	Uses Pearce et al. (2017) lipid binding adjustment for Funbound.plasma (which impacts partition coefficients) when set to TRUE (Default).
adjusted.Clint	Uses Kilford et al. (2008) hepatocyte incubation binding adjustment for Clint when set to TRUE (Default).
restrictive.clearance	In calculating hepatic.bioavailability, protein binding is not taken into account (set to 1) in liver clearance if FALSE.
fup.lod.default	Default value used for fraction of unbound plasma for chemicals where measured value was below the limit of detection. Default value is 0.0005.
suppress.messages	Whether or not the output message is suppressed.
minimum.Funbound.plasma	Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).
Caco2.options	A list of options to use when working with Caco2 apical to basolateral data Caco2.Pab, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = Fabs. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral,

otherwise fgut.oral = Fgut. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See get_fbio for further details.

... Other parameters

Details

We model systemic oral bioavailability as $F_{bio} = F_{abs} * F_{gut} * F_{hep}$. F_{hep} is estimated from in vitro TK data using calc_hep_bioavailability. If F_{bio} has been measured in vivo and is found in table chem.physical_and_invitro.data then we set $F_{abs} * F_{git}$ to the measured value divided by F_{hep} Otherwise, if Caco2 membrane permeability data or predictions are available F_{abs} is estimated using calc_fabs.oral. Intrinsic hepatic metabolism is used to very roughly estimate F_{gut} using calc_fgut.oral.

Per- and polyfluoroalkyl substances (PFAS) are excluded by default because the transporters that often drive PFAS toxicokinetics are not included in this model. However, PFAS chemicals can be included with the argument "class.exclude = FALSE".

Value

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

Fabsgut Fraction of the oral dose absorbed and surviving gut metabolism, that is, the fraction of the dose that enters the gutlumen.

Funbound.plasma
Fraction of plasma that is not bound.

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

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

BW Body Weight, kg

MW Molecular Weight, g/mol

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

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

liver.density Liver tissue density, kg/L.

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

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

Author(s)

John Wambaugh

References

Pearce RG, Setzer RW, Strope CL, Wambaugh JF, Sipes NS (2017). "Httk: R package for high-throughput toxicokinetics." *Journal of Statistical Software*, **79**(4), 1. doi:10.18637/jss.v079.i04.

Kilford PJ, Gertz M, Houston JB, 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), 1194–1197. doi:10.1124/dmd.108.020834.

Wambaugh JF, Schacht CM, Ring CL (2025). "A Simple Physiologically Based Toxicokinetic Model for Multi-Route In Vitro–In Vivo Extrapolation." *Environmental Science & Technology Letters*, **12**(3), 261–268. doi:10.1021/acs.estlett.4c00967.

Rotroff DM, Wetmore BA, Dix DJ, Ferguson SS, Clewell HJ, Houck KA, LeCluyse EL, Andersen ME, Judson RS, Smith CM, others (2010). "Incorporating human dosimetry and exposure into high-throughput in vitro toxicity screening." *Toxicological Sciences*, **117**(2), 348–358. doi:10.1093/toxsci/kfq220.

Wetmore BA, Wambaugh JF, Ferguson SS, Sochaski MA, Rotroff DM, Freeman K, Clewell III HJ, Dix DJ, Andersen ME, Houck KA, others (2012). "Integration of dosimetry, exposure, and high-throughput screening data in chemical toxicity assessment." *Toxicological Sciences*, **125**(1), 157–174. doi:10.1093/toxsci/kfr254.

Wetmore BA, Wambaugh JF, Allen B, Ferguson SS, Sochaski MA, Setzer RW, Houck KA, Strope CL, Cantwell K, Judson RS, others (2015). "Incorporating high-throughput exposure predictions with dosimetry-adjusted in vitro bioactivity to inform chemical toxicity testing." *Toxicological Sciences*, **148**(1), 121–136. doi:10.1093/toxsci/kfv171.

See Also

`calc_analytic_css_3compss`

`apply_clint_adjustment`

`tissue.data`

`physiology.data`

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 (2008). "General approach for the calculation of tissue to plasma partition coefficients." *Toxicology in vitro*, **22**(2), 457–467. doi:10.1016/j.tiv.2007.09.010.

Schmitt W (2008). "Corrigendum to:'General approach for the calculation of tissue to plasma partition coefficients'[Toxicology in Vitro 22 (2008) 457–467]." *Toxicology in Vitro*, **22**(6), 1666. doi:10.1016/j.tiv.2008.04.020.

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 YE, Edginton AN (2013). "Correlation-based prediction of tissue-to-plasma partition coefficients using readily available input parameters." *Xenobiotica*, **43**(10), 839–852. doi:10.3109/00498254.2013.770182.

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

`pearce2017regression` *Pearce et al. 2017 data*

Description

This table includes the adjusted and unadjusted regression parameter estimates for the chemical-specifc plasma protein unbound fraction (fup) in 12 different tissue types.

Usage

```
pearce2017regression
```

Format

data.frame

Details

Predictions were made with regression models, as reported in Pearce et al. (2017).

Author(s)

Robert G. Pearce

Source

Pearce et al. 2017 Regression Models

References

Pearce RG, Setzer RW, Davis JL, Wambaugh JF (2017). "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." *Journal of pharmacokinetics and pharmacodynamics*, **44**, 549–565. doi:10.1007/s1092801795487.

See Also

`predict_partitioning_schmitt`

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

Description

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

Usage

```
pharma
```

Format

An object of class `matrix` (inherits from `array`) with 14 rows and 954 columns.

Source

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

References

Wambaugh JF, Wetmore BA, Ring CL, Nicolas CI, Pearce RG, Honda GS, Dinallo R, Angus D, Gilbert J, Sierra T, others (2019). "Assessing toxicokinetic uncertainty and variability in risk prioritization." *Toxicological Sciences*, **172**(2), 235–251. doi:10.1093/toxsci/kfz205.

physiology.data *Species-specific physiology parameters*

Description

This data set contains values from Davies and Morris (1993) necessary to paramaterize a toxicokinetic model for human, mouse, rat, dog, or rabbit. The temperature for each species are taken from Reece (2015), Jordon (1995), and Stammers (1926). Mean residence time for the small intestine is from Grandoni et al. (2019). Human small intestine radius is from Yu et al. (1999). Rat small intestine radius is from Griffin and O'Driscoll (2008).

Usage

```
physiology.data
```

Format

A data.frame containing 18 rows and 7 columns.

Author(s)

John Wambaugh and Nisha Sipes

References

Davies B, Morris T (1993). "Physiological parameters in laboratory animals and humans." *Pharmaceutical research*, **10**(7), 1093–1095. doi:10.1023/A:1018943613122.

Brown RP, Delp MD, Lindstedt SL, Rhomberg LR, Beliles RP (1997). "Physiological parameter values for physiologically based pharmacokinetic models." *Toxicology and industrial health*, **13**(4), 407–484. doi:10.1177/074823379701300401.

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

Reece WO (2015). "14 Body Temperature and Its Regulation." *Dukes' physiology of domestic animals*, 149.

Stammers AD (1926). "The blood count and body temperature in normal rats." *The Journal of Physiology*, **61**(3), 329. doi:10.1113/jphysiol.1926.sp002297.

Jordan D (1995). "Temperature regulation in laboratory rodents." *Journal of anatomy*, **186**(Pt 1), 228.

Grandoni S, Cesari N, Brogin G, Puccini P, Magni P (2019). "Building in-house PBPK modelling tools for oral drug administration from literature information." *ADMET and DMPK*, **7**(1), 4–21. doi:10.5599/admet.638.

Griffin B, O'Driscoll C (2008). "Models of the Small Intestine." In Ehrhardt C, Kim K (eds.), *Drug Absorption Studies: In Situ, In Vitro and In Silico Models*, chapter 2, 34–76. Springer US, Boston, MA. ISBN 978-0-387-74901-3, doi:10.1007/9780387749013_2.

Examples

```
# We can add a new species (for example, wolverines) by adding new information
# to the physiology.data and tissue.data tables. It can be convenient to start by
# by replicating the data from another species and adjusting as appropriate:

# Copy physiology data from rabbit:
new.species <- physiology.data[,"Rabbit"]
names(new.species) <- physiology.data[,"Parameter"]
rabbit.BW <- new.species["Average BW"]
# Rausch and Pearson (1972) https://doi.org/10.2307/3799057 :
new.species["Average BW"] <- 31.2
# Thiel et al. (2019) https://doi.org/10.1186/s12983-019-0319-8 :
new.species["Average Body Temperature"] <- 38.5

# Add new physiology data column to physiology.data table"
physiology.data <- cbind(physiology.data, new.species)
colnames(physiology.data)[length(colnames(physiology.data))] <- "Wolverine"

# Copy tissue data from rabbit:
new.tissue.data <- subset(tissue.data,Species=="Rabbit")
new.tissue.data$Species <- "Wolverine"
```

```
# Add new tissue data rows to tissue.data table:
tissue.data <- rbind(tissue.data, new.tissue.data)

# Species is now available for calculations:
calc_mc_css(chem.cas="80-05-7",
            species="wolverine",
            parameterize.args.list =list(default.to.human=TRUE),
            suppress.messages=TRUE,
            samples = 100)
```

`pksim.pcs` *Partition Coefficients from PK-Sim*

Description

Dallmann et al. (2018) made use of PK-Sim to predict chemical- and tissue- specific partition coefficients. The methods include both the default PK-Sim approach and PK-Sim Standard and Rodgers & Rowland (2006).

Usage

```
pksim.pcs
```

Format

data.frame

Source

Kapraun DF, Sfeir M, Pearce RG, Davidson-Fritz SE, Lumen A, Dallmann A, Judson RS, Wambaugh JF (2022). "Evaluation of a rapid, generic human gestational dose model." *Reproductive Toxicology*, **113**, 172–188. doi:10.1016/j.reprotox.2022.09.004.

References

Dallmann A, Ince I, Coboeken K, Eissing T, Hempel G (2018). "A physiologically based pharmacokinetic model for pregnant women to predict the pharmacokinetics of drugs metabolized via several enzymatic pathways." *Clinical pharmacokinetics*, **57**(6), 749–768. doi:10.1007/s40262017-05945.

pradeep2020 *Pradeep et al. 2020*

Description

This table includes Support Vector Machine and Random Forest model predicted values for unbound fraction plasma protein (fup) and intrinsic hepatic clearance (clint) values for a subset of chemicals in the Tox21 library (see https://www.epa.gov/chemical-research/toxicology-testing-21st-century-t

Usage

```
pradeep2020
```

Format

data.frame

Details

Prediction were made with Support Vector Machine and Random Forest models, as reported in Pradeep et al. (2020).

References

Pradeep P, Patlewicz G, Pearce R, Wambaugh J, Wetmore B, Judson R (2020). "Using chemical structure information to develop predictive models for in vitro toxicokinetic parameters to inform high-throughput risk-assessment." *Computational Toxicology*, **16**, 100136. ISSN 2468-1113, doi:10.1016/j.comtox.2020.100136.

See Also

load_pradeep2020

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

Description

This function implements the method from Schmitt (2008) for predicting the tissue to unbound plasma partition coefficients for the tissues contained in the tissue.data table. The method has been modified by Pearce et al. (2017) based on an evaluation using in vivo measured partition coefficients.

To understand this method, it is important to recognize that in a given media the fraction unbound in that media is inverse of the media:water partition coefficient. In Schmitt's model, each tissue

is composed of cells and interstitium, with each cell consisting of neutral lipid, neutral phospholipid, water, protein, and acidic phospholipid. Each tissue cell is defined as the sum of separate compartments for each constituent, all of which partition with a shared water compartment. The partitioning between the cell components and cell water is compound specific and determined by log Pow (in neutral lipid partitioning), membrane affinity (phospholipid and protein partitioning), and pKa (neutral lipid and acidic phospholipid partitioning). For a given compound the partitioning into each component is identical across tissues. Thus the differences among tissues are driven by their composition, that is, the varying volumes of components such as neutral lipid. However, pH differences across tissues also determine small differences in partitioning between cell and plasma water. The fup is used as the plasma water to total plasma partition coefficient and to approximate the partitioning between interstitial protein and water.

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

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

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

Human tissue volumes are used for species other than Rat.

Usage

```
predict_partitioning_schmitt(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  species = "Human",
  model = "pbtk",
  default.to.human = FALSE,
  parameters = NULL,
  alpha = 0.001,
  adjusted.Funbound.plasma = TRUE,
  regression = TRUE,
 regression.list = c("brain", "adipose", "gut", "heart", "kidney", "liver", "lung",
    "muscle", "skin", "spleen", "bone"),
  tissues = NULL,
  minimum.Funbound.plasma = 1e-04,
  suppress.messages = FALSE
)
```

Arguments

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

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

`model` Model for which partition coefficients are neeeded (for example, "pbtk", "3compartment")

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

`parameters` Chemical parameters from `parameterize_schmitt` overrides chem.name, dtxsid, and chem.cas.

`alpha` Ratio of Distribution coefficient D of totally charged species and that of the neutral form

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

`regression` Whether or not to use the regressions. Regressions are used by default.

`regression.list` Tissues to use regressions on.

`tissues` Vector of desired partition coefficients. Returns all by default.

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

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

Value

Returns tissue to unbound plasma partition coefficients for each tissue.

Author(s)

Robert Pearce

References

Schmitt W (2008). "General approach for the calculation of tissue to plasma partition coefficients." *Toxicology in vitro*, **22**(2), 457–467. doi:10.1016/j.tiv.2007.09.010.

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

Pearce RG, Setzer RW, Davis JL, Wambaugh JF (2017). "Evaluation and calibration of high-throughput predictions of chemical distribution to tissues." *Journal of pharmacokinetics and pharmacodynamics*, **44**, 549–565. doi:10.1007/s1092801795487.

Yun YE, Edginton AN (2013). "Correlation-based prediction of tissue-to-plasma partition coefficients using readily available input parameters." *Xenobiotica*, **43**(10), 839–852. doi:10.3109/00498254.2013.770182.

See Also

parameterize_schmitt

tissue.data

calc_ma

Examples

```
library(httk)

# Predict the partition coefficients by chemical id:
PCs1 <- predict_partitioning_schmitt(chem.name='ibuprofen')

# Create a list of parameters (that you can potentially change):
p <- parameterize_schmitt(chem.name="ibuprofen")

# Predict the partition coefficients using a list of parameters:
PCs2 <- predict_partitioning_schmitt(parameters = p)

# Check that all the parameter values are the same:
all(unlist(PCs1)==unlist(PCs2))

# Predict partition coefficients without using Pearce et al. (2017) calibrations:
PCs3 <- predict_partitioning_schmitt(chem.name='ibuprofen',regression=FALSE)

# Lump the tissues into the compartments for model "pbtk":
lump_tissues(PCs1)

# Lump the tissues into a single volume of distribution
calc_vdist(parameters=c(p,PCs1))
```

---

pregnonpregaucs *AUCs for Pregnant and Non-Pregnant Women*

Description

Dallmann et al. (2018) includes compiled literature descriptions of toxicokinetic summary statistics, including time-integrated plasma concentrations (area under the curve or AUC) for drugs administered to a sample of subjects including both pregnant and non-pregnant women. The circumstances of the dosing varied slightly between drugs and are summarized in the table.

Usage

```
pregnonpregaucs
```

Format

data.frame

Source

Kapraun DF, Sfeir M, Pearce RG, Davidson-Fritz SE, Lumen A, Dallmann A, Judson RS, Wambaugh JF (2022). "Evaluation of a rapid, generic human gestational dose model." *Reproductive Toxicology*, **113**, 172–188. doi:10.1016/j.reprotox.2022.09.004.

References

Dallmann A, Ince I, Coboeken K, Eissing T, Hempel G (2018). "A physiologically based pharmacokinetic model for pregnant women to predict the pharmacokinetics of drugs metabolized via several enzymatic pathways." *Clinical pharmacokinetics*, **57**(6), 749–768. doi:10.1007/s40262017-05945.

`propagate_invitrouv_1comp`

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

---

Description

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

Usage

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

Arguments

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

Value

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

Author(s)

John Wambaugh

propagate_invitrouv_3comp

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

Description

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

Usage

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

Arguments

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

Value

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

Author(s)

John Wambaugh

propagate_invitrouv_pbtk

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

Description

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

Usage

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

Arguments

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

Value

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

Author(s)

John Wambaugh

`reset_httk` *Reset HTTK to Default Data Tables*

Description

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

Usage

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

Arguments

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

Value

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

Author(s)

John Wambaugh

Examples

```
chem.physical_and_invitro.data <- load_sipes2017()
reset_httk()
```

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

Description

Randomly draws from a one-dimensional KDE

Usage

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

Arguments

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

Value

A vector of n samples from the KDE fhat

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

rmed0non0u95 — *Draw random numbers with LOD median but non-zero upper 95th percentile*

Description

This function draws N random numbers from a distribution that approximates a median that is equal to the limit of detection (LOD, value x.LOD) but has an upper 95th percentile (x.u95) that is above x.LOD. We make the assumption that values above x.u95 are uniformly distributed between x.u95 and x.u95 + (x.u95 - x.LOD)

Usage

```
rmed0non0u95(n, x.u95, x.min = 0, x.LOD = 0.005)
```

Arguments

n	Number of samples to draw
x.u95	The upper limit on the 95th confidence/credible intervale (this is the 97.5 percentile)
x.min	The minimum allowed value (defaults to 0)
x.LOD	The limit of detection (defaults to 0.005)

Value

A vector of N samples where the 50th and 97.5th quantiles approximate x.LOD and x.u95 respectively

Author(s)

John Wambaugh

References

Breen M, Wambaugh JF, Bernstein A, Sfeir M, Ring CL (2022). "Simulating toxicokinetic variability to identify susceptible and highly exposed populations." *Journal of Exposure Science & Environmental Epidemiology*, **32**(6), 855–863. doi:10.1038/s41370022004910.

