# Package 'httk'

February 20, 2023

**Version** 2.2.2

**Date** 2023-02-14

**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

**RdMacros** Rdpack

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

**License** GPL-3

**LazyData** true

**LazyDataCompression** xz

**Encoding** UTF-8

**VignetteBuilder** knitr, R.rsp

**RoxygenNote** 7.2.3

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

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

**NeedsCompilation** yes

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# R topics documented:

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`httk-package` *High-Throughput Toxicokinetics*

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## 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>).

## Author(s)

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

## See Also

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

doi: 10.1080/17425255.2021.1935867Breen et al. (2021): High-throughput PBTK models for in vitro to in vivo extrapolation

doi: 10.18637/jss.v079.i04Pearce et al. (2017): httk: R Package for High-Throughput Toxicokinetics

doi: 10.1021/es501955gArmitage et al. (2014): Application of mass balance models and the chemical activity concept to facilitate the use of in vitro toxicity data for risk assessment

doi: 10.1093/toxsci/kfv171Incorporating High-Throughput Exposure Predictions with Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing

doi: 10.1093/toxsci/kfv118Wambaugh et al. (2015): Toxicokinetic Triage for Environmental Chemicals

doi: 10.1007/s1092801795487Pearce et al. (2017): Evaluation and calibration of high-throughput predictions of chemical distribution to tissues

doi: 10.1016/j.envint.2017.06.004Ring et al. (2017): Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability

doi: 10.1021/acs.est.7b00650Sipes et al. (2017): An Intuitive Approach for Predicting Potential Human Health Risk with the Tox21 10k Library

doi: 10.1093/toxsci/kfy020Wambaugh et al. (2018): Evaluating In Vitro-In Vivo Extrapolation of Toxicokinetics

doi: 10.1371/journal.pone.0217564Honda et al. (2019): Using the concordance of in vitro and in vivo data to evaluate extrapolation assumptions

doi: 10.1093/toxsci/kfz205Wambaugh et al. (2019): Assessing Toxicokinetic Uncertainty and Variability in Risk Prioritization

doi: 10.1038/s413700200238yLinakis et al. (2020): Development and evaluation of a high-throughput inhalation model for organic chemicals

The U.S. EPA ExpoCast (Exposure Forecasting) Project

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

---

## Description

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

## Usage

```
add_chemtable(
  new.table,
  data.list,
  current.table = NULL,
  reference = NULL,
  species = NULL,
  overwrite = 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', 'Fgutabs', 'Rblood2plasma'. |

current.table This is the table to which data are being added.

reference This is the reference for the data in the new table. This may be omitted if a column in data.list gives the reference value for each chemical.

species This is the species for the data in the new table. This may be omitted if a column in data.list gives the species value for each chemical or if the data are not species-specific (e.g., MW).

overwrite If overwrite=TRUE then data in current.table will be replaced by any data in new.table that is for the same chemical and property. If overwrite=FALSE (DEFAULT) then new data for the same chemical and property are ignored. Funbound.plasma values of 0 (below limit of detection) are overwritten either way.

sig.fig Sets the number of significant figures stored (defaults to 4)

clint.pvalue.overwrite
If TRUE then the Cl_int p-value is set to NA when the Cl_int value is changed unless a new p-value is provided. (defaults to TRUE)

allow.na If TRUE (default is FALSE) then NA values are written to the table, otherwise they are ignored.

## Value

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

## Author(s)

John Wambaugh

## Examples

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

---

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

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

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

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

## 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, J. M., Arnot, J. A., Wania, F., & Mackay, D. (2013). Development and evaluation of a mechanistic bioconcentration model for ionogenic organic chemicals in fish. Environmental toxicology and chemistry, 32(1), 115-128.

---

`armitage_eval` *Evaluate the updated Armitage model*

---

## Description

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

## Usage