Examples

```
Fup.95 <- 0.02
N <- 1000

set.seed(1235)
Fup.vec <- rmed0non0u95(n=N, x.u95=Fup.95)
quantile(Fup.vec,c(0.5,0.975))

quantile(rmed0non0u95(200,x.u95=0.05,x.min=10^-4,x.LOD=0.01),c(0.5,0.975))
hist(rmed0non0u95(1000,x.u95=0.05,x.min=10^-4,x.LOD=0.01))

quantile(rmed0non0u95(200,x.u95=0.005,x.min=10^-4,x.LOD=0.01),c(0.5,0.975))
hist(rmed0non0u95(1000,x.u95=0.005,x.min=10^-4,x.LOD=0.01))
```

---

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

Description

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

Usage

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

Arguments

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

Value

A vector of samples from the specified censored distribution.

---

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

Description

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

Usage

```
scale_dosing(
  dosing,
  parameters,
  route,
  input.units = NULL,
  output.units = "uM",
  vol = NULL,
  state = "liquid"
)
```

Arguments

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

parameters	Chemical parameters from parameterize_pbtk function, overrides chem.name and chem.cas.
route	String specification of route of exposure for simulation: "oral", "iv", "inhalation", ...
input.units	Units of the dose values being scaled. (Default is NULL.) Currently supported units "mg/L", "ug/L","ug/mL", "uM", "umol/L", "ug/dL", "ug/g", "nmol/L", "nM", and "ppmw" (supported input.units subject to change).
output.units	Desired units (either "mg/L", "mg", "umol", or default "uM").
vol	Volume for the target tissue of interest. NOTE: Volume should not be in units of per BW, i.e. "kg".
state	Chemical state of matter (gas or default liquid).

Value

A list of numeric values for doses converted to output.units, potentially (depending on argument dosing) including:

initial.dose	The first dose given
dosing.matrix	A 2xN matrix where the first column is dose time and the second is dose amount for N doses
daily.dose	The total cumulative daily dose

Author(s)

John Wambaugh and Sarah E. Davidson

---

scr_h *KDE bandwidths for residual variability in serum creatinine*

Description

Bandwidths used for a one-dimensional kernel density estimation of the distribution of residual errors around smoothing spline fits of serum creatinine vs. age for NHANES respondents in each of ten combinations of sex and race/ethnicity categories.

Usage

```
scr_h
```

Format

A named list with 10 elements, each a numeric value. Each list element corresponds to, and is named for, one combination of NHANES sex categories (Male and Female) and NHANES race/ethnicity categories (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other).

Details

Each matrix is the standard deviation for a normal distribution: this is the bandwidth to be used for a kernel density estimation (KDE) (using a normal kernel) of the distribution of residual errors around smoothing spline fits of serum creatinine vs. age for NHANES respondents in the specified sex and race/ethnicity category. Optimal bandwidths were pre-calculated by doing the smoothing spline fits, getting the residuals, then calling `kde` on the residuals (which calls `hpi` to compute the plug-in bandwidth).

Used by HTTK-Pop only in "virtual individuals" mode (i.e. `httkpop_generate` with `method = "v"`), in `gen_serum_creatinine`.

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

`set_httk_precision` *set_httk_precision*

Description

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

Usage

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

Arguments

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

Value

numeric values

Author(s)

John Wambaugh

sipes2017 *Sipes et al. 2017 data*

Description

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

Usage

```
sipes2017
```

Format

data.frame

Author(s)

Nisha Sipes

Source

ADMET, Simulations Plus

References

Sipes NS, Wambaugh JF, Pearce R, Auerbach SS, Wetmore BA, Hsieh J, Shapiro AJ, Svoboda D, DeVito MJ, Ferguson SS (2017). "An intuitive approach for predicting potential human health risk with the Tox21 10k library." *Environmental science & technology*, **51**(18), 10786–10796. doi:10.1021/acs.est.7b00650.

See Also

load_sipes2017

`skeletal_muscle_mass` *Predict skeletal muscle mass*

Description

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

Usage

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

Arguments

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

Details

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

Value

Vector of skeletal muscle masses in kg.

Author(s)

Caroline Ring

References

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

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

See Also

`skeletal_muscle_mass_children`

skeletal_muscle_mass_children *Predict skeletal muscle mass for children*

Description

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

Usage

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

Arguments

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

Value

Vector of skeletal muscle masses in kg.

Author(s)

Caroline Ring

References

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

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

skin_mass_bosgra *Predict skin mass*

Description

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

Usage

```
skin_mass_bosgra(BSA)
```

Arguments

BSA	Vector of body surface areas in cm^2.

Value

Vector of skin masses in kg.

Author(s)

Caroline Ring

References

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

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

---

solve_1comp *Solve one compartment TK model*

Description

This function solves for the amount or concentration of a chemical in plasma for a one compartment model as a function of time based on the dose and dosing frequency. The model describes blood concentrations in a single compartment. The volume of distribution depends on the physical volume of each tissue and the predicted chemical partitioning into those volumes. Plasma concentration in compartment x is given by $C_{plasma} = \frac{C_{blood}}{R_{b2p}}$ for a tissue independent value of R_{b2p}.

Usage

```
solve_1comp(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  times = NULL,
  parameters = NULL,
  days = 10,
  tsteps = 4,
  daily.dose = NULL,
  dose = NULL,
  doses.per.day = NULL,
  initial.values = NULL,
  plots = FALSE,
  suppress.messages = FALSE,
```

```
  species = "Human",
  iv.dose = FALSE,
  input.units = "mg/kg",
  output.units = NULL,
  default.to.human = FALSE,
  class.exclude = TRUE,
  physchem.exclude = TRUE,
  recalc.blood2plasma = FALSE,
  recalc.clearance = FALSE,
  dosing.matrix = NULL,
  adjusted.Funbound.plasma = TRUE,
  regression = TRUE,
  restrictive.clearance = TRUE,
  minimum.Funbound.plasma = 1e-04,
  monitor.vars = NULL,
  Caco2.options = list(),
  ...
)
```

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
times	Optional time sequence for specified number of days.
parameters	Chemical parameters from parameterize_1comp function, overrides chem.name and chem.cas.
days	Length of the simulation.
tsteps	The number time steps per hour.
daily.dose	Total daily dose, default is mg/kg BW.
dose	Amount of a single dose, default is mg/kg BW.
doses.per.day	Number of doses per day.
initial.values	Vector containing the initial concentrations or amounts of the chemical in specified tissues with units corresponding to output.units. Defaults are zero.
plots	Plots all outputs if true.
suppress.messages	Whether or not the output message is suppressed.
species	Species desired (either "Rat", "Rabbit", "Dog", or default "Human").
iv.dose	Simulates a single i.v. dose if true.
input.units	Input units of interest assigned to dosing, defaults to "mg/kg" BW.
output.units	A named vector of output units expected for the model results. Default, NULL, returns model results in units specified in the 'modelinfo' file. See table below for details.

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

class.exclude
: Exclude chemical classes identified as outside of domain of applicability by relevant modelinfo_[MODEL] file (default TRUE).

physchem.exclude
: Exclude chemicals on the basis of physico-chemical properties (currently only Henry's law constant) as specified by the relevant modelinfo_[MODEL] file (default TRUE).

recalc.blood2plasma
: Whether or not to recalculate the blood:plasma chemical concentrationr ratio

recalc.clearance
: Whether or not to recalculate the elimination rate.

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

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

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

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

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

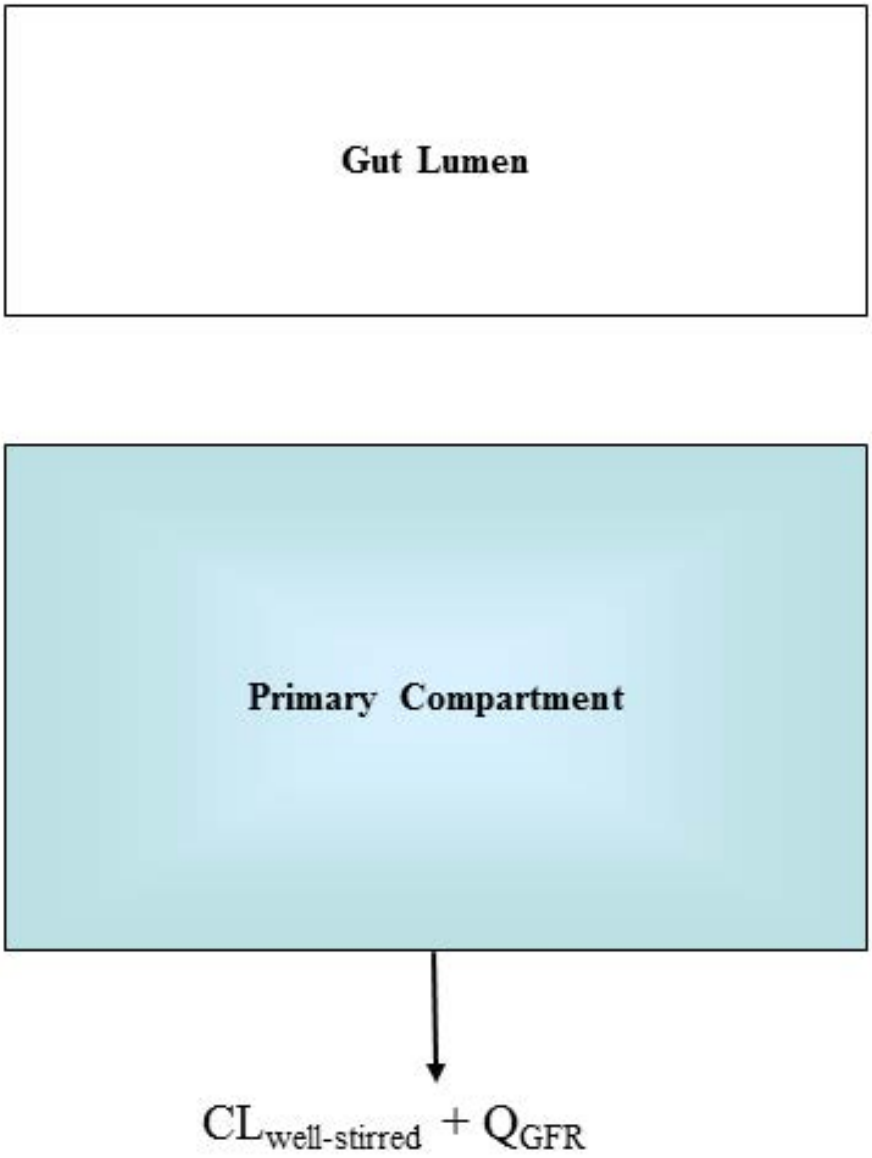
monitor.vars
: Which variables are returned as a function of time. Defaults value of NULL provides "Agutlumen", "Ccompartment", "Ametabolized", "AUC"

Caco2.options
: A list of options to use when working with Caco2 apical to basolateral data `Caco2.Pab`, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = `Fabs`. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = `Fgut`. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See `get_fbio` for further details.

...
: Additional arguments passed to the integrator (deSolve).

Details

Model Figure



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

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

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

Because this model does not simulate exhalation, inhalation, and other processes relevant to volatile chemicals, this model is by default restricted to chemicals with a logHenry's Law Constant less than that of Acetone, a known volatile chemical. That is, chemicals with logHLC > -4.5 (Log10 atm-m3/mole) are excluded. Volatility is not purely determined by the Henry's Law Constant, therefore

this chemical exclusion may be turned off with the argument "physchem.exclude = FALSE". Similarly, per- and polyfluoroalkyl substances (PFAS) are excluded by default because the transporters that often drive PFAS toxicokinetics are not included in this model. However, PFAS chemicals can be included with the argument "class.exclude = FALSE".

Value

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

Author(s)

Robert Pearce

References

Pearce RG, Setzer RW, Strope CL, Wambaugh JF, Sipes NS (2017). "Httk: R package for high-throughput toxicokinetics." *Journal of Statistical Software*, **79**(4), 1. doi:10.18637/jss.v079.i04.

See Also

solve_model

parameterize_1comp

calc_analytic_css_1comp

Examples

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


# By storing the model parameters in a vector first, you can potentially
# edit them before using the model:
params <- parameterize_1comp(chem.cas="80-05-7")
solve_1comp(parameters=params, days=1)

head(solve_1comp(chem.name="Terbufos", daily.dose=NULL, dose=1, days=1))
head(solve_1comp(chem.name="Terbufos", daily.dose=NULL,
                 dose=1,days=1, iv.dose=TRUE))

# A dose matrix specifies times and magnitudes of doses:
dm <- matrix(c(0,1,2,5,5,5),nrow=3)
colnames(dm) <- c("time","dose")
solve_1comp(chem.name="Methenamine", dosing.matrix=dm,
            days=2.5, dose=NULL,daily.dose=NULL)

solve_1comp(chem.name="Besonprodil", daily.dose=1, dose=NULL,
            days=2.5, doses.per.day=4)

# The following will not work because Diquat dibromide monohydrate's
# Henry's Law Constant (-3.912) is higher than that of Acetone (~-4.5):
try(head(solve_1comp(chem.cas = "6385-62-2")))
```

```
# However, we can turn off checking for phys-chem properties, since we know
# that  Diquat dibromide monohydrate is not too volatile:
head(solve_1comp(chem.cas = "6385-62-2", physchem.exclude = FALSE))
```

`solve_1comp_lifestage` *Solve* `1comp_lifestage` *model, which has time-dependent parameters*

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_lifestage(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  times = NULL,
  parameters = NULL,
  days = 10,
  tsteps = 4,
  daily.dose = NULL,
  dose = NULL,
  doses.per.day = NULL,
  initial.values = NULL,
  plots = FALSE,
  suppress.messages = FALSE,
  species = "Human",
  iv.dose = FALSE,
  output.units = "uM",
  method = "lsoda",
  rtol = 1e-08,
  atol = 1e-12,
  default.to.human = FALSE,
  recalc.blood2plasma = FALSE,
  recalc.clearance = FALSE,
  dosing.matrix = NULL,
  adjusted.Funbound.plasma = TRUE,
  regression = TRUE,
  restrictive.clearance = T,
  minimum.Funbound.plasma = 1e-04,
  monitor.vars = NULL,
  time.varying.params = TRUE,
```

```
  start.age = 360,
  ref.pop.dt = NULL,
 httkpop.generate.arg.list = list(method = "virtual individuals", nsamp = 25000),
  ref.params = NULL,
  ...
)
```

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
times	Optional time sequence for specified number of days.
parameters	Chemical parameters from parameterize_1comp function, overrides chem.name and chem.cas.
days	Length of the simulation.
tsteps	The number time steps per hour.
daily.dose	Total daily dose, mg/kg BW.
dose	Amount of a single dose, mg/kg BW.
doses.per.day	Number of doses per day.
initial.values	Vector containing the initial concentrations or amounts of the chemical in specified tissues with units corresponding to output.units. Defaults are zero.
plots	Plots all outputs if true.
suppress.messages	Whether or not the output message is suppressed.
species	Species desired (either "Rat", "Rabbit", "Dog", or default "Human").
iv.dose	Simulates a single i.v. dose if true.
output.units	Desired units (either "mg/L", "mg", "umol", or default "uM").
method	Method used by integrator (deSolve).
rtol	Argument passed to integrator (deSolve).
atol	Argument passed to integrator (deSolve).
default.to.human	Substitutes missing rat values with human values if true.
recalc.blood2plasma	Whether or not to recalculate the blood:plasma chemical concentration ratio
recalc.clearance	Whether or not to recalculate the elimination rate.
dosing.matrix	Vector of dosing times or a matrix consisting of two columns or rows named "dose" and "time" containing the time and amount, in mg/kg BW, of each dose.
adjusted.Funbound.plasma	Uses adjusted Funbound.plasma when set to TRUE along with volume of distribution calculated with this value.

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

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

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

`monitor.vars` Which variables are returned as a function of time. Defaults value of NULL provides "Agutlumen", "Ccompartment", "Ametabolized", "AUC"

`time.varying.params`
Whether or not to allow parameters to vary in time according to the nonparametric regression determined by `get_input_param_timeseries`. Default is TRUE.

`start.age` The age of the individual in months at the beginning of the simulation. Default 360.

`ref.pop.dt` The output of `httkpop_generate` containing physiology of the population used in determining timeseries of parameters. Ignored if `ref.params` is given.

`httkpop.generate.arg.list`
If `ref.pop.dt` is `NULL`, these arguments are used as input to `httkpop_generate` for generating physiology of a reference population.

`ref.params` Model parameters of a reference population used in determining timeseries. Recommended column binding ages in months (as `age_months`) to the output of `create_mc_samples`.

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

Details

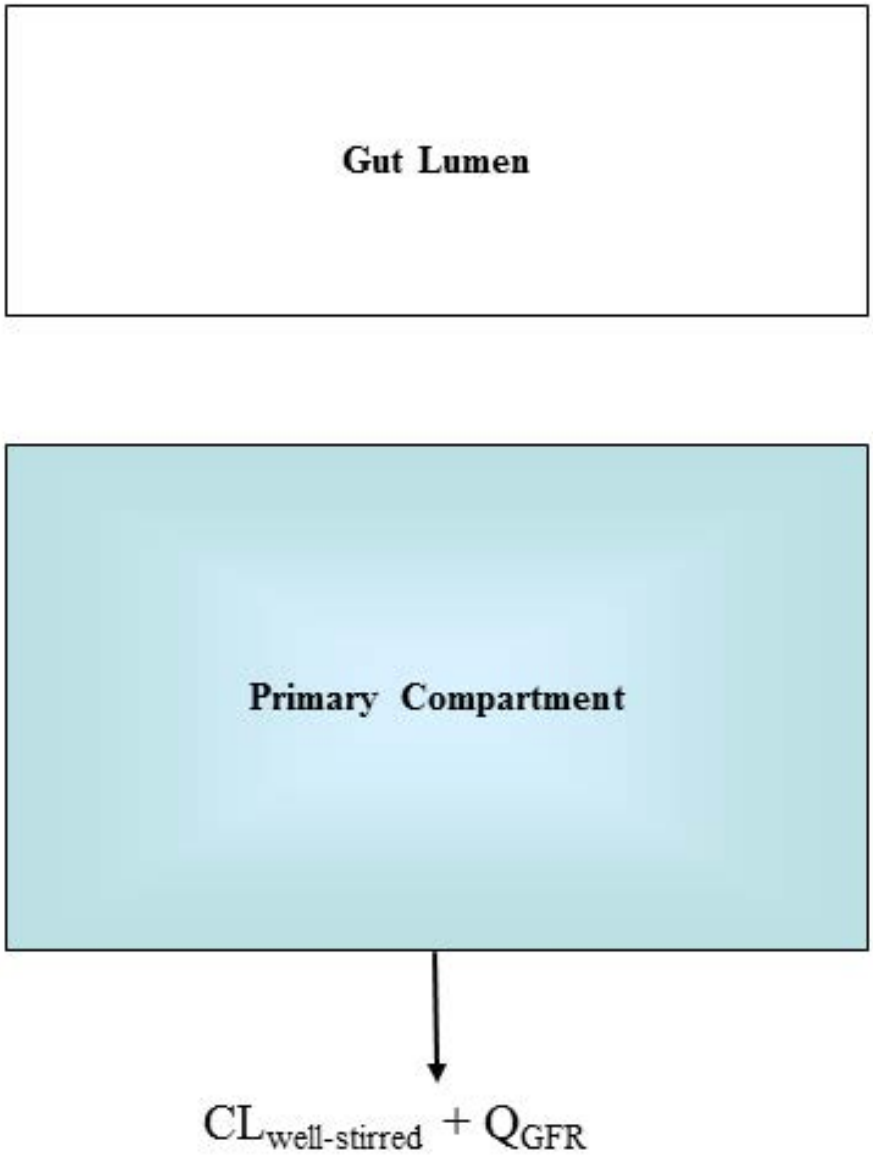
Note that the model parameters have units of hours while the model output is in days.

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

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

AUC is area under plasma concentration curve.

Model Figure



altalt

Value

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

Author(s)

Colin Thomson

Examples

```
params <- parameterize_1comp(chem.name = 'Bisphenol A')

pop.phys <- httkpop_generate(method = 'virtual individuals',
                             nsamp = 25000,
                             agelim_years = c(18, 79),
                             weight_category = c("Normal"))
pop.params <- create_mc_samples(chem.name = 'Bisphenol A',
                                model = '1compartment',
                                httkpop.dt = pop.phys)
ref.params <- cbind(pop.params,
                    age_months = pop.phys$age_months)
out <- solve_1comp_lifestage(chem.name = 'Bisphenol A',
                             parameters = params,
                             days = 365,
                             start.age = 600, # age fifty
                             ref.params = ref.params,
                             doses.per.day = 3,
                             daily.dose = 1)
```

---

solve_1tri_pbtk *Solve_1tri_PBTK*

Description

This function solves for the amounts (in umol) or concentrations (in uM) of a chemical in different tissues of a pregnant woman (and her conceptus, i.e., products of conception) as functions of time based on the dose and dosing frequency.

Usage

```
solve_1tri_pbtk(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  times = seq(0, 13 * 7, 1),
  parameters = NULL,
  days = NULL,
  species = "human",
  tsteps = 4,
  dose = NULL,
  dosing.matrix = NULL,
  daily.dose = NULL,
```

```
  doses.per.day = NULL,
  initial.values = NULL,
  plots = FALSE,
  suppress.messages = FALSE,
  iv.dose = FALSE,
  input.units = "mg/kg",
  output.units = NULL,
  physchem.exclude = TRUE,
  class.exclude = TRUE,
  recalc.blood2plasma = FALSE,
  recalc.clearance = FALSE,
  adjusted.Funbound.plasma = TRUE,
  regression = TRUE,
  restrictive.clearance = TRUE,
  minimum.Funbound.plasma = 1e-04,
  monitor.vars = NULL,
  Caco2.options = list(),
  atol = 1e-08,
  rtol = 1e-08,
  ...
)
```

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
dtxsid	EPA's DSSTox Structure ID (http://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
times	Optional time sequence in days. Dosing sequence begins at the beginning of times. Default is from 0th week of pregnancy to 13th due to model representation.
parameters	Chemical parameters from parameterize_1tri_pbtk function, overrides chem.name and chem.cas.
days	Length of the simulation.
species	Included for compatibility with other functions, but the model will not run for non-human species (default "Human").
tsteps	The number time steps per hour. Default of 4.
dose	Amount of a single, initial oral dose in mg/kg BW.
dosing.matrix	A matrix of either one column (or row) with a set of dosing times or with two columns (or rows) correspondingly named "dose" and "time" containing the time and amount, in mg/kg BW, of each dose.
daily.dose	Total daily dose, mg/kg BW.
doses.per.day	Number of doses per day.
initial.values	Vector containing the initial concentrations or amounts of the chemical in specified tissues with units corresponding to compartment.units. Defaults are zero.

plots Plots all outputs if true.

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

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

input.units Input units of interest assigned to dosing, defaults to mg/kg BW

output.units A named vector of output units expected for the model results. Default, NULL, returns model results in units specified in the 'modelinfo' file. See table below for details.

physchem.exclude
Exclude chemicals on the basis of physico-chemical properties (currently only Henry's law constant) as specified by the relevant modelinfo_[MODEL] file (default TRUE).

class.exclude Exclude chemical classes identified as outside of domain of applicability by relevant modelinfo_[MODEL] file (default TRUE).

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

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

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

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

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

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

monitor.vars Which variables to track by default

Caco2.options A list of options to use when working with Caco2 apical to basolateral data Caco2.Pab, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = Fabs. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = Fgut. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See get_fbio for further details.

atol Argument passed to integrator (deSolve).

rtol Argument passed to integrator (deSolve).

... Additional arguments passed to the integrator.

Details

The model begins by default at non-pregnancy (0th week) and ends at the 13th week of pregnancy, thereby simulating the 1st trimester. This is meant to augment the fetal_pbtk model (Kapraun et al. 2022) which is limited to the 13th to 40th week window.

Note that the model parameters have units of hours while the model output is in days. Dose is in mg, not scaled for body weight.

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

The maternal compartments used in this model are the gut lumen, gut, liver, venous blood, arterial blood, lung, adipose tissue, kidney, thyroid, and rest of body. The "conceptus" compartment models an early developing fetus along with the products of conception (i.e. placenta, amniotic fluid) through which chemical exchange can occur with the maternal blood.

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.

This gestational model is only parameterized for humans.

Because this model does not simulate exhalation, inhalation, and other processes relevant to volatile chemicals, this model is by default restricted to chemicals with a logHenry's Law Constant less than that of Acetone, a known volatile chemical. That is, chemicals with logHLC > -4.5 (Log10 atm-m3/mole) are excluded. Volatility is not purely determined by the Henry's Law Constant, therefore this chemical exclusion may be turned off with the argument "physchem.exclude = FALSE". Similarly, per- and polyfluoroalkyl substances (PFAS) are excluded by default because the transporters that often drive PFAS toxicokinetics are not included in this model. However, PFAS chemicals can be included with the argument "class.exclude = FALSE".

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)

Kimberly Truong, John Wambaugh, Mark Sfeir, Dustin Kapraun

References

Truong KT, Wambaugh JF, Kapraun DF, Davidson-Fritz SE, Eytcheson S, Judson RS, Paul Friedman K (2025). "Interpretation of thyroid-relevant bioactivity data for comparison to in vivo exposures: A prioritization approach for putative chemical inhibitors of in vitro deiodinase activity." *Toxicology*. doi:10.1016/j.tox.2025.154157.

See Also

`solve_model`

`parameterize_1tri_pbtk`

Examples

```
out = solve_1tri_pbtk(chem.name = 'Bisphenol-A', daily.dose = 1,
doses.per.day = 3)
```

`solve_3comp` *Solve_3comp*

Description

This function solves for the amounts or concentrations of a chemical in the blood of three different compartments representing the body. The volumes of the three compartments are chemical specific, determined from the true tissue volumes multipled by the partition coefficients:

$$V_{pv} = V_{gut}$$

$$V_{liv} = \frac{K_{liv} * f_{up}}{R_{b:p}} V_{liver}$$

$$V_{sc} = \frac{K_{sc} * f_{up}}{R_{b:p}} V_{rest}$$

where "pv" is the portal vein, "liv" is the liver, and "sc" is the systemic compartment; V_gut, V_liver, and V_rest are physiological tissue volumes; K_x are chemical- and tissue-specific equlibrium partition coefficients between tissue and free chemcial concentration in plasma; f_up is the chemical-specific fraction unbound in plasma; and R_b:p is the chemical specific ratio of concentrations in blood:plasma. The blood concentrations evolve according to:

$$\frac{dC_{pv}}{dt} = \frac{1}{V_{pv}} \left(k_{abs} A_{si} + Q_{pv} C_{sc} - Q_{pv} C_{pv} \right)$$

$$\frac{dC_{liv}}{dt} = \frac{1}{V_{liv}} \left(Q_{pv} C_{pv} + Q_{ha} C_{sc} - \left(Q_{pv} + Qha \right) C_{liv} - \frac{1}{R_{b:p}} Cl_h C_{liv} \right)$$

$$\frac{dC_{sc}}{dt} = \frac{1}{V_{sc}} \left(\left(Q_{pv} + Q_{ha} \right) C_{liv} - \left(Q_{pv} + Q_{ha} \right) C_{sc} - \frac{f_{up}}{R_{b:p}} * Q_{GFR} * C_{sc} \right)$$

where "ha" is the hepatic artery, Q's are flows, "GFR" is the glomerular filtration rate in the kidney, clearance (scaled up from intrinsic clearance, which does not depend on flow). Plasma concentration in compartment x is given by $C_{x,plasma} = \frac{C_x}{R_{b2p}}$ for a tissue independent value of R_{b2p}.

Usage

```
solve_3comp(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  times = NULL,
  parameters = NULL,
```

```
  days = 10,
  tsteps = 4,
  daily.dose = NULL,
  dose = NULL,
  doses.per.day = NULL,
  initial.values = NULL,
  plots = FALSE,
  suppress.messages = FALSE,
  species = "Human",
  iv.dose = FALSE,
  input.units = "mg/kg",
  output.units = NULL,
  default.to.human = FALSE,
  class.exclude = TRUE,
  physchem.exclude = TRUE,
  recalc.blood2plasma = FALSE,
  recalc.clearance = FALSE,
  clint.pvalue.threshold = 0.05,
  dosing.matrix = NULL,
  adjusted.Funbound.plasma = TRUE,
  regression = TRUE,
  restrictive.clearance = TRUE,
  minimum.Funbound.plasma = 1e-04,
  Caco2.options = list(),
  monitor.vars = NULL,
  ...
)
```

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
times	Optional time sequence for specified number of days. The dosing sequence begins at the beginning of times.
parameters	Chemical parameters from parameterize_3comp function, overrides chem.name and chem.cas.
days	Length of the simulation.
tsteps	The number time steps per hour.
daily.dose	Total daily dose, mg/kg BW.
dose	Amount of a single dose, mg/kg BW.
doses.per.day	Number of doses per day.
initial.values	Vector containing the initial concentrations or amounts of the chemical in specified tissues with units corresponding to output.units. Defaults are zero.
plots	Plots all outputs if true.

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

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

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

input.units
: Input units of interest assigned to dosing, defaults to mg/kg BW

output.units
: A named vector of output units expected for the model results. Default, NULL, returns model results in units specified in the 'modelinfo' file. See table below for details.

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

class.exclude
: Exclude chemical classes identified as outside of domain of applicability by relevant modelinfo_[MODEL] file (default TRUE).

physchem.exclude
: Exclude chemicals on the basis of physico-chemical properties (currently only Henry's law constant) as specified by the relevant modelinfo_[MODEL] file (default TRUE).

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

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

clint.pvalue.threshold
: Hepatic clearances with clearance assays having p-values greater than the threshold are set to zero.

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

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

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

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

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

Caco2.options
: A list of options to use when working with Caco2 apical to basolateral data `Caco2.Pab`, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = `Fabs`. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = `Fgut`. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See `get_fbio` for further details.

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

... Additional arguments passed to the integrator (deSolve).

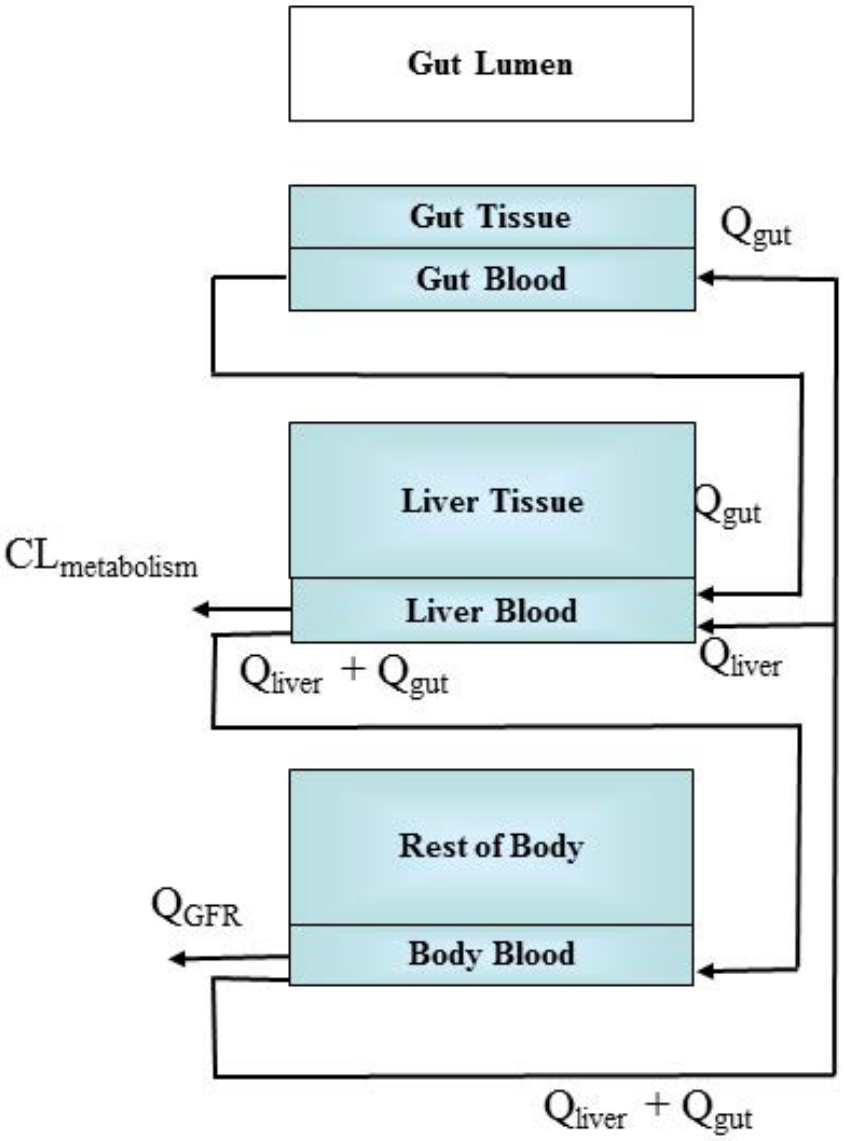
Details

Note that the timescales for 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 related to the concentration in the blood in the systemic compartment by the blood:plasma ratio.

Model Figure



altalt

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

Because this model does not simulate exhalation, inhalation, and other processes relevant to volatile chemicals, this model is by default restricted to chemicals with a logHenry's Law Constant less than that of Acetone, a known volatile chemical. That is, chemicals with logHLC > -4.5 (Log10 atm-m3/mole) are excluded. Volatility is not purely determined by the Henry's Law Constant, therefore this chemical exclusion may be turned off with the argument "physchem.exclude = FALSE". Similarly, per- and polyfluoroalkyl substances (PFAS) are excluded by default because the transporters that often drive PFAS toxicokinetics are not included in this model. However, PFAS chemicals can

be included with the argument "class.exclude = FALSE".

Value

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

Author(s)

John Wambaugh and Robert Pearce

References

Pearce RG, Setzer RW, Strope CL, Wambaugh JF, Sipes NS (2017). "Httk: R package for high-throughput toxicokinetics." *Journal of Statistical Software*, **79**(4), 1. doi:10.18637/jss.v079.i04.