```
armitage_eval(
  casrn.vector = NA_character_,
  nomconc.vector = 1,
  this.well_number = 384,
  this.FBSf = NA_real_,
  tcdata = NA,
  this.sarea = NA_real_,
  this.v_total = NA_real_,
  this.v_working = NA_real_,
  this.cell_yield = NA_real_,
  this.Tsys = 37,
  this.Tref = 298.15,
  this.option.kbsa2 = 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
)
```

## Arguments

| | |
|---|---|
| `casrn.vector` | For vector or single value, CAS number |
| `nomconc.vector` | For vector or single value, micromolar nominal concentration (e.g. AC50 value) |

`this.well_number`
: For single value, plate format default is 384, used if is.na(tcdata)==TRUE

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

`tcdata`
: A data.table with casrn, nomconc, MP, gkow, gkaw, gswat, sarea, v_total, v_working. Otherwise supply single values to this.params.

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

`this.v_total`
: Total volume per well (m^3)

`this.v_working`
: Working volume per well (m^3)

`this.cell_yield`
: Number of cells per well

`this.Tsys`
: System temperature (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 conent 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, mol/L

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

`this.cellmass`
: Mass per cell, ng/cell

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

`this.conc_ser_alb`
: 24 g/L, mass concentration of albumin in serum.

`this.conc_ser_lip`
: 1.9 g/L, mass concentration of lipids in serum.

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

## Value

| Column | Description | units |
|---|---|---|
| casrn | Chemical Abstracts Service Registry Number | |
| nomconc | Nominal Concentration | mol/L |
| well_number | Number of wells in plate | unitless |
| sarea | Surface area of well | m^2 |
| v_total | Total volume of well | m^3 |
| v_working | Filled volume of well | m^3 |
| cell_yield | Number of cells | cells |
| gkow | log10 octanol to water partition coefficient (PC) | log10 |
| logHenry | log10 Henry's law constant ' | log10 atm-m3/mol |

| | | |
|---|---|---|
| gswat | log10 Water solubility | log10 mol/L |
| MP | Melting Point | degrees Celsius |
| MW | Molecular Weight | g/mol |
| gkaw | air-water partition coefficient | (mol/m3)/(mol/m3) |
| dsm | | |
| duow | | |
| duaw | | |
| dumw | | |
| gkmw | | |
| gkcw | | |
| gkbsa | | |
| gkpl | | |
| ksalt | | |
| Tsys | | |
| Tref | | |
| option.kbsa2 | | |
| option.swat2 | | |
| FBSf | | |
| pseudooct | | |
| memblip | | |
| nlom | | |
| P_nlom | | |
| P_dom | dissolved organic matter to water PC | Dimensionless |
| P_cells | | |
| csalt | | |
| celldensity | | |
| cellmass | | |
| 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 | |
| Valb | volume of serum albumin | |
| Vslip | volume of serum lipids | |
| Vdom | volume of dissolved organic matter | |
| F_ratio | | |
| gs1.GSE | | |
| s1.GSE | | |
| gss.GSE | | |
| ss.GSE | | |
| kmw | | |
| kow | octanol to water PC | |
| kaw | the air towater PC | dimensionless |
| swat | | |
| kpl | | |
| kcw | cell/tissue to water PC | dimensionless |
| kbsa | | |
| swat_L | | |
| oct_L | | |
| scell_L | | |

| | | |
|---|---|---|
| cinit | Initial concentration | mol |
| mtot | Total moles | mol |
| cwat | Total concentration in water | mol/L |
| cwat_s | Dissolved concentration in water | mol/L |
| csat | Is the solution saturated (1/0) | Boolean |
| activity | | |
| cair | | mol/L |
| calb | | mol/L |
| cslip | | mol/L |
| cdom | concentration of/in dissolved organic matter | mol/L |
| ccells | | mol/L |
| cplastic | | mol/L |
| mwat_s | Mass dissolved in water | mols |
| mair | Mass in air | mols |
| mbsa | Mass bound to bovine serum albumin | mols |
| mslip | Mass bound to serum lipids | mols |
| mdom | Mass bound to dissolved organic matter | mols |
| mcells | Mass in cells | mols |
| mplastic | Mass bond to plastic | mols |
| mprecip | Mass precipitated out of solution | |
| 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) | micromolar |

## Author(s)

Greg Honda

## References

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

Honda et al. PloS one 14.5 (2019): e0217564. https://doi.org/10.1371/journal.pone.0217564

## Examples

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

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

---

# augment.table *Add a 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,
  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. |
| 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 et al. 2021 (submitted)

### 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.

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

### Description

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

### Usage

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

### Arguments

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

## Value

A vector of blood masses in kg.

## Author(s)

Caroline Ring

## References

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

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

---

`blood_weight` *Predict blood mass.*

---

## Description

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

## Usage

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

## Arguments

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

## Value

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

## Author(s)

Caroline Ring

## References

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

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

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

## Description

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

## Usage

```
bmiage
```

## Format

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

## body_surface_area *Predict body surface area.*

### Description

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

### Usage

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

### Arguments

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

### Value

A vector of body surface areas in cm^2.

### Author(s)

Caroline Ring

### References

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

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

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

## bone_mass_age *Predict bone mass*

### Description

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

### Usage

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

### Arguments

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

### Value

Vector of bone masses.

### Author(s)

Caroline Ring

### References

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

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

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

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

---

## brain_mass *Predict brain mass.*

---

### Description

Predict brain mass from gender and age.

### Usage

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

### Arguments

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

### Value

A vector of brain masses in kg.

### Author(s)

Caroline Ring

## References

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

---

`calc_analytic_css` *Calculate the analytic steady state 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 = 1,
  route = "oral",
  exp.conc = 1,
  period = 24,
  exp.duration = 24,
  output.units = "uM",
  model = "pbtk",
  concentration = "plasma",
  suppress.messages = FALSE,
  tissue = NULL,
  restrictive.clearance = TRUE,
  bioactive.free.invivo = FALSE,
  IVIVE = NULL,
  parameterize.args = 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. |

route — Route of exposure (either "oral", "iv", or "inhalation" default "oral").

exp.conc — Specified inhalation exposure concentration for use in assembling 'forcings' data series argument for integrator. Defaults to uM/L

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

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.

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

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

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

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

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

## Details

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

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

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

## Value

Steady state plasma concentration in specified units

## Author(s)

Robert Pearce, John Wambaugh, Greg Honda, Miyuki Breen

## References

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

## See Also

calc_css

## Examples

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

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

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

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

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

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

```
# 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")
```

---

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

---

## Description

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

## Usage

```
calc_analytic_css_1comp(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  hourly.dose = 1/24,
  concentration = "plasma",
  suppress.messages = FALSE,
  recalc.blood2plasma = FALSE,
  tissue = NULL,
  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_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. |
| `hourly.dose` | Hourly dose rate mg/kg BW/h. |
| `concentration` | Desired concentration type, 'blood' or default 'plasma'. |
| `suppress.messages` | Whether or not the output message is suppressed. |

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

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

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

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

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

## Value

Steady state 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 3comp*

---

## Description

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

## Usage

```
calc_analytic_css_3comp(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  hourly.dose = 1/24,
  concentration = "plasma",
  suppress.messages = FALSE,
  recalc.blood2plasma = FALSE,
  tissue = NULL,
  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_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. |
| hourly.dose | Hourly dose rate mg/kg BW/h. |
| concentration | Desired concentration type, 'blood' or default 'plasma'. |
| suppress.messages | Whether or not the output message is suppressed. |
| recalc.blood2plasma | Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters. Use this if you have 'altered hematocrit, Funbound.plasma, or Krbc2pu. |
| tissue | Desired tissue conentration (defaults to whole body concentration.) |
| restrictive.clearance | If TRUE (default), then only the fraction of chemical not bound to protein is available for metabolism in the liver. If FALSE, then all chemical in the liver is metabolized (faster metabolism due to rapid off-binding). |
| bioactive.free.invivo | If FALSE (default), then the total concentration is treated as bioactive in vivo. If TRUE, the the unbound (free) plasma concentration is treated as bioactive in vivo. Only works with tissue = NULL in current implementation. |
| ... | Additional parameters passed to parameterize function if parameters is NULL. |

## Value

Steady state plasma concentration in mg/L units

## Author(s)

Robert Pearce and John Wambaugh

## References

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

## 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 analytic steady state plasma or venous blood concentrations as a result of infusion dosing.

## Usage