See Also

solve_model

parameterize_3comp

calc_analytic_css_3comp

Examples

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


# By storing the model parameters in a vector first, you can potentially
# edit them before using the model:
params <-parameterize_3comp(chem.cas="80-05-7")
solve_3comp(parameters=params, days=1)

head(solve_3comp(chem.name="Terbufos", daily.dose=NULL, dose=1, days=1))
head(solve_3comp(chem.name="Terbufos", daily.dose=NULL, dose=1,
                 days=1, iv.dose=TRUE))

# A dose matrix specifies times and magnitudes of doses:
dm <- matrix(c(0,1,2,5,5,5),nrow=3)
colnames(dm) <- c("time","dose")
solve_3comp(chem.name="Methenamine", dosing.matrix=dm,
            dose=NULL, daily.dose=NULL,
            days=2.5)

solve_3comp(chem.name="Besonprodil",
            daily.dose=1, dose=NULL,
            days=2.5, doses.per.day=4)
```

```
# The following will not work because Diquat dibromide monohydrate's
# Henry's Law Constant (-3.912) is higher than that of Acetone (~-4.5):
try(head(solve_3comp(chem.cas = "6385-62-2")))
# However, we can turn off checking for phys-chem properties, since we know
# that  Diquat dibromide monohydrate is not too volatile:
head(solve_3comp(chem.cas = "6385-62-2", physchem.exclude = FALSE))

# Try different ways of calling the function:
head(solve_3comp(chem.name="bisphenol a",days=1))
head(solve_3comp(chem.cas="80-05-7",days=1))
head(solve_3comp(parameters=parameterize_3comp(chem.cas="80-05-7"),days=1))
```

`solve_3comp2` *Solve_3comp2*

Description

This function solves for the amounts or concentrations of a chemical in the blood of three different compartments representing the body. The volumes of the three compartments are chemical specific, determined from the true tissue volumes multipled by the partition coefficients:

$$V_{pv} = V_{gut}$$

$$V_{liv} = \frac{K_{liv} * f_{up}}{R_{b:p}} V_{liver}$$

$$V_{sc} = \frac{K_{sc} * f_{up}}{R_{b:p}} V_{rest}$$

where "pv" is the portal vein, "liv" is the liver, and "sc" is the systemic compartment; V_gut, V_liver, and V_rest are physiological tissue volumes; K_x are chemical- and tissue-specific equlibrium partition coefficients between tissue and free chemcial concentration in plasma; f_up is the chemical-specific fraction unbound in plasma; and R_b:p is the chemical specific ratio of concentrations in blood:plasma. The blood concentrations evolve according to:

$$\frac{dC_{pv}}{dt} = \frac{1}{V_{pv}} \left(k_{abs} A_{si} + Q_{pv} C_{sc} - Q_{pv} C_{pv} \right)$$

$$\frac{dC_{liv}}{dt} = \frac{1}{V_{liv}} \left(Q_{pv} C_{pv} + Q_{ha} C_{sc} - \left(Q_{pv} + Qha \right) C_{liv} - \frac{1}{R_{b:p}} Cl_h C_{liv} \right)$$

$$\frac{dC_{sc}}{dt} = \frac{1}{V_{sc}} \left(\left(Q_{pv} + Q_{ha} \right) C_{liv} - \left(Q_{pv} + Q_{ha} \right) C_{sc} - \frac{f_{up}}{R_{b:p}} * Q_{GFR} * C_{sc} \right)$$

where "ha" is the hepatic artery, Q's are flows, "GFR" is the glomerular filtration rate in the kidney, clearance (scaled up from intrinsic clearance, which does not depend on flow). Plasma concentration in compartment x is given by $C_{x,plasma} = \frac{C_x}{R_{b2p}}$ for a tissue independent value of R_{b2p}.

Usage

```
solve_3comp2(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  times = NULL,
  parameters = NULL,
  days = 10,
  tsteps = 4,
  daily.dose = NULL,
  dose = NULL,
  doses.per.day = NULL,
  initial.values = NULL,
  plots = FALSE,
  suppress.messages = FALSE,
  species = "Human",
  route = "oral",
  iv.dose = FALSE,
  input.units = "mg/kg",
  output.units = NULL,
  default.to.human = FALSE,
  physchem.exclude = TRUE,
  class.exclude = TRUE,
  recalc.blood2plasma = FALSE,
  recalc.clearance = FALSE,
  clint.pvalue.threshold = 0.05,
  dosing.matrix = NULL,
  adjusted.Funbound.plasma = TRUE,
  regression = TRUE,
  restrictive.clearance = TRUE,
  minimum.Funbound.plasma = 1e-04,
  Caco2.options = list(),
  monitor.vars = NULL,
  ...
)
```

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
times	Optional time sequence for specified number of days. The dosing sequence begins at the beginning of times.
parameters	Chemical parameters from parameterize_3comp function, overrides chem.name and chem.cas.
days	Length of the simulation.

tsteps	The number time steps per hour.
daily.dose	Total daily dose, mg/kg BW.
dose	Amount of a single dose, mg/kg BW.
doses.per.day	Number of doses per day.
initial.values	Vector containing the initial concentrations or amounts of the chemical in specified tissues with units corresponding to output.units. Defaults are zero.
plots	Plots all outputs if true.
suppress.messages	Whether or not the output message is suppressed.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
route	Route of exposure ("inhalation", "intravenous" or [DEFAULT] "oral") passed to solve_model.
iv.dose	Simulates a single i.v. dose if true.
input.units	Input units of interest assigned to dosing, defaults to mg/kg BW
output.units	A named vector of output units expected for the model results. Default, NULL, returns model results in units specified in the 'modelinfo' file. See table below for details.
default.to.human	Substitutes missing animal values with human values if true (hepatic intrinsic clearance or fraction of unbound plasma).
physchem.exclude	Exclude chemicals on the basis of physico-chemical properties (currently only Henry's law constant) as specified by the relevant modelinfo_[MODEL] file (default TRUE).
class.exclude	Exclude chemical classes identified as outside of domain of applicability by relevant modelinfo_[MODEL] file (default TRUE).
recalc.blood2plasma	Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters, calculated with hematocrit, Funbound.plasma, and Krbc2pu.
recalc.clearance	Recalculates the the hepatic clearance (Clmetabolism) with new million.cells.per.gliver parameter.
clint.pvalue.threshold	Hepatic clearances with clearance assays having p-values greater than the threshold are set to zero.
dosing.matrix	Vector of dosing times or a matrix consisting of two columns or rows named "dose" and "time" containing the time and amount, in mg/kg BW, of each dose.
adjusted.Funbound.plasma	Uses adjusted Funbound.plasma when set to TRUE along with partition coefficients calculated with this value.
regression	Whether or not to use the regressions in calculating partition coefficients.
restrictive.clearance	Protein binding not taken into account (set to 1) in liver clearance if FALSE.

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

`Caco2.options`
: A list of options to use when working with Caco2 apical to basolateral data `Caco2.Pab`, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = `Fabs`. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = `Fgut`. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See `get_fbio` for further details.

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

`...`
: Additional arguments passed to the integrator (deSolve).

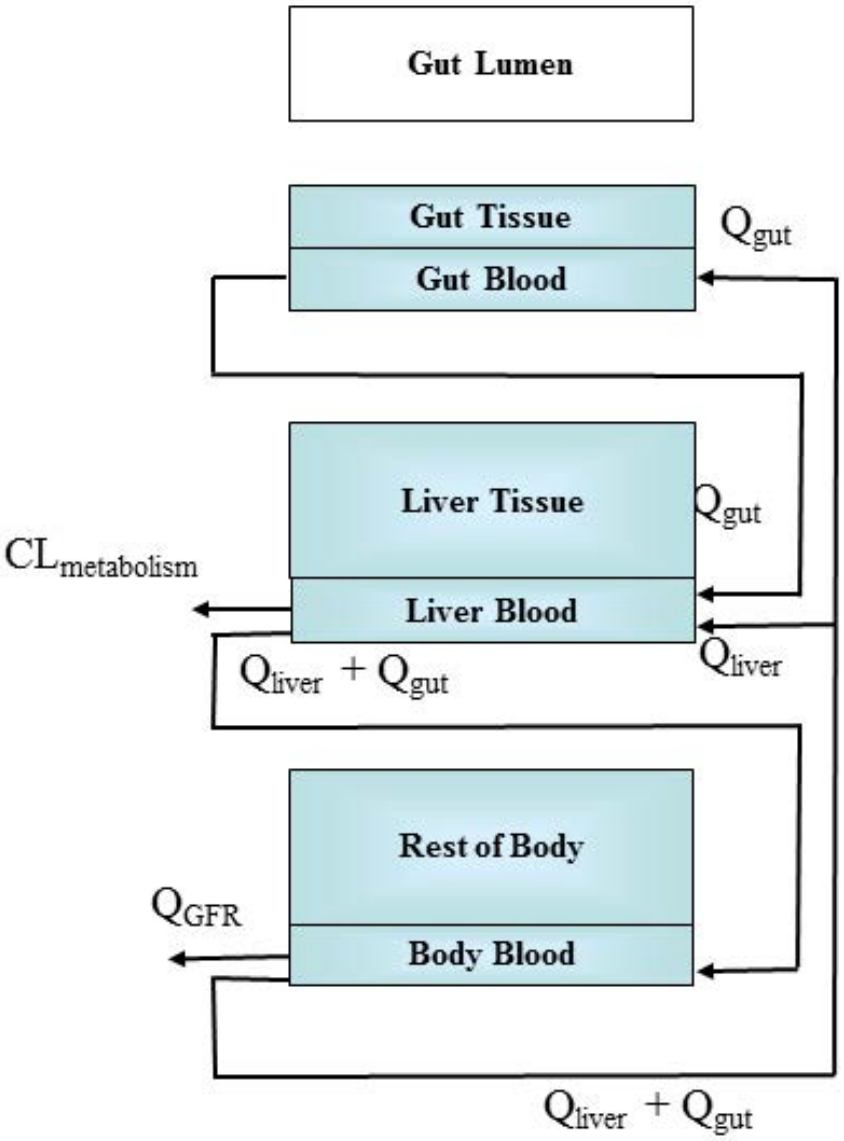
Details

Note that the timescales for 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 related to the concentration in the blood in the systemic compartment by the blood:plasma ratio.

Model Figure



altalt

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

Per- and polyfluoroalkyl substances (PFAS) are excluded by default because the transporters that often drive PFAS toxicokinetics are not included in this model. However, PFAS chemicals can be included with the argument "class.exclude = FALSE".

Value

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

Author(s)

John Wambaugh and Robert Pearce

References

Wambaugh JF, Schacht CM, Ring CL (2025). "A Simple Physiologically Based Toxicokinetic Model for Multi-Route In Vitro–In Vivo Extrapolation." *Environmental Science & Technology Letters*, **12**(3), 261–268. doi:10.1021/acs.estlett.4c00967.

See Also

`solve_model`

`parameterize_3comp`

`calc_analytic_css_3comp`

Examples

```
solve_3comp2(dtxsid="DTXSID0020573",route="inhalation",dose=1,input.units="ppmv")
```

`solve_3comp_lifestage` *Solve the* `3comp_lifestage` *model, which has time-dependent parameters*

Description

This function solves for the amounts or concentrations of a chemical in the blood of three different compartments representing the body. The volumes of the three compartments are chemical specific, determined from the true tissue volumes multipled by the partition coefficients:

$$V_{pv} = V_{gut}$$

$$V_{liv} = \frac{K_{liv} * f_{up}}{R_{b:p}} V_{liver}$$

$$V_{sc} = \frac{K_{sc} * f_{up}}{R_{b:p}} V_{rest}$$

where "pv" is the portal vein, "liv" is the liver, and "sc" is the systemic compartment; V_gut, V_liver, and V_rest are physiological tissue volumes; K_x are chemical- and tissue-specific equlibrium partition coefficients between tissue and free chemcial concentration in plasma; f_up is the chemical-specific fraction unbound in plasma; and R_b:p is the chemical specific ratio of concentrations in blood:plasma. The blood concentrations evolve according to:

$$\frac{dC_{pv}}{dt} = \frac{1}{V_{pv}}\left(k_{abs}A_{si} + Q_{pv}C_{sc} - Q_{pv}C_{pv}\right)$$

$$\frac{dC_{liv}}{dt} = \frac{1}{V_{liv}}\left(Q_{pv}C_{pv} + Q_{ha}C_{sc} - \left(Q_{pv} + Qha\right)C_{liv} - \frac{1}{R_{b:p}}Cl_hC_{liv}\right)$$

$$\frac{dC_{sc}}{dt} = \frac{1}{V_{sc}}\left(\left(Q_{pv} + Q_{ha}\right)C_{liv} - \left(Q_{pv} + Q_{ha}\right)C_{sc} - \frac{f_{up}}{R_{b:p}} * Q_{GFR} * C_{sc}\right)$$

where "ha" is the hepatic artery, Q's are flows, "GFR" is the glomerular filtration rate in the kidney, clearance (scaled up from intrinsic clearance, which does not depend on flow). Plasma concentration in compartment x is given by $C_{x,plasma} = \frac{C_x}{R_{b2p}}$ for a tissue independent value of R_{b2p}.

Usage

```
solve_3comp_lifestage(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  times = NULL,
  parameters = NULL,
  days = 10,
  tsteps = 4,
  daily.dose = NULL,
  dose = NULL,
  doses.per.day = NULL,
  initial.values = NULL,
  plots = FALSE,
  suppress.messages = FALSE,
  species = "Human",
  iv.dose = FALSE,
  input.units = "mg/kg",
  output.units = NULL,
  default.to.human = FALSE,
  recalc.blood2plasma = FALSE,
  recalc.clearance = FALSE,
  clint.pvalue.threshold = 0.05,
  dosing.matrix = NULL,
  adjusted.Funbound.plasma = TRUE,
  regression = TRUE,
  restrictive.clearance = TRUE,
  minimum.Funbound.plasma = 1e-04,
  Caco2.options = list(),
  monitor.vars = NULL,
```

```
  time.varying.params = TRUE,
  start.age = 360,
  ref.pop.dt = NULL,
 httkpop.generate.arg.list = list(method = "virtual individuals", nsamp = 25000),
  ref.params = NULL,
  ...
)
```

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
dtxsid	EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
times	Optional time sequence for specified number of days. The dosing sequence begins at the beginning of times.
parameters	Chemical parameters from parameterize_3comp function, overrides chem.name and chem.cas.
days	Length of the simulation.
tsteps	The number time steps per hour.
daily.dose	Total daily dose, mg/kg BW.
dose	Amount of a single dose, mg/kg BW.
doses.per.day	Number of doses per day.
initial.values	Vector containing the initial concentrations or amounts of the chemical in specified tissues with units corresponding to output.units. Defaults are zero.
plots	Plots all outputs if true.
suppress.messages	Whether or not the output message is suppressed.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
iv.dose	Simulates a single i.v. dose if true.
input.units	Input units of interest assigned to dosing, defaults to mg/kg BW
output.units	A named vector of output units expected for the model results. Default, NULL, returns model results in units specified in the 'modelinfo' file. See table below for details.
default.to.human	Substitutes missing animal values with human values if true (hepatic intrinsic clearance or fraction of unbound plasma).
recalc.blood2plasma	Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters, calculated with hematocrit, Funbound.plasma, and Krbc2pu.
recalc.clearance	Recalculates the the hepatic clearance (Clmetabolism) with new million.cells.per.gliver parameter.

clint.pvalue.threshold
: Hepatic clearances with clearance assays having p-values greater than the threshold are set to zero.

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

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

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

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

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

Caco2.options
: A list of options to use when working with Caco2 apical to basolateral data Caco2.Pab, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = Fabs. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = Fgut. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See get_fbio for further details.

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

time.varying.params
: Whether or not to allow parameters to vary in time according to the nonparametric regression determined by get_input_param_timeseries. Default is TRUE.

start.age
: The age of the individual in months at the beginning of the simulation. Default 360.

ref.pop.dt
: The output of httkpop_generate containing physiology of the population used in determining timeseries of parameters. Ignored if ref.params is given.

httkpop.generate.arg.list
: If ref.pop.dt is NULL, these arguments are used as input to httkpop_generate for generating physiology of a reference population.

ref.params
: Model parameters of a reference population used in determining timeseries. Recommended column binding ages in months (as age_months) to the output of create_mc_samples.

...
: Additional arguments passed to the integrator (deSolve).

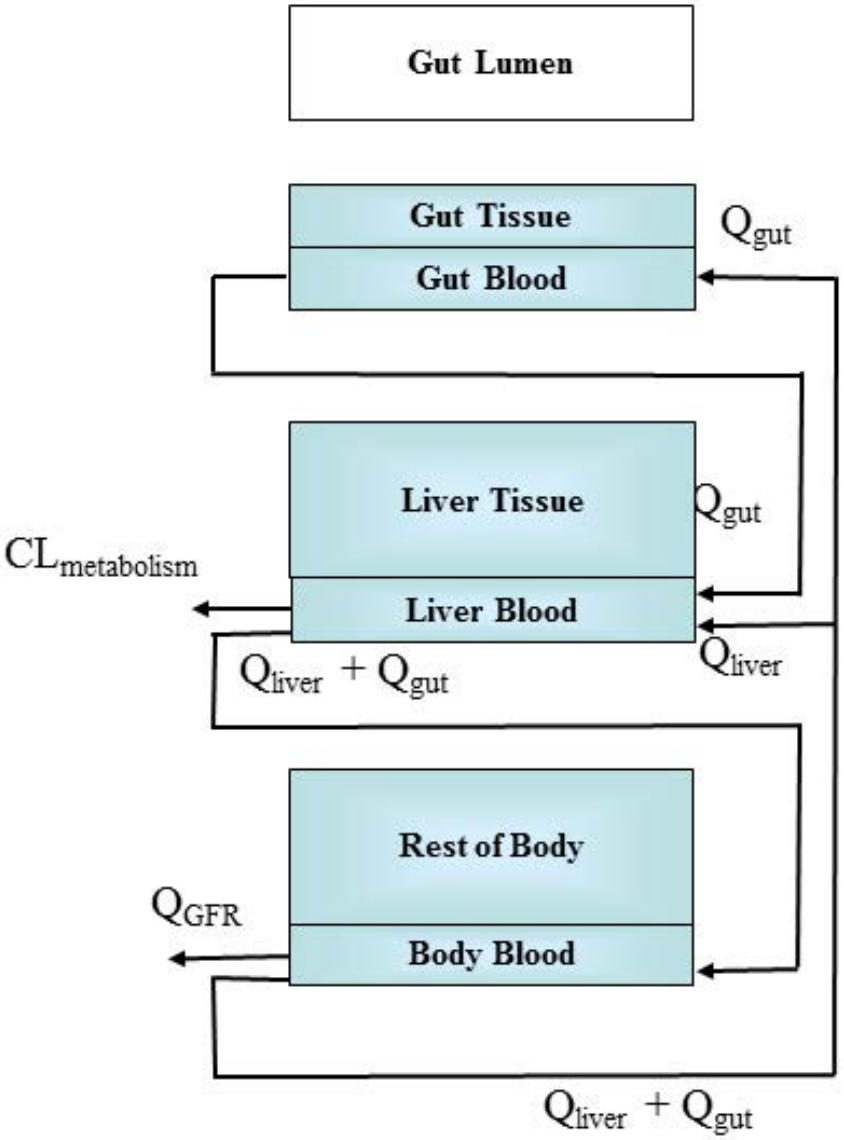
Details

Note that the timescales for 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 related to the concentration in the blood in the systemic compartment by the blood:plasma ratio.

Model Figure



altalt

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

Value

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

Author(s)

Colin Thomson

See Also

solve_model

parameterize_3comp

Examples

```
params <- parameterize_3comp(chem.name = 'Bisphenol A')

pop.phys <- httkpop_generate(method = 'virtual individuals',
                             nsamp = 25000,
                             agelim_years = c(18, 79),
                             weight_category = c("Normal"))
pop.params <- create_mc_samples(chem.name = 'Bisphenol A',
                                model = '3compartment',
                                httkpop.dt = pop.phys)
ref.params <- cbind(pop.params,
                    age_months = pop.phys$age_months)
out <- solve_3comp_lifestage(chem.name = 'Bisphenol A',
                             parameters = params,
                             days = 365,
                             start.age = 600, # age fifty
                             ref.params = ref.params,
                             doses.per.day = 3,
                             daily.dose = 1)
```

---

solve_fetal_pbtk *Solve_fetal_PBTK*

Description

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

Usage