```
calc_analytic_css_3compss(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  parameters = NULL,
  hourly.dose = 1/24,
  concentration = "plasma",
  suppress.messages = FALSE,
  recalc.blood2plasma = FALSE,
  tissue = NULL,
  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_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. |
| `hourly.dose` | Hourly dose rate mg/kg BW/h. |
| `concentration` | Desired concentration type, 'blood' or default 'plasma'. |
| `suppress.messages` | Whether or not the output message is suppressed. |
| `recalc.blood2plasma` | Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters. Use this if you have 'altered hematocrit, Funbound.plasma, or Krbc2pu. |
| `tissue` | Desired tissue concentration (defaults to whole body concentration.) |
| `restrictive.clearance` | If TRUE (default), then only the fraction of chemical not bound to protein is available for metabolism in the liver. If FALSE, then all chemical in the liver is metabolized (faster metabolism due to rapid off-binding). |

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

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

## Value

Steady state plasma concentration in mg/L units

## Author(s)

Robert Pearce and John Wambaugh

## References

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

## 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 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,
  hourly.dose = 1/24,
  concentration = "plasma",
  suppress.messages = FALSE,
  recalc.blood2plasma = FALSE,
  tissue = NULL,
  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_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. |
| hourly.dose | Hourly dose rate mg/kg BW/h. |
| concentration | Desired concentration type, 'blood', 'tissue', or default 'plasma'. |
| suppress.messages | Whether or not the output message is suppressed. |
| recalc.blood2plasma | Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters. Use this if you have 'altered hematocrit, Funbound.plasma, or Krbc2pu. |
| tissue | Desired tissue conentration (defaults to whole body concentration.) |
| restrictive.clearance | If TRUE (default), then only the fraction of chemical not bound to protein is available for metabolism in the liver. If FALSE, then all chemical in the liver is metabolized (faster metabolism due to rapid off-binding). |
| bioactive.free.invivo | If FALSE (default), then the total concentration is treated as bioactive in vivo. If TRUE, the the unbound (free) plasma concentration is treated as bioactive in vivo. Only works with tissue = NULL in current implementation. |
| ... | Additional parameters passed to parameterize function if parameters is NULL. |

## Details

The PBTK model (Pearce et al., 2017) predicts the amount of chemical in various tissues of the body. A system of oridinary 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 cardiace 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 n plasma, R_b2p is the chemical specific ratio of concentrations in blood:plasma, K_tissue2fuplasma is the chemical- and tissue-specufic 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, Robert G., et al. "Httk: R package for high-throughput toxicokinetics." Journal of statistical software 79.4 (2017): 1.

## See Also

calc_analytic_css

parameterize_pbtk

---

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

---

## Description

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

## Usage

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

## Arguments

| | |
|---|---|
| chem.name | Either the chemical name, CAS number, or parameters must be specified. |
| chem.cas | Either the chemical name, CAS number, or parameters must be specified. |
| dtxsid | EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs |
| parameters | Chemical parameters from parameterize_pbtk function, overrides chem.name and chem.cas. |
| species | Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human"). |
| f | Fractional distance from the final steady state concentration that the average concentration must come within to be considered at steady state. |
| daily.dose | Total daily dose, mg/kg BW. |
| doses.per.day | Number of doses per day. |
| days | Initial number of days to run simulation that is multiplied on each iteration. |
| output.units | Units for returned concentrations, defaults to uM (specify units = "uM") but can also be mg/L. |
| suppress.messages | Whether or not to suppress messages. |
| tissue | Desired tissue concentration (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. |
| default.to.human | Substitutes missing animal values with human values if true (hepatic intrinsic clearance or fraction of unbound plasma). |
| f.change | Fractional change of daily steady state concentration reached to stop calculating. |
| adjusted.Funbound.plasma | Uses adjusted Funbound.plasma when set to TRUE along with partition coefficients calculated with this value. |
| regression | Whether or not to use the regressions in calculating partition coefficients. |
| well.stirred.correction | Uses correction in calculation of hepatic clearance for well-stirred model if TRUE for model 1compartment elimination rate. This assumes clearance relative to amount unbound in whole blood instead of plasma, but converted to use with plasma concentration. |
| restrictive.clearance | Protein binding not taken into account (set to 1) in liver clearance if FALSE. |
| dosing | The dosing object for more complicated scenarios. Defaults to repeated daily.dose spread out over doses.per.day |
| ... | Additional arguments passed to model solver (default of solve_pbtk). |

## Value

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

## Author(s)

Robert Pearce, John Wambaugh

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

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

Strope, Cory L., et al. "High-throughput in-silico prediction of ionization equilibria for pharmacokinetic modeling." Science of The Total Environment 615 (2018): 150-160.

## 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",
  suppress.messages = FALSE,
  default.to.human = FALSE,
  restrictive.clearance = TRUE,
  adjusted.Funbound.plasma = TRUE,
  adjusted.Clint = TRUE,
  regression = TRUE,
  well.stirred.correction = TRUE,
  clint.pvalue.threshold = 0.05,
  minimum.Funbound.plasma = 1e-04
)
```

## Arguments

| | |
|---|---|
| `chem.cas` | Either the cas number or the chemical name must be specified. |
| `chem.name` | Either the chemical name or the cas number must be specified. |
| `dtxsid` | EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs |
| `parameters` | Chemical parameters from parameterize_steadystate or 1compartment function, overrides chem.name and chem.cas. |
| `species` | Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human"). |
| `suppress.messages` | Whether or not the output message is suppressed. |
| `default.to.human` | Substitutes missing animal values with human values if true. |
| `restrictive.clearance` | In calculating elimination rate, protein binding is not taken into account (set to 1) in liver clearance if FALSE. |
| `adjusted.Funbound.plasma` | Uses adjusted Funbound.plasma when set to TRUE along with partition coefficients calculated with this value. |
| `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. |

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

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

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

## Details

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

## Value

`Elimination rate`
: Units of 1/h.

## Author(s)

John Wambaugh

## References

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

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

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

## Examples

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

---

# calc_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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

$$Vplasma = Vplasma_model_logistic_theta0/(1+exp(-Vplasma_model_logistic_theta1*(tw-Vplasma_model_logistic_theta$$

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

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

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

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

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

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

$$Vrest = Vffmx - Vallx;$$

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

$$Qfartb = Qflvtl + Qfda;$$

$$Qfcardiac = Qfartb;$$

$$Qflung = Qfrvtl - Qfda;$$

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

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

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

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

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

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

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

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

$$Qfbypass = Qfcardiac - Qflung;$$

## 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, Dustin F., et al. "Empirical models for anatomical and physiological changes in a human mother and fetus during pregnancy and gestation." PloS one 14.5 (2019): e0215906.

---

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

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

Poulin, Patrick, and Sami Haddad. "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 (2012): 2250-2261.

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

Waters, Nigel J., et al. "Validation of a rapid equilibrium dialysis approach for the measurement of plasma protein binding." Journal of pharmaceutical sciences 97.10 (2008): 4586-4595.

## 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",
  suppress.messages = FALSE,
  default.to.human = FALSE,
  restrictive.clearance = TRUE,
  adjusted.Funbound.plasma = TRUE,
  regression = TRUE,
  well.stirred.correction = TRUE,
  clint.pvalue.threshold = 0.05,
  minimum.Funbound.plasma = 1e-04
)
```

## Arguments

| | |
|---|---|
| `chem.cas` | Either the cas number or the chemical name must be specified. |
| `chem.name` | Either the chemical name or the cas number must be specified. |
| `dtxsid` | EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs |
| `parameters` | Chemical parameters from parameterize_steadystate or 1compartment function, overrides chem.name and chem.cas. |
| `species` | Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human"). |
| `suppress.messages` | Whether or not the output message is suppressed. |
| `default.to.human` | Substitutes missing animal values with human values if true. |
| `restrictive.clearance` | In calculating elimination rate, protein binding is not taken into account (set to 1) in liver clearance if FALSE. |
| `adjusted.Funbound.plasma` | Uses adjusted Funbound.plasma when set to TRUE along with partition coefficients calculated with this value. |

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

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

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

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

## Details

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()] for the elimination rate calculation

## 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")
```

---

# 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 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 Equaation 29, where k21 is blood flow through the liver and k23 is clearance from the liver in Figure 1).

## Usage

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

## Arguments

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

## Value

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

## Author(s)

John Wambaugh

## References

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

---

`calc_hep_clearance` *Calculate the hepatic clearance.*

---

## Description

This function calculates the hepatic clearance in plasma for using the Houston (2004) are also available. In vitro measured hepatic clearace is corrected for the free fraction in the assay using the model of Kilford et al. (2008).

## 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 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.

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

`adjusted.Funbound.plasma`
: Uses Pearce et al. (2017) lipid binding adjustment for Funbound.plasma (which impacts partition coefficients) 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

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.

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

## Examples

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

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

## 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 NA is taken as no equlibria

## Usage

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

## Arguments

| | |
|---|---|
| `chem.cas` | Either the chemical name or the CAS number must be specified. |
| `chem.name` | Either the chemical name or the CAS number must be specified. |
| `dtxsid` | EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs |
| `parameters` | Chemical parameters from a parameterize_MODEL function, overrides chem.name and chem.cas. |
| `pH` | pH where ionization is evaluated. |
| `pKa_Donor` | Compound H dissociation equilibirum constant(s). Overwrites chem.name and chem.cas. |
| `pKa_Accept` | Compound H association equilibirum constant(s). Overwrites chem.name and chem.cas. |

## Details

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

$$zwitter/netural = 1$$

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

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

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

## Value

`fraction_neutral`
: fraction of compound neutral

`fraction_charged`
: fraction of compound charged

`fraction_negative`
: fraction of compound negative

`fraction_positive`
: fraction of compound positive

`fraction_zwitter`
: fraction of compound zwitterionic

## Author(s)

Robert Pearce and John Wambaugh

## References

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

Strope, Cory L., et al. "High-throughput in-silico prediction of ionization equilibria for pharmacokinetic modeling." Science of The Total Environment 615 (2018): 150-160.

## Examples

```
# 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))

# Fictitious 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))

#Fictious 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,
  default.to.human = FALSE,
  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. 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). |
| `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. |

## 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, Matthew W., et al. "Development and evaluation of a high throughput inhalation model for organic chemicals." Journal of exposure Science & Environmental Epidemiology 30.5 (2020): 866-877.

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.

---

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

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

---

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

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

---

## 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, Dustin F., et al. "Empirical models for anatomical and physiological changes in a human mother and fetus during pregnancy and gestation." PloS one 14.5 (2019): e0215906.

---

## 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 measurment 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,
  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.arg.list = NULL,
  calc.analytic.css.arg.list = 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'. |
| 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.arg.list`
: A list of arguments to be passed to the model parameterization function (that is, parameterize_MODEL) corresponding to argument "model". (Defaults to NULL.)