```
solve_fetal_pbtk(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  times = seq(13 * 7, 40 * 7, 1),
  parameters = NULL,
  days = NULL,
  species = "human",
  tsteps = 1,
  dose = NULL,
  dosing.matrix = NULL,
  daily.dose = NULL,
  doses.per.day = NULL,
  initial.values = NULL,
  plots = FALSE,
  suppress.messages = FALSE,
  iv.dose = FALSE,
  input.units = "mg/kg",
  output.units = NULL,
  physchem.exclude = TRUE,
  class.exclude = TRUE,
  recalc.blood2plasma = FALSE,
  recalc.clearance = FALSE,
  adjusted.Funbound.plasma = TRUE,
  regression = TRUE,
  restrictive.clearance = TRUE,
  minimum.Funbound.plasma = 1e-04,
  monitor.vars = NULL,
  Caco2.options = list(),
  atol = 1e-06,
  rtol = 1e-06,
  ...
)
```

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
dtxsid	EPA's DSSTox Structure ID (http://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
times	Optional time sequence in days. Dosing sequence begins at the beginning of times. Default is from 13th week of pregnancy to 40th due to data constraints.
parameters	Chemical parameters from parameterize_fetal_pbtk function, overrides chem.name and chem.cas.
days	Length of the simulation.

species	Included for compatibility with other functions, but the model will not run for non-human species (default "Human").
tsteps	The number time steps per hour. Default of 4.
dose	Amount of a single, initial oral dose in mg/kg BW.
dosing.matrix	A matrix of either one column (or row) with a set of dosing times or with two columns (or rows) correspondingly named "dose" and "time" containing the time and amount, in mg/kg BW, of each dose.
daily.dose	Total daily dose, mg/kg BW.
doses.per.day	Number of doses per day.
initial.values	Vector containing the initial concentrations or amounts of the chemical in specified tissues with units corresponding to compartment.units. Defaults are zero.
plots	Plots all outputs if true.
suppress.messages	Whether or not the output message is suppressed.
iv.dose	Simulates a single i.v. dose if true.
input.units	Input units of interest assigned to dosing, defaults to mg/kg BW
output.units	A named vector of output units expected for the model results. Default, NULL, returns model results in units specified in the 'modelinfo' file. See table below for details.
physchem.exclude	Exclude chemicals on the basis of physico-chemical properties (currently only Henry's law constant) as specified by the relevant modelinfo_[MODEL] file (default TRUE).
class.exclude	Exclude chemical classes identified as outside of domain of applicability by relevant modelinfo_[MODEL] file (default TRUE).
recalc.blood2plasma	Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters, calculated with hematocrit, Funbound.plasma, and Krbc2pu.
recalc.clearance	Recalculates the the hepatic clearance (Clmetabolism) with new million.cells.per.gliver parameter.
adjusted.Funbound.plasma	Uses adjusted Funbound.plasma when set to TRUE along with partition coefficients calculated with this value.
regression	Whether or not to use the regressions in calculating partition coefficients.
restrictive.clearance	Protein binding not taken into account (set to 1) in liver clearance if FALSE.
minimum.Funbound.plasma	Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset).
monitor.vars	Which variables to track by default

Caco2.options	A list of options to use when working with Caco2 apical to basolateral data Caco2.Pab, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = Fabs. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = Fgut. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See get_fbio for further details.
atol	Absolute tolerance used by integrator (deSolve) to determine numerical precision– defaults to 1e-8.
rtol	Relative tolerance used by integrator (deSolve) to determine numerical precision – defaults to 1e-8.
...	Additional arguments passed to the integrator.

Details

The stage of pregnancy simulated here begins by default at the 13th week due to a relative lack of data to support parameterization prior, in line with the recommendations of Kapraun et al. 2019 ("Empirical models for anatomical and physiological..."), and ends at the 40th week of pregnancy.

Note that the model parameters have units of hours while the model output is in days. Dose is in mg, not scaled for body weight.

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

The maternal compartments used in this model are the gut lumen, gut, liver, venous blood, arterial blood, lung, adipose tissue, kidney, thyroid, and rest of body. A placenta is modeled as a joint organ shared by mother and fetus, through which chemical exchange can occur with the fetus. Fetal compartments include arterial blood, venous blood, kidney, thyroid, liver, lung, gut, brain, and rest of 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.

This gestational model is only parameterized for humans.

Because this model does not simulate exhalation, inhalation, and other processes relevant to volatile chemicals, this model is by default restricted to chemicals with a logHenry's Law Constant less than that of Acetone, a known volatile chemical. That is, chemicals with logHLC > -4.5 (Log10 atm-m3/mole) are excluded. Volatility is not purely determined by the Henry's Law Constant, therefore this chemical exclusion may be turned off with the argument "physchem.exclude = FALSE". Similarly, per- and polyfluoroalkyl substances (PFAS) are excluded by default because the transporters that often drive PFAS toxicokinetics are not included in this model. However, PFAS chemicals can be included with the argument "class.exclude = FALSE".

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, Mark Sfeir, and Dustin Kapraun

References

Kapraun DF, Sfeir M, Pearce RG, Davidson-Fritz SE, Lumen A, Dallmann A, Judson RS, Wambaugh JF (2022). "Evaluation of a rapid, generic human gestational dose model." *Reproductive Toxicology*, **113**, 172–188. doi:10.1016/j.reprotox.2022.09.004.

See Also

solve_model

parameterize_fetal_pbtk

Examples

```
out = solve_fetal_pbtk(chem.name = 'bisphenol a', daily.dose = 1,
doses.per.day = 3)

# With adjustement to fraction unbound plasma for fetus:
fetal_parms_fup_adjusted <-
  parameterize_fetal_pbtk(chem.name = "triclosan")
head(solve_fetal_pbtk(parameters = fetal_parms_fup_adjusted))

# Without adjustement to fraction unbound plasma for fetus:
fetal_parms_fup_unadjusted <-
  parameterize_fetal_pbtk(chem.name = "triclosan",
                          fetal_fup_adjustment = FALSE)
head(solve_fetal_pbtk(parameters = fetal_parms_fup_unadjusted))

# The following will not work because Diquat dibromide monohydrate's
# Henry's Law Constant (-3.912) is higher than that of Acetone (~-4.5):
try(head(solve_fetal_pbtk(chem.cas = "6385-62-2")))
# However, we can turn off checking for phys-chem properties, since we know
# that  Diquat dibromide monohydrate is not too volatile:
head(solve_fetal_pbtk(chem.cas = "6385-62-2", physchem.exclude = FALSE))

# Try different ways to call the function:
head(solve_fetal_pbtk(chem.cas="80-05-7"))
head(solve_fetal_pbtk(parameters=parameterize_fetal_pbtk(chem.cas="80-05-7")))
```

---

solve_full_pregnancy *Solve_full_pregnancy*

Description

This function solves for the amounts (in umol) or concentrations (in uM) of a chemical in different tissues of a maternal-fetal system over the full course of human pregnancy given a dose and dosing frequency.

Usage

```
solve_full_pregnancy(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  time.course = seq(0, 40 * 7, 1),
  dose = NULL,
  daily.dose = NULL,
  doses.per.day = NULL,
  class.exclude = TRUE,
  physchem.exclude = TRUE,
  track.vars = NULL,
  plt = FALSE
)
```

Arguments

chem.name	Either the chemical name, CAS number, or DTXSID must be specified.
chem.cas	Either the chemical name, CAS number, or DTXSID must be specified.
dtxsid	EPA's DSSTox Structure ID (http://comptox.epa.gov/dashboard)
time.course	Time sequence in days. Default is from 0th week of pregnancy to 40th, incremented by day.
dose	Amount of a single, initial dose (on day 0) in mg/kg BW.
daily.dose	Total daily dose, mg/kg BW for 40 weeks.
doses.per.day	Number of doses per day for 40 weeks.
class.exclude	Exclude chemical classes identified as outside of domain of applicability for fetal_pbtk and 1tri_pbtk models (i.e. PFAS chemicals).
physchem.exclude	Exclude chemicals on the basis of physico-chemical properties (currently only Henry's law constant) as specified by the modelinfo files for fetal_pbtk and 1tri_pbtk.
track.vars	which variables to return in solution output dataframe
plt	plots all outputs, if TRUE

Details

The simulation starts at the 0th week and ends at 40 weeks of pregnancy (term), covering all trimesters of human pregnancy. This is accomplished by stitching together the 1tri and fetal PBTK models with appropriate initial conditions, as described in Truong et al. (TBD).

Value

A matrix with columns for time (in days), each compartment, the area under the curve (for plasma vs time), and plasma, and a row for each time point.

Author(s)

Kimberly Truong

References

Kapraun DF, Sfeir M, Pearce RG, Davidson-Fritz SE, Lumen A, Dallmann A, Judson RS, Wambaugh JF (2022). "Evaluation of a rapid, generic human gestational dose model." *Reproductive Toxicology*, **113**, 172–188. doi:10.1016/j.reprotox.2022.09.004.

Truong KT, Wambaugh JF, Kapraun DF, Davidson-Fritz SE, Eytcheson S, Judson RS, Paul Friedman K (2025). "Interpretation of thyroid-relevant bioactivity data for comparison to in vivo exposures: A prioritization approach for putative chemical inhibitors of in vitro deiodinase activity." *Toxicology*. doi:10.1016/j.tox.2025.154157.

See Also

solve_1tri_pbtk

solve_fetal_pbtk

parameterize_1tri_pbtk

parameterize_fetal_pbtk

Examples

```
# dosing schedule of 1 mg/kg BW/day for 40 weeks
# return solution by hour
out <- solve_full_pregnancy(chem.name = "fipronil",
                            daily.dose = 1,
                            doses.per.day = 1,
                            time.course = seq(0, 40*7, 1/24))


# return solution in chemical amounts for fetal compartments + placenta
maternal_compts <- c('gutlumen', 'gut', 'liver', 'kidney', 'lung', 'ven', 'art',
'adipose','thyroid', 'rest')

fetal_compts <- c(maternal_compts[! maternal_compts %in% c('adipose', 'gutlumen') ],
"brain")

amt.out <- solve_full_pregnancy(chem.name = "fipronil",
                                daily.dose = 1,
                                doses.per.day = 1,
                                time.course = seq(0, 40*7, 1),
                                track.vars = c(paste0("Af", fetal_compts), "Aplacenta"))
```

```
# return solution in concentrations for fetal compartments + placenta
conc.out <- solve_full_pregnancy(chem.name = "fipronil",
                                 daily.dose = 1,
                                 doses.per.day = 1,
                                 time.course = seq(0, 40*7, 1),
                                 track.vars = c(paste0("Cf", fetal_compts), "Cplacenta"))

# plot solution based on output
plt.out <- solve_full_pregnancy(chem.name = "genistein",
                                 dose = 1, plt = TRUE)
```

`solve_gas_pbtk` *solve_gas_pbtk*

Description

This function solves for the amounts or concentrations of a chemical in different tissues as functions of time as a result of inhalation exposure to an ideal gas. In this PBTK formulation. C_{tissue} is the concentration in tissue at time t. Since the perfusion limited partition coefficients describe instantaneous equilibrium between the tissue and the free fraction in plasma, the whole plasma concentration is $C_{tissue,plasma} = \frac{1}{f_{up} * K_{tissue2fup}} * C_{tissue}$. Note that we use a single, constant value of f_{up} across all tissues. Corespondingly the free plasma concentration is modeled as $C_{tissue,freeplasma} = \frac{1}{K_{tissue2fup}} * C_tissue$. The amount of blood flowing from tissue x is Q_{tissue} (L/h) at a concentration $C_{x,blood} = \frac{R_{b2p}}{f_{up} * K_{tissue2fup}} * C_{tissue}$, where we use a single R_{b2p} value throughout the body. Metabolic clearance is modelled as being from the total plasma concentration here, though it is restricted to the free fraction in `calc_hep_clearance` by default. Renal clearance via glomerulsr filtration is from the free plasma concentration.

Usage

```
solve_gas_pbtk(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  times = NULL,
  days = 10,
  tsteps = 4,
  daily.dose = NULL,
  doses.per.day = NULL,
  dose = NULL,
  dosing.matrix = NULL,
  forcings = NULL,
  exp.start.time = 0,
  exp.conc = 1,
```

```
  period = 24,
  exp.duration = 12,
  initial.values = NULL,
  plots = FALSE,
  suppress.messages = FALSE,
  species = "Human",
  iv.dose = FALSE,
  input.units = "ppmv",
  output.units = NULL,
  default.to.human = FALSE,
  class.exclude = TRUE,
  physchem.exclude = TRUE,
  recalc.blood2plasma = FALSE,
  recalc.clearance = FALSE,
  adjusted.Funbound.plasma = TRUE,
  regression = TRUE,
  restrictive.clearance = FALSE,
  minimum.Funbound.plasma = 1e-04,
  monitor.vars = NULL,
  vmax = 0,
  km = 1,
  exercise = FALSE,
  fR = 12,
  VT = 0.75,
  VD = 0.15,
  Caco2.options = list(),
  ...
)
```

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
parameters	Chemical parameters from parameterize_gas_pbtk (or other bespoke) function, overrides chem.name and chem.cas.
times	Optional time sequence for specified number of days. Dosing sequence begins at the beginning of times.
days	Length of the simulation.
tsteps	The number of time steps per hour.
daily.dose	Total daily dose
doses.per.day	Number of doses per day.
dose	Amount of a single dose
dosing.matrix	Vector of dosing times or a matrix consisting of two columns or rows named "dose" and "time" containing the time and amount of each dose.

forcings	Manual input of 'forcings' data series argument for ode integrator. If left unspecified, 'forcings' defaults to NULL, and then other input parameters (see exp.start.time, exp.conc, exp.duration, and period) provide the necessary information to assemble a forcings data series.
exp.start.time	Start time in specifying forcing exposure series, default 0.
exp.conc	Specified inhalation exposure concentration for use in assembling "forcings" data series argument for integrator. Defaults to units of ppmv.
period	For use in assembling forcing function data series 'forcings' argument, specified in hours
exp.duration	For use in assembling forcing function data series 'forcings' argument, specified in hours
initial.values	Vector containing the initial concentrations or amounts of the chemical in specified tissues with units corresponding to those specified for the model outputs. Default values 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.
input.units	Input units of interest assigned to dosing, including forcings. Defaults to "ppmv" as applied to the default forcings scheme.
output.units	A named vector of output units expected for the model results. Default, NULL, returns model results in units specified in the 'modelinfo' file. See table below for details.
default.to.human	Substitutes missing animal values with human values if true (hepatic intrinsic clearance or fraction of unbound plasma).
class.exclude	Exclude chemical classes identified as outside of domain of applicability by relevant modelinfo_[MODEL] file (default TRUE).
physchem.exclude	Exclude chemicals on the basis of physico-chemical properties (currently only Henry's law constant) as specified by the relevant modelinfo_[MODEL] file (default TRUE).
recalc.blood2plasma	Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters, calculated with hematocrit, Funbound.plasma, and Krbc2pu.
recalc.clearance	Recalculates the hepatic clearance (Clmetabolism) with new million.cells.per.gliver parameter.
adjusted.Funbound.plasma	Uses adjusted Funbound.plasma when set to TRUE along with partition coefficients calculated with this value.
regression	Whether or not to use the regressions in calculating partition coefficients.

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

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

monitor.vars
: Which variables are returned as a function of time. Defaults value of NULL provides "Cgut", "Cliver", "Cven", "Clung", "Cart", "Crest", "Ckidney", "Cplasma", "Calv", "Cendexh", "Cmixexh", "Cmuc", "Atubules", "Ametabolized", "AUC"

vmax
: Michaelis-Menten vmax value in reactions/min

km
: Michaelis-Menten concentration of half-maximal reaction velocity in desired output concentration units.

exercise
: Logical indicator of whether to simulate an exercise-induced heightened respiration rate

fR
: Respiratory frequency (breaths/minute), used especially to adjust breathing rate in the case of exercise. This parameter, along with VT and VD (below) gives another option for calculating Qalv (Alveolar ventilation) in case pulmonary ventilation rate is not known

VT
: Tidal volume (L), to be modulated especially as part of simulating the state of exercise

VD
: Anatomical dead space (L), to be modulated especially as part of simulating the state of exercise

Caco2.options
: A list of options to use when working with Caco2 apical to basolateral data `Caco2.Pab`, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = `Fabs`. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = `Fgut`. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See `get_fbio` for further details.

...
: Additional arguments passed to the integrator (deSolve). (Note: There are precision differences between M1 Mac and other OS systems for this function due to how long doubles are handled. To replicate results between various OS systems we suggest changing the default method of "lsoda" to "lsode" and also adding the argument mf = 10. See [deSolve::ode()] for further details.)

Details

The default dosing scheme involves a specification of the start time of exposure (exp.start.time), the concentration of gas inhaled (exp.conc), the period of a cycle of exposure and non-exposure (period), the duration of the exposure during that period (exp.duration), and the total days simulated. Together,these arguments determine the "forcings" passed to the ODE integrator. Forcings can also be specified manually, or effectively turned off by setting exposure concentration to zero, if the user prefers to simulate dosing by other means.

The "forcings" object is configured to be passed to the integrator with, at the most, a basic unit conversion among ppmv, mg/L, and uM. No scaling by BW is set to be performed on the forcings series.

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

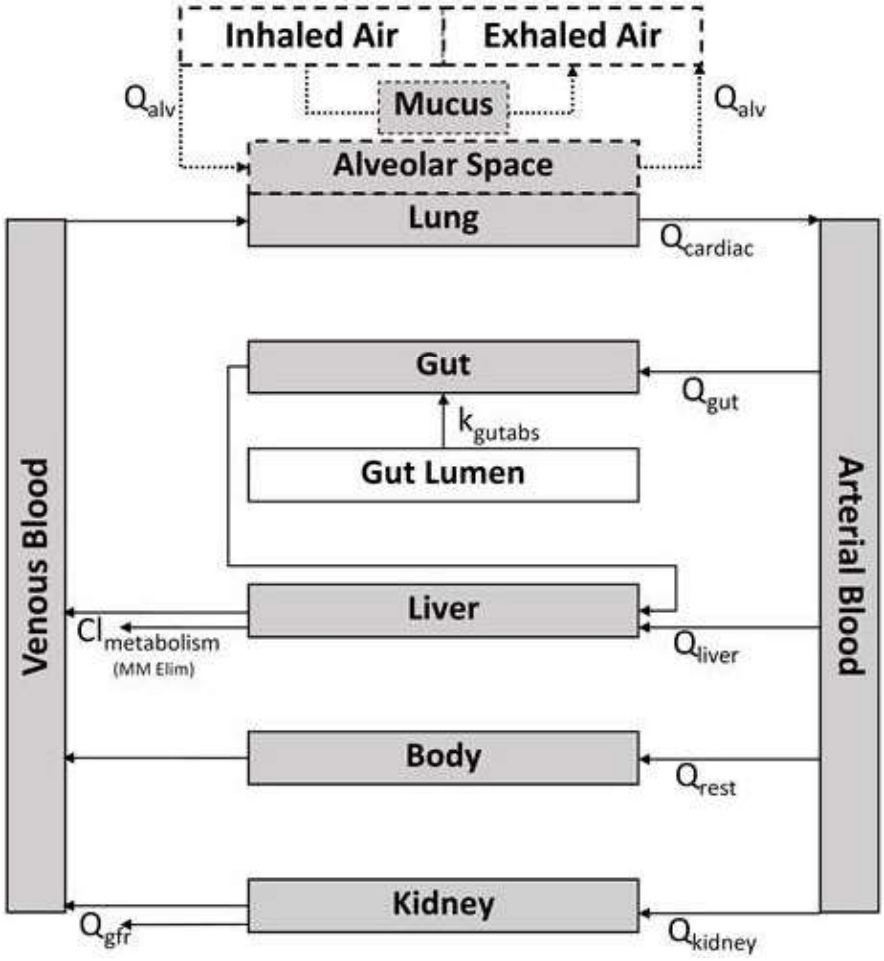
Default NULL value for doses.per.day solves for a single dose.

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

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

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

Model Figure from (Linakis et al. 2020):



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Model parameters are named according to the following convention:

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

When species is specified but chemical-specific in vitro data are not available, the function uses the

appropriate physiological data (volumes and flows) but default.to.human = TRUE must be used to substitute human fraction unbound, partition coefficients, and intrinsic hepatic clearance.

Per- and polyfluoroalkyl substances (PFAS) are excluded by default because the transporters that often drive PFAS toxicokinetics are not included in this model. However, PFAS chemicals can be included with the argument "class.exclude = FALSE".

Value

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

Author(s)

Matt Linakis, John Wambaugh, Mark Sfeir, Miyuki Breen

References

Linakis MW, Sayre RR, Pearce RG, Sfeir MA, Sipes NS, Pangburn HA, Gearhart JM, Wambaugh JF (2020). "Development and evaluation of a high-throughput inhalation model for organic chemicals." *Journal of exposure science & environmental epidemiology*, **30**(5), 866–877. doi:10.1038/s41370-0200238y.

See Also

solve_model

parameterize_gas_pbtk

Examples