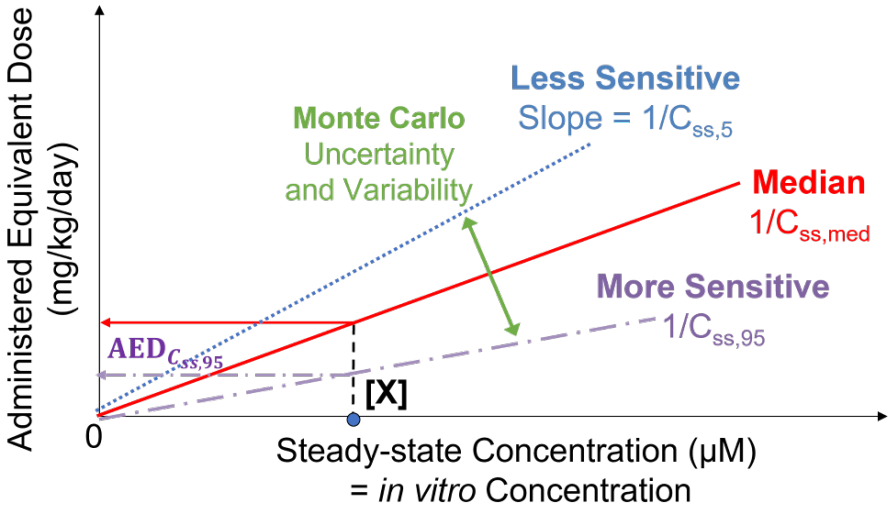
`calc.analytic.css.arg.list`
: Additional parameters passed to `calc_analytic_css`.

## 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

## References

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

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

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

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

## 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))
```

---

`calc_mc_oral_equiv` *Calculate Monte Carlo Oral Equivalent Dose*

---

## Description

This function converts a chemical plasma concetration 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,
  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",
  ...
)
```

## Arguments

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

## Details

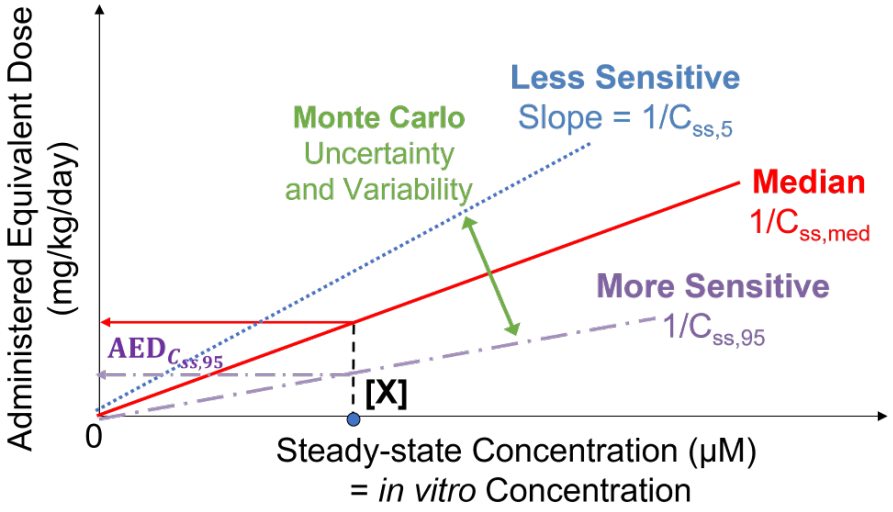
The chemical-specific steady-state concentration for a dose rate of 1 mg/kg body weight/day can be used for in IVIVE of a bioactive *in vitro* concentration by dividing the *in vitro* concentration by the

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

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

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

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

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

## 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')
```

---

`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,
  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)),
  invitro.mc.arg.list = NULL,
  httkpop.generate.arg.list = list(method = "direct resampling"),
  convert.httkpop.arg.list = NULL,
  parameterize.arg.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'. |
| 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 |
| invitro.mc.arg.list | List of additional parameters passed to invitro_mc |

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

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

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

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

## Details

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))
}
```

---

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

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

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

## 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,
  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

## 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_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,
  species = "Human",
  suppress.messages = FALSE,
  default.to.human = FALSE,
  well.stirred.correction = TRUE,
  restrictive.clearance = TRUE,
  adjusted.Funbound.plasma = TRUE,
  ...
)
```

## Arguments

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

## Value

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

## Author(s)

John Wambaugh

## Examples

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

---

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

---

## Description

This function predicts partition coefficients for all tissues using `predict_partitioning_schmitt`, then lumps them into a single compartment.

## Usage

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

## Arguments

| | |
|---|---|
| `chem.cas` | Either the CAS number or the chemical name must be specified when Funbound.plasma is not given in parameter list. |
| `chem.name` | Either the chemical name or the CAS number must be specified when Funbound.plasma is not given in parameter list. |
| `dtxsid` | EPA's DSSTox Structure ID (`https://comptox.epa.gov/dashboard`) the chemical must be identified by either CAS, name, or DTXSIDs |
| `parameters` | Parameters from parameterize_3comp, parameterize_pbtk or predict_partitioning_schmitt. |
| `default.to.human` | Substitutes missing animal values with human values if true. |
| `species` | Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human"). |

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

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

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

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

## Details

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

## Value

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

## Author(s)

John Wambaugh and Robert Pearce

## References

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

## 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")
```

## 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

## chem.invivo.PK.aggregate.data *Parameter Estimates from Wambaugh et al. (2018)*

### Description

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

### Usage

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

### Format

data.frame

### Author(s)

John Wambaugh

### Source

Wambaugh et al. 2018 Toxicological Sciences, in press

---

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

---

### Description

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

### Usage

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

### Format

A data.frame containing 597 rows and 13 columns.

### Author(s)

Sieto Bosgra

### Source

Wambaugh et al. 2018 Toxicological Sciences, in press

### References

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

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

---

`chem.invivo.PK.summary.data`

*Summary of published toxicokinetic time course experiments*

---

## Description

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

## Usage

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

## Format

A data.frame containing 100 rows and 25 columns.