```
solve_gas_pbtk(chem.name = 'pyrene', exp.conc = 1, period = 24, expduration = 24)

out <- solve_gas_pbtk(chem.name='pyrene',
                      exp.conc = 0, doses.per.day = 2,
                      daily.dose = 3, input.units = "umol",
                      days=2.5,
                      plots=TRUE, initial.values=c(Aven=20))

out <- solve_gas_pbtk(chem.name = 'pyrene', exp.conc = 3,
                      period = 24, days=2.5,
                      exp.duration = 6, exercise = TRUE)

params <- parameterize_gas_pbtk(chem.cas="80-05-7")
solve_gas_pbtk(parameters=params, days=2.5)

# Oral dose with exhalation as a route of elimination:
out <- solve_gas_pbtk(chem.name = 'bisphenol a', exp.conc = 0, dose=100,
                      days=2.5, input.units="mg/kg")

# Note that different model compartments for this model have different units
# and that the final units can be controlled with the output.units argument:
```

```
head(solve_gas_pbtk(chem.name="lindane", days=2.5))
# Convert all compartment units to mg/L:
head(solve_gas_pbtk(chem.name="lindane", days=2.5, output.units="mg/L"))
# Convert just the plasma to mg/L:
head(solve_gas_pbtk(chem.name="lindane", days=2.5,
                    output.units=list(Cplasma="mg/L")))

signif(head(solve_gas_pbtk(chem.cas="129-00-0",times=c(0,0.1,0.05),
                    method = "lsode",mf = 10)),2)
signif(head(solve_gas_pbtk(
  parameters=parameterize_gas_pbtk(chem.cas="129-00-0"),
  times=c(0,0.1,0.05),
  method = "lsode",mf = 10)),2)
```

`solve_model` *Solve_model*

Description

solve_model is designed to accept systematized metadata (provided by the model.list defined in the modelinfo files) for a given toxicokinetic model, including names of variables, parameterization functions, and key units, and use it along with chemical information to prepare an ode system for numerical solution over time of the amounts or concentrations of chemical in different bodily compartments of a given species (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").

Usage

```
solve_model(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  times = NULL,
  parameters = NULL,
  model = NULL,
  route = "oral",
  dosing = NULL,
  days = 10,
  tsteps = 4,
  initial.values = NULL,
  initial.value.units = NULL,
  plots = FALSE,
  monitor.vars = NULL,
  suppress.messages = FALSE,
  species = "Human",
  input.units = "mg/kg",
  output.units = NULL,
```

```
  method = NULL,
  rtol = 1e-06,
  atol = 1e-06,
  recalc.blood2plasma = FALSE,
  recalc.clearance = FALSE,
  parameterize.args.list = list(),
  small.time = 1e-04,
  forcings = NULL,
  ...
)
```

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
times	Optional time sequence for specified number of output times (in days) to be returned by the function. The model is solved explicitly at the time sequence specified. Dosing sequence begins at the first time provided.
parameters	List of chemical parameters, as output by parameterize_pbtk function. Overrides chem.name and chem.cas.
model	Specified model to use in simulation: "pbtk", "3compartment", "3compartmentss", "1compartment", "schmitt", ...
route	String specification of route of exposure for simulation: "oral", "iv", "inhalation", ...
dosing	List of dosing metrics used in simulation, which includes the namesake entries of a model's associated dosing.params. In the case of most httk models, these should include "initial.dose", "doses.per.day", "daily.dose", and "dosing.matrix". The "dosing.matrix" is used for more precise dose regimen specification, and is a matrix consisting of two columns or rows named "time" and "dose" containing the time and amount of each dose. If none of the namesake entries of the dosing list is set to a non-NULL value, solve_model uses a default initial dose of 1 mg/kg BW along with the dose type (add/multiply) specified for a given route (for example, add the dose to gut lumen for oral route)
days	Simulated period. Default 10 days.
tsteps	The number of time steps per hour. Default of 4.
initial.values	Vector of numeric values containing the initial concentrations or amounts of the chemical in specified tissues with units corresponding to those specified for the model outputs. Default values are zero.
initial.value.units	Vector of character strings containing the units corresponding to 'initial.values' specified for the model outputs. Default is assuming the units match expected compartment units for the model.
plots	Plots all outputs if true.

`monitor.vars` Which variables are returned as a function of time. Default values of NULL looks up variables specified in modelinfo_MODEL.R

`suppress.messages` Whether or not the output messages are suppressed.

`species` Species desired (models have been designed to be parameterized for some subset of the following species: "Rat", "Rabbit", "Dog", "Mouse", or default "Human").

`input.units` Input units of interest assigned to dosing. Defaults to mg/kg BW, in line with the default dosing scheme of a one-time dose of 1 mg/kg in which no other dosing parameters are specified.

`output.units` Output units of interest for the compiled components. Defaults to NULL, and will provide values in model units if unspecified.

`method` Method used by integrator (deSolve).

`rtol` Relative tolerance used by integrator (deSolve) to determine numerical precision – defaults to 1e-6.

`atol` Absolute tolerance used by integrator (deSolve) to determine

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

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

`parameterize.args.list` Additional parameters passed to the model parameterization function (other than chemical identifier, ‘species‘, ‘suppress.messages‘, ‘restrictive.clearance‘, ‘adjusted.Funbound.plasma‘, and ‘minimum.Funbound.plasma‘)

`small.time` A tiny amount of time used to provide predictions on either side of an instantaneous event (like an iv injection). This helps ensure that abrupt changes plot well. Defaults to 1e-4.

`forcings` A way of passing time-dependent quantities to the ODE solver. Should take the form of a list of two-column matrices with the first column containing time values and the second column the value of quantity at those times. Default NULL.

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

Details

Dosing values with certain acceptable associated input.units (like mg/kg BW) are configured to undergo a unit conversion. All model simulations are intended to run with units as specifed by "compartment.units" in the model.list (as defined by the modelinfo files).

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

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

Model parameters are named according to the following convention:

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

When species is specified but chemical-specific in vitro data are not available, the function uses the appropriate physiological data (volumes and flows) but default.to.human = TRUE must be used to substitute human fraction unbound, partition coefficients, and intrinsic hepatic clearance. (NOTE: The 'default.to.human' specification should be included as part of the arguments listed in 'parameterize.args.list'.)

For both plotting purposes and helping the numerical equation solver, it is helpful to specify that time points shortly before and after dosing are included. This function automatically add these points, and they are returned to the user unless the times argument is used, in which case only the time points specified by that argument are provided.

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, Robert Pearce, Miyuki Breen, Mark Sfeir, and Sarah E. Davidson

References

Pearce RG, Setzer RW, Strope CL, Wambaugh JF, Sipes NS (2017). "Httk: R package for high-throughput toxicokinetics." *Journal of Statistical Software*, **79**(4), 1. doi:10.18637/jss.v079.i04. Davidson-Fritz SE, Ring CL, Evans MV, Schacht CM, Chang X, Breen M, Honda GS, Kenyon E, Linakis MW, Meade A, others (2025). "Enabling Transparent Toxicokinetic Modeling for Public Health Risk Assessment." *PLOS ONE*, **20**(4), 1-40. doi:10.1371/journal.pone.0321321.

Examples

```
# The various "solve_x" functions are wrappers for solve_model:
head(solve_pbtk(chem.name="Terbufos", days=1))

head(solve_model(chem.name="Terbufos",model="pbtk",
                 days=1,
                 dosing=list(
                   initial.dose = 1, # Assume dose is in mg/kg BW/day
                   doses.per.day=NULL,
                   dosing.matrix = NULL,
```

```
                    daily.dose = NULL)))


# A dose matrix specifies times and magnitudes of doses:
dm <- matrix(c(0,1,2,5,5,5),nrow=3)
colnames(dm) <- c("time","dose")

solve_pbtk(chem.name="Methenamine",
           dosing.matrix=dm,
           dose=NULL,
           days=2.5,
           daily.dose=NULL)

solve_model(chem.name="Methenamine",
            model="pbtk",
            days=2.5,
            dosing=list(
              initial.dose =NULL,
              doses.per.day=NULL,
              daily.dose=NULL,
              dosing.matrix=dm))

solve_model(chem.name="Besonprodil",
            model="pbtk",
            days=2.5,
            dosing=list(
              initial.dose=NULL,
              doses.per.day=4,
              daily.dose=1,
              dosing.matrix=NULL))

solve_pbtk(chem.name="Besonprodil",
           daily.dose=1,
           dose=NULL,
           doses.per.day=4,
           days=2.5)
```

`solve_pbtk` *Solve_PBTK*

Description

This function solves for the amounts or concentrations in uM of a chemical in different tissues as functions of time based on the dose and dosing frequency. In this PBTK formulation. C_{tissue} is the concentration in tissue at time t. Since the perfusion limited partition coefficients describe instantaneous equilibrium between the tissue and the free fraction in plasma, the whole plasma concentration is $C_{tissue,plasma} = \frac{1}{f_{up} * K_{tissue2fup}} * C_{tissue}$. Note that we use a single, constant value of f_{up} across all tissues. Corespondingly the free plasma concentration is modeled

as $C_{tissue,freeplasma} = \frac{1}{K_{tissue2fup}} * C_tissue$. The amount of blood flowing from tissue x is Q_{tissue} (L/h) at a concentration $C_{x,blood} = \frac{R_{b2p}}{f_{up} * K_{tissue2fup}} * C_{tissue}$, where we use a single R_{b2p} value throughout the body. Metabolic clearance is modelled as being from the total plasma concentration here, though it is restricted to the free fraction in calc_hep_clearance by default. Renal clearance via glomerulsr filtration is from the free plasma concentration. 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.

Usage

```
solve_pbtk(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  times = NULL,
  parameters = NULL,
  days = 10,
  tsteps = 4,
  daily.dose = NULL,
  dose = NULL,
  doses.per.day = NULL,
  initial.values = NULL,
  plots = FALSE,
  suppress.messages = FALSE,
  species = "Human",
  iv.dose = FALSE,
  input.units = "mg/kg",
  output.units = NULL,
  default.to.human = FALSE,
  class.exclude = TRUE,
  physchem.exclude = TRUE,
  recalc.blood2plasma = FALSE,
  recalc.clearance = FALSE,
  dosing.matrix = NULL,
  adjusted.Funbound.plasma = TRUE,
  regression = TRUE,
  restrictive.clearance = TRUE,
  minimum.Funbound.plasma = 1e-04,
  Caco2.options = list(),
  monitor.vars = NULL,
  ...
)
```

Arguments

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

dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
times	Optional time sequence for specified number of days. Dosing sequence begins at the beginning of times.
parameters	Chemical parameters from parameterize_pbtk function, overrides chem.name and chem.cas.
days	Length of the simulation.
tsteps	The number of time steps per hour.
daily.dose	Total daily dose, defaults to mg/kg BW.
dose	Amount of a single, initial oral dose in mg/kg BW.
doses.per.day	Number of doses per day.
initial.values	Vector containing the initial concentrations or amounts of the chemical in specified tissues with units corresponding to output.units. Defaults are zero.
plots	Plots all outputs if true.
suppress.messages	Whether or not the output message is suppressed.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
iv.dose	Simulates a single i.v. dose if true.
input.units	Input units of interest assigned to dosing, defaults to mg/kg BW
output.units	A named vector of output units expected for the model results. Default, NULL, returns model results in units specified in the 'modelinfo' file. See table below for details.
default.to.human	Substitutes missing animal values with human values if true (hepatic intrinsic clearance or fraction of unbound plasma).
class.exclude	Exclude chemical classes identified as outside of domain of applicability by relevant modelinfo_[MODEL] file (default TRUE).
physchem.exclude	Exclude chemicals on the basis of physico-chemical properties (currently only Henry's law constant) as specified by the relevant modelinfo_[MODEL] file (default TRUE).
recalc.blood2plasma	Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters, calculated with hematocrit, Funbound.plasma, and Krbc2pu.
recalc.clearance	Recalculates the the hepatic clearance (Clmetabolism) with new million.cells.per.gliver parameter.
dosing.matrix	Vector of dosing times or a matrix consisting of two columns or rows named "dose" and "time" containing the time and amount, in mg/kg BW, of each dose.
adjusted.Funbound.plasma	Uses adjusted Funbound.plasma when set to TRUE along with partition coefficients calculated with this value.
regression	Whether or not to use the regressions in calculating partition coefficients.

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

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

`Caco2.options`
: A list of options to use when working with Caco2 apical to basolateral data `Caco2.Pab`, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = `Fabs`. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = `Fgut`. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See `get_fbio` for further details.

`monitor.vars`
: Which variables are returned as a function of time. The default value of NULL provides "Cgut", "Cliver", "Cven", "Clung", "Cart", "Crest", "Ckidney", "Cplasma", "Atubules", "Ametabolized", and "AUC"

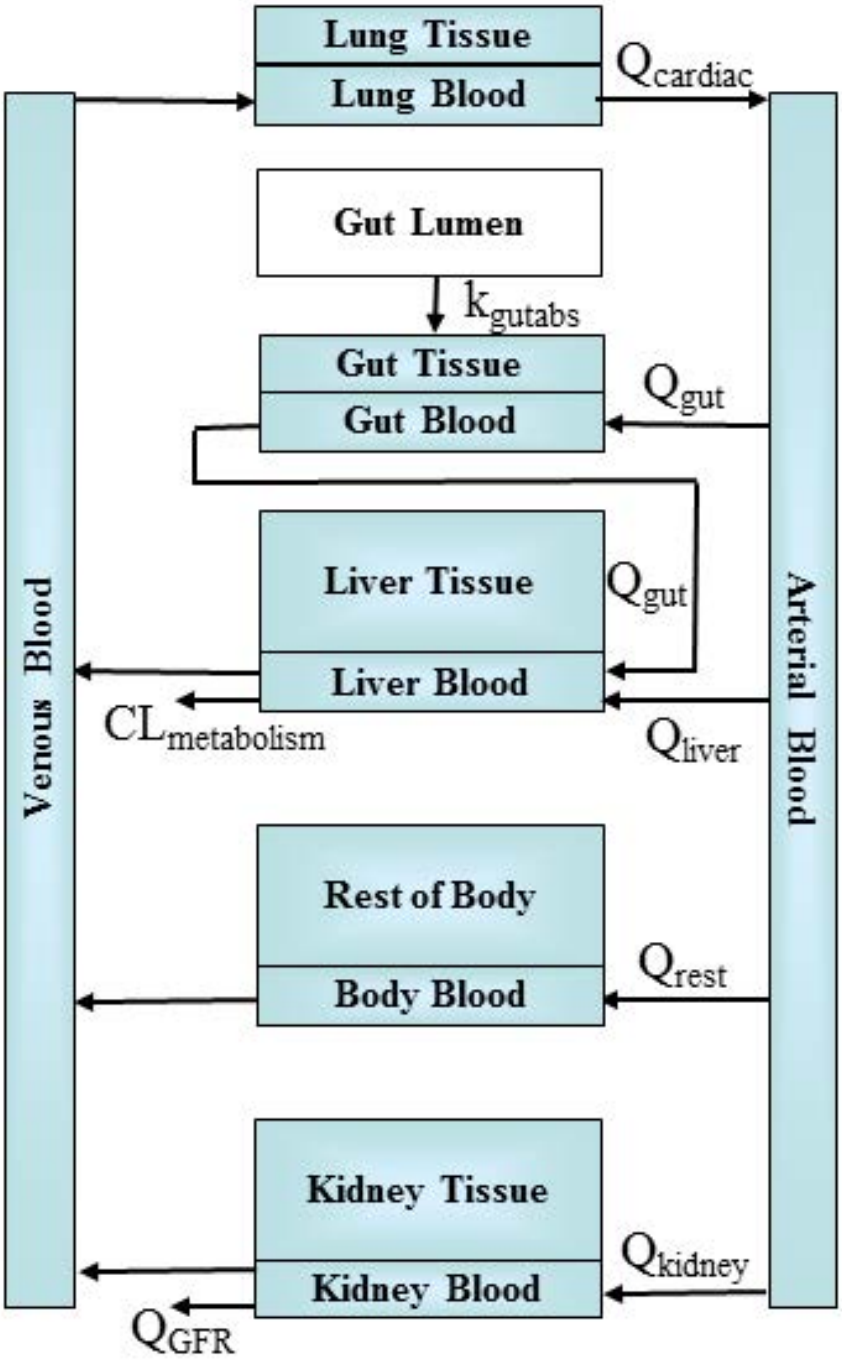
`...`
: Additional arguments passed to the integrator (deSolve).

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.

Model Figure



altalt

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

Because this model does not simulate exhalation, inhalation, and other processes relevant to volatile chemicals, this model is by default restricted to chemicals with a logHenry's Law Constant less than that of Acetone, a known volatile chemical. That is, chemicals with logHLC > -4.5 (Log10 atm-m3/mole) are excluded. Volatility is not purely determined by the Henry's Law Constant, therefore this chemical exclusion may be turned off with the argument "physchem.exclude = FALSE". Similarly, per- and polyfluoroalkyl substances (PFAS) are excluded by default because the transporters that often drive PFAS toxicokinetics are not included in this model. However, PFAS chemicals can be included with the argument "class.exclude = FALSE".

Value

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

Author(s)

John Wambaugh and Robert Pearce

References

Pearce RG, Setzer RW, Strope CL, Wambaugh JF, Sipes NS (2017). "Httk: R package for high-throughput toxicokinetics." *Journal of Statistical Software*, **79**(4), 1. doi:10.18637/jss.v079.i04.

See Also

solve_model

parameterize_gas_pbtk

calc_analytic_css_pbtk

Examples

```
# Multiple doses per day:
head(solve_pbtk(
  chem.name='Bisphenol-A',
  daily.dose=.5,
  days=2.5,
  doses.per.day=2,
  tsteps=2))

# Starting with an initial concentration:
out <- solve_pbtk(
  chem.name='bisphenola',
  dose=0,
  days=2.5,
  output.units="mg/L",
  initial.values=c(Agut=200))

# Working with parameters (rather than having solve_pbtk retrieve them):
params <- parameterize_pbtk(chem.cas="80-05-7")
head(solve_pbtk(parameters=params, days=2.5))
```

```
# We can change the parameters given to us by parameterize_pbtk:
params <- parameterize_pbtk(dtxsid="DTXSID4020406", species = "rat")
params["Funbound.plasma"] <- 0.1
out <- solve_pbtk(parameters=params, days=2.5)

# A fifty day simulation:
out <- solve_pbtk(
  chem.name = "Bisphenol A",
  days = 50,
  daily.dose=1,
  doses.per.day = 3)
plot.data <- as.data.frame(out)
css <- calc_analytic_css(chem.name = "Bisphenol A")

library("ggplot2")
c.vs.t <- ggplot(plot.data, aes(time, Cplasma)) +
  geom_line() +
  geom_hline(yintercept = css) +
  ylab("Plasma Concentration (uM)") +
  xlab("Day") +
  theme(
    axis.text = element_text(size = 16),
    axis.title = element_text(size = 16),
    plot.title = element_text(size = 17)) +
  ggtitle("Bisphenol A")
print(c.vs.t)

# The following will not work because Diquat dibromide monohydrate's
# Henry's Law Constant (-3.912) is higher than that of Acetone (~-4.5):
try(head(solve_pbtk(chem.cas = "6385-62-2")))
# However, we can turn off checking for phys-chem properties, since we know
# that  Diquat dibromide monohydrate is not too volatile:
head(solve_pbtk(chem.cas = "6385-62-2", physchem.exclude = FALSE))

# Caco-2 absorption tests:
p <- parameterize_pbtk(chem.name="Aminopterin")
# calculate what initial dose of 1 mg/kg should be in uM in the gut:
initial.dose <- signif(1/1e3*1e6/p[["MW"]]*p[["BW"]]*p[["Fabsgut"]],
                       4)
# This should be the same as what solve_pbtk givesus:
initial.dose == solve_pbtk(chem.cas="80-05-7",days=1)[1,"Agutlumen"]

# By default we now include calculation of Fabs and Fgut (we explicitly model
# first-pass hepatic metabolism in the model "pbtk")
head(solve_pbtk(chem.cas="80-05-7",days=1))
# Therefore if we set Fabs = Fgut = 1 with keetit100=TRUE, we should get a
# higher tissue concentrations:
head(solve_pbtk(chem.cas="80-05-7",days=1,
                Caco2.options=list(keepit100=TRUE)))

# Different ways to call the function:
head(solve_pbtk(chem.cas="80-05-7",days=1))
```

```
head(solve_pbtk(parameters=parameterize_pbtk(chem.cas="80-05-7"),days=1))
```

`solve_pbtk_lifestage` *Solve the* `pbtk_lifestage` *model, which has time-dependent parameters*

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. In this PBTK formulation. C_{tissue} is the concentration in tissue at time t. Since the perfusion limited partition coefficients describe instantaneous equilibrium between the tissue and the free fraction in plasma, the whole plasma concentration is $C_{tissue,plasma} = \frac{1}{f_{up} * K_{tissue2fup}} * C_{tissue}$. Note that we use a single, constant value of f_{up} across all tissues. Corespondingly the free plasma concentration is modeled as $C_{tissue,freeplasma} = \frac{1}{K_{tissue2fup}} * C_tissue$. The amount of blood flowing from tissue x is Q_{tissue} (L/h) at a concentration $C_{x,blood} = \frac{R_{b2p}}{f_{up} * K_{tissue2fup}} * C_{tissue}$, where we use a single R_{b2p} value throughout the body. Metabolic clearance is modelled as being from the total plasma concentration here, though it is restricted to the free fraction in `calc_hep_clearance` by default. Renal clearance via glomerulsr filtration is from the free plasma concentration. 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.

Usage

```
solve_pbtk_lifestage(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  times = NULL,
  parameters = NULL,
  days = 10,
  tsteps = 4,
  daily.dose = NULL,
  dose = NULL,
  doses.per.day = NULL,
  initial.values = NULL,
  plots = FALSE,
  suppress.messages = FALSE,
  species = "Human",
  iv.dose = FALSE,
  input.units = "mg/kg",
  output.units = NULL,
  default.to.human = FALSE,
  class.exclude = TRUE,
```

```
  recalc.blood2plasma = FALSE,
  recalc.clearance = FALSE,
  dosing.matrix = NULL,
  adjusted.Funbound.plasma = TRUE,
  regression = TRUE,
  restrictive.clearance = TRUE,
  minimum.Funbound.plasma = 1e-04,
  Caco2.options = list(),
  monitor.vars = NULL,
  time.varying.params = TRUE,
  start.age = 360,
  ref.pop.dt = NULL,
 httkpop.generate.arg.list = list(method = "virtual individuals", nsamp = 25000),
  ref.params = NULL,
  ...
)
```

Arguments

chem.name	Either the chemical name, CAS number, or the parameters must be specified.
chem.cas	Either the chemical name, CAS number, or the parameters must be specified.
dtxsid	EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs
times	Optional time sequence for specified number of days. Dosing sequence begins at the beginning of times.
parameters	Chemical parameters from parameterize_pbtk function, overrides chem.name and chem.cas.
days	Length of the simulation.
tsteps	The number of time steps per hour.
daily.dose	Total daily dose, defaults to mg/kg BW.
dose	Amount of a single, initial oral dose in mg/kg BW.
doses.per.day	Number of doses per day.
initial.values	Vector containing the initial concentrations or amounts of the chemical in specified tissues with units corresponding to output.units. Defaults are zero.
plots	Plots all outputs if true.
suppress.messages	Whether or not the output message is suppressed.
species	Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human").
iv.dose	Simulates a single i.v. dose if true.
input.units	Input units of interest assigned to dosing, defaults to mg/kg BW
output.units	A named vector of output units expected for the model results. Default, NULL, returns model results in units specified in the 'modelinfo' file. See table below for details.

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

class.exclude
: Exclude chemical classes identified as outside of domain of applicability by relevant modelinfo_[MODEL] file (default TRUE).

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

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

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

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

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

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

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

Caco2.options
: A list of options to use when working with Caco2 apical to basolateral data Caco2.Pab, default is Caco2.options = list(Caco2.Pab.default = 1.6, Caco2.Fabs = TRUE, Caco2.Fgut = TRUE, overwrite.invivo = FALSE, keepit100 = FALSE). Caco2.Pab.default sets the default value for Caco2.Pab if Caco2.Pab is unavailable. Caco2.Fabs = TRUE uses Caco2.Pab to calculate fabs.oral, otherwise fabs.oral = Fabs. Caco2.Fgut = TRUE uses Caco2.Pab to calculate fgut.oral, otherwise fgut.oral = Fgut. overwrite.invivo = TRUE overwrites Fabs and Fgut in vivo values from literature with Caco2 derived values if available. keepit100 = TRUE overwrites Fabs and Fgut with 1 (i.e. 100 percent) regardless of other settings. See get_fbio for further details.

monitor.vars
: Which variables are returned as a function of time. The default value of NULL provides "Cgut", "Cliver", "Cven", "Clung", "Cart", "Crest", "Ckidney", "Cplasma", "Atubules", "Ametabolized", and "AUC"

time.varying.params
: Whether or not to allow parameters to vary in time according to the nonparametric regression determined by get_input_param_timeseries. Default is TRUE.

start.age
: The age of the individual in months at the beginning of the simulation. Default 360.

ref.pop.dt
: The output of httkpop_generate containing physiology of the population used in determining timeseries of parameters. Ignored if ref.params is given.

httkpop.generate.arg.list
: If ref.pop.dt is NULL, these arguments are used as input to httkpop_generate for generating physiology of a reference population.

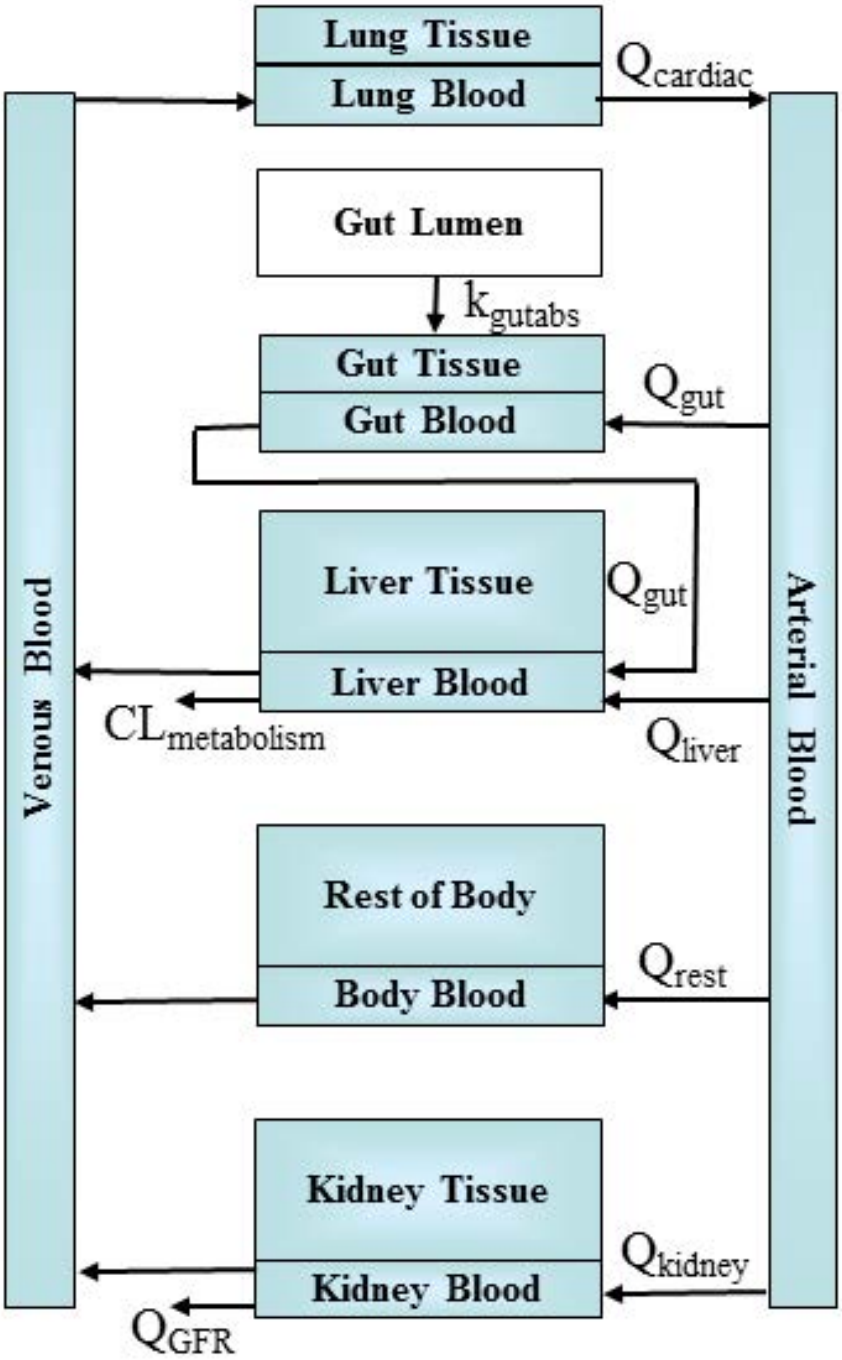
ref.params	Model parameters of a reference population used in determining timeseries. Recommended column binding ages in months (as age_months) to the output of create_mc_samples.
...	Additional arguments passed to the integrator (deSolve).

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.

Model Figure



altalt

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

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)

Colin Thomson

See Also

solve_model

parameterize_pbtk

get_input_param_timeseries

Examples

```
params <- parameterize_pbtk(chem.name = 'Bisphenol A')

pop.phys <- httkpop_generate(method = 'virtual individuals',
                             nsamp = 25000,
                             agelim_years = c(18, 79),
                             weight_category = c("Normal"))
pop.params <- create_mc_samples(chem.name = 'Bisphenol A',
                                model = 'pbtk',
                                httkpop.dt = pop.phys)
ref.params <- cbind(pop.params,
                    age_months = pop.phys$age_months)
out <- solve_pbtk_lifestage(chem.name = 'Bisphenol A',
                            parameters = params,
                            days = 365,
                            start.age = 600, # age fifty
                            ref.params = ref.params,
                            doses.per.day = 3,
                            daily.dose = 1)
```

---

spleen_mass_children *Predict spleen mass for children*

Description

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

Usage

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

Arguments

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

Value

A vector of spleen masses in kg.

Author(s)

Caroline Ring

References

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

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

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

---

supptab1_Linakis2020 *Supplementary output from Linakis 2020 vignette analysis.*

Description

Supplementary output from Linakis 2020 vignette analysis.

Usage

```
supptab1_Linakis2020
```

Format

A data.frame containing x rows and y columns.

Author(s)

Matt Linakis

Source

Matt Linakis

References

Linakis MW, Sayre RR, Pearce RG, Sfeir MA, Sipes NS, Pangburn HA, Gearhart JM, Wambaugh JF (2020). "Development and evaluation of a high-throughput inhalation model for organic chemicals." *Journal of exposure science & environmental epidemiology*, **30**(5), 866–877. doi:10.1038/s41370-0200238y.

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

Description

More supplementary output from Linakis 2020 vignette analysis.

Usage

```
supptab2_Linakis2020
```

Format

A data.frame containing x rows and y columns.

Author(s)

Matt Linakis

Source

Matt Linakis

References

Linakis MW, Sayre RR, Pearce RG, Sfeir MA, Sipes NS, Pangburn HA, Gearhart JM, Wambaugh JF (2020). "Development and evaluation of a high-throughput inhalation model for organic chemicals." *Journal of exposure science & environmental epidemiology*, **30**(5), 866–877. doi:10.1038/s41370-0200238y.

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

Description

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

Usage

```
Tables.Rdata.stamp
```

Format

An object of class `character` of length 1.

Author(s)

John Wambaugh

thyroid.ac50s *ToxCast thyroid-related bioactivity data*

Description

Truong et al. 2025 uses ToxCast data for 4 thyroid-related assay endpoints concerning inhibition of deiodinases ("DIO1", "DIO2", "DIO3", and "IYD") and identified 120 priority chemicals with activity for at least one deiodinase. These 120 chemicals were curated after assessment for target selectivity and assay interference.

Usage

```
thyroid.ac50s
```

Format

data.table and data.frame

Details

The AC50s (in uM) for each of the 120 chemicals were retrieved from ToxCast invitrodb v3.5 and are used in the "Full Human Gestational IVIVE" vignette.

References

Truong KT, Wambaugh JF, Kapraun DF, Davidson-Fritz SE, Eytcheson S, Judson RS, Paul Friedman K (2025). "Interpretation of thyroid-relevant bioactivity data for comparison to in vivo exposures: A prioritization approach for putative chemical inhibitors of in vitro deiodinase activity." *Toxicology*. doi:10.1016/j.tox.2025.154157.

`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 406 rows and 5 columns.

Column	Description
Tissue	The tissue being described
Species	The species being described
Reference	The reference for the value reported
variable	The aspect of the tissue being characterized
value	The value for the variable for the given tissue and species

Details

Many of the parameters were compiled initially in Table 2 of Schmitt (2009). The full list of tissue variables described is:

Variable	Description	Units
Fcell	Cellular fraction of total tissue volume	fraction
Fint	Interstitial fraction of total tissue volume	fraction
FWc	Fraction of cell volume that is water	fraction
FLc	Fraction of cell volume that is lipid	fraction
FPc	Fraction of cell volume that is protein	fraction
Fn_Lc	Fraction of cellular lipid tht is neutral lipid	fraction
Fn_PLc	Fraction of cellular lipid tht is neutral phospholipid	fraction

Fa_PLc	Fraction of cellular lipid tht is acidic phospholipid	fraction
pH	Negative logarithm of H+ ion concentration	unitless
Density	Tissue density	g/cm^3
Vol	Tissue volume	L/kg
Flow	Blood flow to tissue	mL/min/kg^(3/4)

New tissues can be added to this table to generate their partition coefficients.

Author(s)

John Wambaugh, Robert Pearce, and Nisha Sipes

References

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

Ruark CD, Hack CE, Robinson PJ, Mahle DA, Gearhart JM (2014). "Predicting passive and active tissue: plasma partition coefficients: interindividual and interspecies variability." *Journal of pharmaceutical sciences*, **103**(7), 2189–2198. doi:10.1002/jps.24011.

Schmitt W (2008). "General approach for the calculation of tissue to plasma partition coefficients." *Toxicology in vitro*, **22**(2), 457–467. doi:10.1016/j.tiv.2007.09.010.

Snyder WS (1974). "Report of the task group on reference man." *ICRP publication*.

Wambaugh JF, Wetmore BA, Pearce R, Strope C, Goldsmith R, Sluka JP, Sedykh A, Tropsha A, Bosgra S, Shah I, others (2015). "Toxicokinetic triage for environmental chemicals." *Toxicological Sciences*, **147**(1), 55–67. doi:10.1093/toxsci/kfv118.

See Also

predict_partitioning_schmitt

Examples