## Author(s)

John Wambaugh

## Source

Wambaugh et al. 2018 Toxicological Sciences, in press

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Wang X, Lee WY, Or PM, Yeung JH (2010). Pharmacokinetic interaction studies of tanshinones with tolbutamide, a model CYP2C11 probe substrate, using liver microsomes, primary hepatocytes and in vivo in the rat. Phytomedicine. 17(3-4):203-11. PMID: 19679455

Yang SH, Lee MG (2008). Dose-independent pharmacokinetics of ondansetron in rats: contribution of hepatic and intestinal first-pass effects to low bioavailability. Biopharm Drug Dispos. 29(7):414-26. PMID: 18697186

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

---

`chem.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 | Units |
|---|---|---|
| Compound | The preferred name of the chemical compound | none |
| CAS | The preferred Chemical Abstracts Service Registry Number | none |
| CAS.Checksum | A logical indicating whether the CAS number is valid | none |
| DTXSID | DSSTox Structure ID (http://comptox.epa.gov/dashboard) | none |
| Formula | The proportions of atoms within the chemical compound | none |
| SMILES.desalt | The simplified molecular-input line-entry system structure | none |
| All.Compound.Names | All names of the chemical as they occured in the data | none |
| logHenry | The log10 Henry's law constant | log10(atmosphers |
| logHenry.Reference | Reference for Henry's law constant | |
| logP | The log10 octanol:water partition coefficient (PC) | log10 unitless ratio |
| logP.Reference | Reference for logPow | |
| logPwa | The log10 water:air PC | log10 unitless ratio |
| logPwa.Reference | Reference for logPwa | |
| logMA | The log10 phospholipid:water PC or "Membrane affinity" | unitless ratio |
| logMA.Reference | Reference for membrane affinity | |
| #' logWSol | The log10 water solubility | log10(mole/L) |
| logWSol.Reference | Reference for logWsol | |
| MP | The chemical compound melting point | degrees Celsius |
| MP.Reference | Reference for melting point | |
| MW | The chemical compound molecular weight | g/mol |
| MW.Reference | Reference for molecular weight | |
| pKa_Accept | The hydrogen acceptor equilibria concentrations | logarithm |
| pKa_Accept.Reference | Reference for pKa_Accept | |

| | | |
|---|---|---|
| pKa_Donor | The hydrogen acceptor equilibria concentrations | logarithm |
| pKa_Donor.Reference | Reference for pKa_Donor | |
| All.Species | All species for which data were available | none |
| DTXSID.Reference | Reference for DTXSID | |
| Formula.Reference | Reference for chemical formulat | |
| [SPECIES].Clint | (Primary hepatocyte suspension) intrinsic hepatic clearance | uL/min/10^6 hepa |
| [SPECIES].Clint.pValue | Probability that there is no clearance observed. | none |
| [SPECIES].Clint.pValue.Ref | Reference for Clint pValue | |
| [SPECIES].Clint.Reference | Reference for Clint | |
| [SPECIES].Fgutabs | Fraction of chemical absorbed from the gut | unitless fraction |
| [SPECIES].Fgutabs.Reference | Reference for Fgutabs | |
| [SPECIES].Funbound.plasma | Chemical fraction unbound in presence of plasma proteins | unitless fraction |
| [SPECIES].Funbound.plasma.Ref | Reference for Funbound.plasma | |
| [SPECIES].Rblood2plasma | Chemical concentration blood to plasma ratio | unitless ratio |
| [SPECIES].Rblood2plasma.Ref | Reference for Rblood2plasma | |
| SMILES.desalt.Reference" | Reference for SMILES structure | |
| 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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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

---

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

---

## concentration_data_Linakis2020

*Concentration data involved in Linakis 2020 vignette analysis.*

---

### Description

Concentration data involved in Linakis 2020 vignette analysis.

### Usage

```
concentration_data_Linakis2020
```

### Format

A data.frame containing x rows and y columns.

### Author(s)

Matt Linakis

### Source

Matt Linakis

## References

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

---

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

---

## Description

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

## Usage

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

## Arguments

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

## Value

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

## Author(s)

Caroline Ring, John Wambaugh, and Greg Honda

## References

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

---

`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 . (http://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")
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,
  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 (http://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) |
| 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:*

- 1Check Your Units
- 2**Check Your Units**
- 3Check 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")
```

```
convert_units("uM","ppmv",chem.name="styrene")

# 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")
# 1 pppmv Toluene, 0.0038 mg/L
convert_units("ppmv","mg/L",chem.name="toluene")

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

---

`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,
```

```
  httkpop.generate.arg.list = list(method = "direct resampling"),
  convert.httkpop.arg.list = NULL,
  propagate.invitrouv.arg.list = NULL,
  parameterize.arg.list = 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`.

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

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

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

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

## Details

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

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

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

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

## Examples

```
sample_set = create_mc_samples(chem.name = 'bisphenol a')
```

## 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

### Source

Dawson et al. 2021 Random Forest QSAR Model

### References

Dawson, Daniel E. et al. "Designing QSARs for parameters of high-throughput toxicokinetic models using open-source descriptors." Environmental Science & Technology____. (2021):_____.

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

`estimate_gfr_ped` *Predict GFR in children.*

## Description

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

## Usage

```
estimate_gfr_ped(BSA)
```

## Arguments

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

## Value

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

## Author(s)

Caroline Ring

## References

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

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

---

## 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

## example.toxcast *ToxCast Example Data The main page for the ToxCast data is here: https://www.epa.gov/chemical-research/exploring-toxcast-data-downloadable-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),
  filename = "default.jan",
  digits = 4
)
```

### Arguments

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

### Details

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

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

### 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",
  digits = 4
)
```

### Arguments

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

### Details

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

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

### 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 et al. 2021 (submitted)

## 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. 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. 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.

---

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

importFrom survey svymean

---

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

---

## Description

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

---

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

---

`get_cheminfo` *Retrieve chemical information 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", "CASRN", "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,
  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`
: Cutoff for the level of uncertainty in fup estimates. This value should be between (0,1). Default is 'NULL' specifying no filtering.