```
# We can add thyroid to the tissue data by making a row containing
# its data, subtracting the volumes and flows from the rest-of-body,
# and binding the row to tissue.data. Here we assume it contains the same
# partition coefficient data as the spleen and a tenth of the volume and
# blood flow:
new.tissue <- subset(tissue.data,Tissue == "spleen")
new.tissue[, "Tissue"] <- "thyroid"
new.tissue[new.tissue$variable %in% c("Vol (L/kg)",
"Flow (mL/min/kg^(3/4))"),"value"] <- new.tissue[new.tissue$variable
%in% c("Vol (L/kg)","Flow (mL/min/kg^(3/4))"),"value"] / 10
tissue.data[tissue.data$Tissue == "rest", "value"] <-
tissue.data[tissue.data$Tissue == "rest", "value"] -
new.tissue[new.tissue$variable %in% c("Vol (L/kg)",
"Flow (mL/min/kg^(3/4))"),"value"]
tissue.data <- rbind(tissue.data, new.tissue)
```

```
# We can add a new species (for example, wolverines) by adding new information
# to the physiology.data and tissue.data tables. It can be convenient to start by
# by replicating the data from another species and adjusting as appropriate:

# Copy physiology data from rabbit:
new.species <- physiology.data[,"Rabbit"]
names(new.species) <- physiology.data[,"Parameter"]
rabbit.BW <- new.species["Average BW"]
# Rausch and Pearson (1972) https://doi.org/10.2307/3799057 :
new.species["Average BW"] <- 31.2
# Thiel et al. (2019) https://doi.org/10.1186/s12983-019-0319-8 :
new.species["Average Body Temperature"] <- 38.5

# Add new physiology data column to physiology.data table"
physiology.data <- cbind(physiology.data, new.species)
colnames(physiology.data)[length(colnames(physiology.data))] <- "Wolverine"

# Copy tissue data from rabbit:
new.tissue.data <- subset(tissue.data,Species=="Rabbit")
new.tissue.data$Species <- "Wolverine"

# Add new tissue data rows to tissue.data table:
tissue.data <- rbind(tissue.data, new.tissue.data)

# Species is now available for calculations:
calc_mc_css(chem.cas="80-05-7",
            species="wolverine",
            parameterize.args.list =list(default.to.human=TRUE),
            suppress.messages=TRUE,
            samples = 100)
```

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

Description

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

Usage

```
tissue_masses_flows(tmf_dt, add_variability = TRUE)
```

Arguments

tmf_dt	A data.table generated by gen_age_height_weight(), containing variables gender, reth, age_months, age_years, weight, and height.
add_variability	An option to add variability to calculated masses and flows. Default is TRUE; use FALSE for repeatable calculations.

Value

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

Author(s)

Caroline Ring

References

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

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

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

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

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

---

tissue_scale *Allometric scaling.*

Description

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

Usage

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

Arguments

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

Value

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

Author(s)

Caroline Ring

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

`truong25.seem3` *SEEM3 Example Data for Truong et al. 2025*

Description

We can grab SEEM daily intake rate predictions already in RData format from https://github.com/HumanExposure/SEEM3RF
Download the file chem.preds-2018-11-28.RData

Usage

```
truong25.seem3
```

Format

data.table and data.frame

Details

We do not have the space to distribute all the SEEM predictions within this R package, but we can give you our "Full Human Gestational IVIVE" example chemicals.

References

Truong KT, Wambaugh JF, Kapraun DF, Davidson-Fritz SE, Eytcheson S, Judson RS, Paul Friedman K (2025). "Interpretation of thyroid-relevant bioactivity data for comparison to in vivo exposures: A prioritization approach for putative chemical inhibitors of in vitro deiodinase activity." *Toxicology*. doi:10.1016/j.tox.2025.154157.

Ring CL, Arnot JA, Bennett DH, Egeghy PP, Fantke P, Huang L, Isaacs KK, Jolliet O, Phillips KA, Price PS, others (2018). "Consensus modeling of median chemical intake for the US population based on predictions of exposure pathways." *Environmental science & technology*, **53**(2), 719–732. doi:10.1021/acs.est.8b04056.

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

Description

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

Usage

```
wambaugh2019
```

Format

A data frame with 496 rows and 17 variables:

Compound The name of the chemical

CAS The Chemical Abstracts Service Registry Number

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

Human.Clint.pValue Probability that there is no clearance

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

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

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

DSSTox_Substance_Id Identifier for CompTox Chemical Dashboard

SMILES Simplified Molecular-Input Line-Entry System structure description

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

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

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

Human.Funbound.plasma.Low95 Lower 95th percentile of Bayesian credible interval for fraction of chemical free in the presence of plasma

Human.Funbound.plasma.High95 Upper 95th percentile of Bayesian credible interval for fraction of chemical free in the presence of plasma

Human.Funbound.plasma.Point Point estimate of the fraction of chemical free in the presence of plasma

MW Molecular weight (Daltons)

logP log base ten of octanol:water partiion coefficient

Author(s)

John Wambaugh

Source

Wambaugh et al. (2019)

References

Wambaugh JF, Wetmore BA, Ring CL, Nicolas CI, Pearce RG, Honda GS, Dinallo R, Angus D, Gilbert J, Sierra T, others (2019). "Assessing toxicokinetic uncertainty and variability in risk prioritization." *Toxicological Sciences*, **172**(2), 235–251. doi:10.1093/toxsci/kfz205.

`wambaugh2019.nhanes` *NHANES Chemical Intake Rates for chemicals in Wambaugh et al. (2019)*

Description

These data are a subset of the Bayesian inferrences reported by Ring et al. (2017) from the U.S. Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES). They reflect the populaton median intake rate (mg/kg body weight/day), with uncertainty.

Usage

```
wambaugh2019.nhanes
```

Format

A data frame with 20 rows and 4 variables:

lP The median of the Bayesian credible interval for median population intake rate (mg/kg bodyweight/day)

lP.min The lower 95th percentile of the Bayesian credible interval for median population intake rate (mg/kg bodyweight/day)

lP.max The upper 95th percentile of the Bayesian credible interval for median population intake rate (mg/kg bodyweight/day)

CASRN The Chemical Abstracts Service Registry Number

Author(s)

John Wambaugh

Source

Wambaugh et al. (2019)

References

Ring CL, Pearce RG, Setzer RW, Wetmore BA, Wambaugh JF (2017). "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." *Environment International*, **106**, 105–118. doi:10.1016/j.envint.2017.06.004.

Wambaugh JF, Wetmore BA, Ring CL, Nicolas CI, Pearce RG, Honda GS, Dinallo R, Angus D, Gilbert J, Sierra T, others (2019). "Assessing toxicokinetic uncertainty and variability in risk prioritization." *Toxicological Sciences*, **172**(2), 235–251. doi:10.1093/toxsci/kfz205.

`wambaugh2019.raw` *Raw Bayesian in vitro Toxicokinetic Data Analysis from Wambaugh et al. (2019)*

Description

These data are the new HTTK in vitro data for chemicals reported in Wambaugh et al. (2019) They are the output of different Bayesian models evaluated to compare using a single protein concentration vs. the new three concentration titration protocol. These data summarize the results of Bayesian analysis of the in vitro toxicokinetic experiments conducted by Cyprotex to characterize fraction unbound in the presence of pooled human plasma protein and the intrnsic hepatic clearance of the chemical by pooled human hepatocytes. This file includes replicates (diferent CompoundName id's but same chemical')

Usage

```
wambaugh2019.raw
```

Format

A data frame with 530 rows and 28 variables:

DTXSID Identifier for CompTox Chemical Dashboard

Name The name of the chemical

CAS The Chemical Abstracts Service Registry Number

CompoundName Sample name provided by EPA to Cyprotex

Fup.point Point estimate of the fraction of chemical free in the presence of plasma

Base.Fup.Med Median of Bayesian credible interval for fraction of chemical free in the presence of plasma for analysis of 100 physiological plasma protein data only (base model)

Base.Fup.Low Lower 95th percentile of Bayesian credible interval for fraction of chemical free in the presence of plasma for analysis of 100 physiological plasma protein data only (base model)

Base.Fup.High Upper 95th percentile of Bayesian credible interval for fraction of chemical free in the presence of plasma for analysis of 100 physiological plasma protein data only (base model)

Affinity.Fup.Med Median of Bayesian credible interval for fraction of chemical free in the presence of plasma for analysis of protein titration protocol data (affinity model)

Affinity.Fup.Low Lower 95th percentile of Bayesian credible interval for fraction of chemical free in the presence of plasma for analysis of protein titration protocol data (affinity model)

Affinity.Fup.High Upper 95th percentile of Bayesian credible interval for fraction of chemical free in the presence of plasma for analysis of protein titration protocol data (affinity model)

Affinity.Kd.Med Median of Bayesian credible interval for protein binding affinity from analysis of protein titration protocol data (affinity model)

Affinity.Kd.Low Lower 95th percentile of Bayesian credible interval for protein binding affinity from analysis of protein titration protocol data (affinity model)

Affinity.Kd.High Upper 95th percentile of Bayesian credible interval for protein binding affinity from analysis of protein titration protocol data (affinity model)

Decreases.Prob Probability that the chemical concentration decreased systematiclally during hepatic clearance assay.

Saturates.Prob Probability that the rate of chemical concentration decrease varied between the 1 and 10 uM hepatic clearance experiments.

Slope.1uM.Median Estimated slope for chemcial concentration decrease in the 1 uM hepatic clearance assay.

Slope.10uM.Median Estimated slope for chemcial concentration decrease in the 10 uM hepatic clearance assay.

CLint.1uM.Median Median of Bayesian credible interval for intrinsic hepatic clearance at 1 uM inititial chemical concentration (uL/min/million hepatocytes)]

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

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

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

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

CLint.10uM.High95th Uppper 95th percentile of Bayesian credible interval for intrinsic hepatic clearance at 10 uM inititial chemical concentration(uL/min/million hepatocytes)

CLint.1uM.Point Point estimate of intrinsic hepatic clearance (uL/min/million hepatocytes) for 1 uM initial chemical concentration

CLint.10uM.Point Point estimate of intrinsic hepatic clearance (uL/min/million hepatocytes) for 10 uM initial chemical concentration

Fit Classification of clearance observed

SMILES Simplified Molecular-Input Line-Entry System structure description

Author(s)

John Wambaugh

Source

Wambaugh et al. (2019)

References

Wambaugh JF, Wetmore BA, Ring CL, Nicolas CI, Pearce RG, Honda GS, Dinallo R, Angus D, Gilbert J, Sierra T, others (2019). "Assessing toxicokinetic uncertainty and variability in risk prioritization." *Toxicological Sciences*, **172**(2), 235–251. doi:10.1093/toxsci/kfz205.

`wambaugh2019.seem3` *ExpoCast SEEM3 Consensus Exposure Model Predictions for Chemical Intake Rates*

Description

These data are a subset of the Bayesian inferrences reported by Ring et al. (2019) for a consensus model of twelve exposue predictors. The predictors were calibrated based upon their ability to predict intake rates inferred National Health and Nutrition Examination Survey (NHANES). They reflect the populaton median intake rate (mg/kg body weight/day), with uncertainty.

Usage

```
wambaugh2019.seem3
```

Format

A data frame with 385 rows and 38 variables:

Author(s)

John Wambaugh

Source

Wambaugh et al. (2019)

References

Ring CL, Arnot JA, Bennett DH, Egeghy PP, Fantke P, Huang L, Isaacs KK, Jolliet O, Phillips KA, Price PS, others (2018). "Consensus modeling of median chemical intake for the US population based on predictions of exposure pathways." *Environmental science & technology*, **53**(2), 719–732. doi:10.1021/acs.est.8b04056.

Wambaugh JF, Wetmore BA, Ring CL, Nicolas CI, Pearce RG, Honda GS, Dinallo R, Angus D, Gilbert J, Sierra T, others (2019). "Assessing toxicokinetic uncertainty and variability in risk prioritization." *Toxicological Sciences*, **172**(2), 235–251. doi:10.1093/toxsci/kfz205.

`wambaugh2019.tox21` *Tox21 2015 Active Hit Calls (EPA)*

Description

The ToxCast and Tox21 research programs employ batteries of high-throughput assays to assess chemical bioactivity in vitro. Not every chemical is tested through every assay. Most assays are conducted in concentration response, and each corresponding assay endpoint is analyzed statistically to determine if there is a concentration-dependent response or "hit" using the ToxCast Pipeline. Most assay endpoint-chemical combinations are non-responsive. Here, only the hits are treated as potential indicators of bioactivity. This bioactivity does not have a direct toxicological interpretation. The October 2015 release (invitrodb_v2) of the ToxCast and Tox21 data were used for this analysis. This object contains just the chemicals in Wambaugh et al. (2019) and only the quantiles across all assays for the ACC.

Usage

```
wambaugh2019.tox21
```

Format

A data.table with 401 rows and 6 columns

Author(s)

John Wambaugh

References

Kavlock, Robert, et al. "Update on EPA's ToxCast program: providing high-throughput decision support tools for chemical risk management." Chemical research in toxicology 25.7 (2012): 1287-1302.

Tice, Raymond R., et al. "Improving the human hazard characterization of chemicals: a Tox21 update." Environmental health perspectives 121.7 (2013): 756-765.

Richard, Ann M., et al. "ToxCast chemical landscape: paving the road to 21st century toxicology." Chemical research in toxicology 29.8 (2016): 1225-1251.

Filer, Dayne L., et al. "tcpl: the ToxCast pipeline for high-throughput screening data." Bioinformatics 33.4 (2016): 618-620.

Wambaugh, John F., et al. "Assessing Toxicokinetic Uncertainty and Variability in Risk Prioritization." Toxicological Sciences 172.2 (2019): 235-251.

wang2018 *Wang et al. 2018 Wang et al. (2018) screened the blood of 75 pregnant women for the presence of environmental organic acids (EOAs) and identified mass spectral features corresponding to 453 chemical formulae of which 48 could be mapped to likely structures. Of the 48 with tentative structures the identity of six were confirmed with available chemical standards.*

Description

Wang et al. 2018 Wang et al. (2018) screened the blood of 75 pregnant women for the presence of environmental organic acids (EOAs) and identified mass spectral features corresponding to 453 chemical formulae of which 48 could be mapped to likely structures. Of the 48 with tentative structures the identity of six were confirmed with available chemical standards.

Usage

```
wang2018
```

Format

data.frame

Source

Kapraun DF, Sfeir M, Pearce RG, Davidson-Fritz SE, Lumen A, Dallmann A, Judson RS, Wambaugh JF (2022). "Evaluation of a rapid, generic human gestational dose model." *Reproductive Toxicology*, **113**, 172–188. doi:10.1016/j.reprotox.2022.09.004.

References

Wang A, Gerona RR, Schwartz JM, Lin T, Sirota M, Morello-Frosch R, Woodruff TJ (2018). "A Suspect Screening Method for Characterizing Multiple Chemical Exposures among a Demographically Diverse Population of Pregnant Women in San Francisco." *Environmental Health Perspectives*, **126**(7), 077009. doi:10.1289/EHP2920.

well_param *Microtiter Plate Well Descriptions for Armitage et al. (2014) Model*

Description

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

Usage

```
well_param
```

Format

A data frame / data table with 11 rows and 8 variables:

sysID Identifier for each multi-well plate system
well_desc Well description
well_number Number of wells on plate
area_bottom Area of well bottom in mm^2
cell_yield Number of cells
diam Diameter of well in mm
v_total Total volume of well in uL)
v_working Working volume of well in uL

Author(s)

Greg Honda

References

Armitage JM, Wania F, Arnot JA (2014). "Application of mass balance models and the chemical activity concept to facilitate the use of in vitro toxicity data for risk assessment." *Environmental science & technology*, **48**(16), 9770–9779. doi:10.1021/es501955g.

Honda GS, Pearce RG, Pham LL, Setzer RW, Wetmore BA, Sipes NS, Gilbert J, Franz B, Thomas RS, Wambaugh JF (2019). "Using the concordance of in vitro and in vivo data to evaluate extrapolation assumptions." *PloS one*, **14**(5), e0217564. doi:10.1371/journal.pone.0217564.

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 BA, Wambaugh JF, Ferguson SS, Sochaski MA, Rotroff DM, Freeman K, Clewell III HJ, Dix DJ, Andersen ME, Houck KA, others (2012). "Integration of dosimetry, exposure, and high-throughput screening data in chemical toxicity assessment." *Toxicological Sciences*, **125**(1), 157–174. doi:10.1093/toxsci/kfr254.

`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 with 262 rows and 4 variables:

Sex "Male" or "Female"

Length Recumbent length in cm

P2.3 The 2.3rd percentile weight in kg for the corresponding sex and recumbent length

P97.7 The 97.7th percentile weight in kg for the corresponding sex and recumbent length

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

https://www.who.int/tools/child-growth-standards/standards/weight-for-length-height

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