`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.

`class.exclude`
: Exclude chemical classes identified as outside of domain of applicability by 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 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 (this value is configurable via the argument fup.lod.default). 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. If argument meadian.only == TRUE then only the median is reported for parameters with Bayesian analysis distributions. If the 95 credible interval is larger than fup.ci.cutoff (defaults to NULL) 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 | units |
|---|---|---|

| | | |
|---|---|---|
| Compound | The preferred name of the chemical compound | none |
| CAS | The preferred Chemical Abstracts Service Registry Number | none |
| DTXSID | DSSTox Structure ID (http://comptox.epa.gov/dashboard) | none |
| logP | The log10 octanol:water partition coefficient | log10 unitless ratio |
| MW | The chemical compound molecular weight | g/mol |
| pKa_Accept | The hydrogen acceptor equilibria concentrations | logarithm |
| pKa_Donor | The hydrogen donor equilibria concentrations | logarithm |
| [SPECIES].Clint | (Primary hepatocyte suspension) intrinsic hepatic clearance | uL/min/10^6 hepatocy |
| [SPECIES].Clint.pValue | Probability that there is no clearance observed. | none |
| [SPECIES].Funbound.plasma | Chemical fraction unbound in presence of plasma proteins | unitless fraction |
| [SPECIES].Rblood2plasma | Chemical concentration blood to plasma ratio | unitless ratio |

## Author(s)

John Wambaugh, Robert Pearce, and Sarah E. Davidson

## References

Rotroff, Daniel M., et al. "Incorporating human dosimetry and exposure into high-throughput in vitro toxicity screening." Toxicological Sciences 117.2 (2010): 348-358.

Waters, Nigel J., et al. "Validation of a rapid equilibrium dialysis approach for the measurement of plasma protein binding." Journal of pharmaceutical sciences 97.10 (2008): 4586-4595.

Wambaugh, John F., et al. "Assessing toxicokinetic uncertainty and variability in risk prioritization." Toxicological Sciences 172.2 (2019): 235-251.

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

---

`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) from the main HTTK data. This function looks for species-specific values.

### Usage

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

### Arguments

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

### Details

Note that this function works with a local version of the get.physical_and_invitro.data table to allow users to add/modify chemical data (for example, via `add_chemtable` or `load_sipes2017`).

### Value

The value of the parameter, if found

### Author(s)

John Wambaugh and Robert Pearce

### See Also

`get_physchem_param`

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.Unbou "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_95t and "Species". |
| species | Species desired (either "Rat" or default "Human"). |

## Value

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

## Author(s)

John Wambaugh

## References

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

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

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

## Examples

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

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

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

## Examples

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

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

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

---

# get_lit_oral_equiv *Get Literature Oral Equivalent Dose*

---

## Description

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

## Usage

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

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

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

## Examples

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

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

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

---

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

---

## Description

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

## Usage

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

## Arguments

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

## Details

Note that this function works with a local version of the get.physical_and_invitro.data table to allow users to add/modify chemical data (for example, via `add_chemtable` or `load_sipes2017`).

## 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

`get_invitroPK_param`

## Examples

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

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

## Description

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

## Usage

```
get_rblood2plasma(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  species = "Human",
  default.to.human = 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 CDC (https://www.cdc.gov/obesity/basics/adult-defining.html), adult weight classes are defined using 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, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

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.Unbou "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_95t 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, B.A., Wambaugh, J.F., Ferguson, S.S., Sochaski, M.A., Rotroff, D.M., Freeman, K., Clewell, H.J., Dix, D.H., Andersen, M.E., Houck, K.A., Allen, B., Judson, R.S., Sing, R., Kavlock, R.J., Richard, A.M., and Thomas, R.S., "Integration of Dosimetry, Exposure and High-Throughput Screening Data in Chemical Toxicity Assessment," Toxicological Sciences 125 157-174 (2012)

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

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

## Examples

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

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

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

## Examples

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

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

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

---

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

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

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

## Examples

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

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

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

---

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

---

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

---

## Description

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

## Usage

```
hematocrit_infants(age_months)
```

## Arguments

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

## Details

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

## Value

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

## Author(s)

Caroline Ring

## References

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

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

## Description

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

## Usage

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

## Arguments

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

## Details

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

## Value

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

## Author(s)

Greg Honda and John Wambaugh

## References

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

## Examples

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

---

# howgate *Howgate 2006*

---

## Description

This data set is only used in Vignette 5.

## Usage

```
howgate
```

## Format

A data.table containing 24 rows and 11 columns.

## Author(s)

Caroline Ring

## References

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

---

# httkpop *httkpop: Virtual population generator for HTTK.*

---

## Description

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

## 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 smooth-

ing 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

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

`httkpop_direct_resample` *Generate a virtual population by directly resampling the NHANES data.*

## Description

Generate a virtual population by directly resampling the NHANES data.

## Usage

```
httkpop_direct_resample(
  nsamp = NULL,
  gendernum = NULL,
  agelim_years = NULL,
  agelim_months = NULL,
  weight_category = c("Underweight", "Normal", "Overweight", "Obese"),
  gfr_category = c("Normal", "Kidney Disease", "Kidney Failure"),
  reths = c("Mexican American", "Other Hispanic", "Non-Hispanic White",
    "Non-Hispanic Black", "Other"),
  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'` 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, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

---

# `httkpop_direct_resample_inner`

*Inner loop function called by* `httkpop_direct_resample`.

---

## Description

Inner loop function called by `httkpop_direct_resample`.

## Usage

```
httkpop_direct_resample_inner(
  nsamp,
  gendernum,
  agelim_months,
  agelim_years,
  reths,
  weight_category,
  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' 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, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

`httkpop_generate` *Generate a virtual population 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'
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 | D |
|---|---|
| seqn | NHANES unique identifier (only included if method = "direct resam |
| gender | Sex: "Male" or " |
| reth | Race/ethnicity: "Non-Hispanic Black", "Non-Hispanic white", "Mexican American", "Other Hispanic", or |
| age_years | Age (0-7 |
| age_months | Age (0-959 |

## 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 | |
| Brain_mass | |
| Gonads_mass | |
| Heart_mass | |
| Kidneys_mass | |
| Large_intestine_mass | Mass o |
| Liver_mass | |
| Lung_mass | |
| Muscle_mass | Mass of |
| Pancreas_mass | M |
| Skeleton_mass | Mass of skeleton (including bone, red and yellow marrow, cartilage, per |
| Skin_mass | |
| Small_intestine_mass | Mass o |
| Spleen_mass | |
| Stomach_mass | Mass o |
| Other_mass | Mass of GI tract contents (1.4% of body weight) and tissues not otherwise enumerated (3.3% o |
| org_mass_sum | Sum of the above tissue masses. A check to ensure this is less th |
| Adipose_mass | Mass of adipose tissue. Assigned as weight - |

**Tissue flows**

| Name | Definiti |
|---|---|
| Adipose_flow | Blood flow to adipose tiss |
| Brain_flow | Blood flow to brain tiss |
| CO | Cardiac outp |
| Gonads_flow | Blood flow to gonads tiss |
| Heart_flow | Blood flow to heart tiss |
| Kidneys_flow | Blood flow to kidneys tissue (not for glomerular filtratio |
| Large_intestine_flow | Blood flow to large intestine tiss |
| Liver_flow | Blood flow to liver tiss |
| Lung_flow | Blood flow to lung tiss |
| Muscle_flow | Blood flow to skeletal muscle tiss |
| Pancreas_flow | Blood flow to pancreas tiss |
| Skeleton_flow | Blood flow to skelet |
| Skin_flow | Blood flow to sk |
| Small_intestine_flow | Blood flow to small intest |
| Spleen_flow | Blood flow to sple |
| Stomach_flow | Blood flow to stoma |

| | |
|---|---|
| org_flow_check | Sum of blood flows as a fraction of cardiac output (CO). A check to make sure this is less than |

## Adjusted variables

| Name | |
|---|---|
| weight_adj | |
| BSA_adj | |
| million.cells.per.gliver | |
| gfr_est | Glomerular filtration rate (GFR) estimated using either the CKD-EPI equ |
| bmi_adj | |
| weight_class | Weight category based on bmi_adj: "Underweight" (BMI < 18.5), "Normal" (18.5 < BM |
| gfr_class | Kidney function category based on GFR: "Normal" (GFR >=60 mL/min/1.73 m^2), " |

## Author(s)

Caroline Ring

## References

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

## 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
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'))
```

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

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

## Examples

```
set.seed(42)
indiv_examp <- httkpop_generate(method="d", nsamp=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'
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, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

---

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

---

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

---

## Description

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

## Usage

```
in.list(chem.cas = NULL, which.list = "ToxCast")
```

## Arguments

| | |
|---|---|
| `chem.cas` | The Chemical Abstracts Service Resgistry Number (CAS-RN) corresponding to the chemical of interest. |
| `which.list` | A character string that can take the following values: "ToxCast", "Tox21", "ExpoCast", "NHANES", ""NHANES.serum.parent", "NHANES.serum.analyte","NHANES.blood.pare "NHANES.urine.parent","NHANES.urine.analyte" |

## Details

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

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

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

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

## Value

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

## Author(s)

John Wambaugh

## References

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

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

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

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

## See Also

`is.httk` for determining inclusion in httk project

## Examples

```
httk.table <- get_cheminfo(info=c("CAS","Compound"))
httk.table[,"Rat"] <- ""
httk.table[,"NHANES"] <- ""
httk.table[,"Tox21"] <- ""
httk.table[,"ToxCast"] <- ""
httk.table[,"ExpoCast"] <- ""
httk.table[,"PBTK"] <- ""
# To make this example run quickly, this loop is only over the first 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,
  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. |
| 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 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. (submitted).

## Value

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

## Author(s)

Caroline Ring and John Wambaugh

## References

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

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

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

## Examples

```
#Simply generate a virtual population of 100 individuals,
#using the direct-resampling method
set.seed(42)
# Pull mean vchemical=specific values:
chem.props <- parameterize_pbtk(chem.name="bisphenolaf")
# 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, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118

## johnson *Johnson 2006*

### Description

This data set is only used in Vignette 5.

### Usage

```
johnson
```

### Format

A data.table containing 60 rows and 11 columns.

### Author(s)

Caroline Ring

### References

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

## 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 et al. 2019 Fetal PBTK Model

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

## liver_mass_children *Predict liver mass for children*

### Description

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

### Usage

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

### Arguments

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

### Value

A vector of liver masses in kg.

### Author(s)

Caroline Ring

### References

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

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

## load_dawson2021 *Load data from Dawson et al. 2021.*

### Description

This function returns an updated version of chem.physical_and_invitro.data that includes data predicted with Random Forest QSAR models developed and presented in Dawson et al. 2021, included in dawson2021.

### Usage

```
load_dawson2021(overwrite = FALSE, exclude_oad = TRUE, target.env = .GlobalEnv)
```

### Arguments

| | |
|---|---|
| overwrite | Only matters if load.image=FALSE. If overwrite=TRUE then existing data in chem.physical_and_invitro.data will be replaced by any data/predictions in 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 exlude_oad=TRUE (DEFAULT) chemicals outside the applicability domain do not have their predicted values loaded. |
| target.env | The environment where the new chem.physical_and_invitro.data is loaded. Defaults to global environment. |

### Value

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

### Author(s)

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.

### Examples

```
## Not run:
chem.physical_and_invitro.data <- load_dawson2021()
chem.physical_and_invitro.data <- load_dawson2021(overwrite=TRUE)

## End(Not run)
```

---

## load_pradeep2020 *Load data from Pradeep et al. 2020.*

---

### Description

This function returns an updated version of chem.physical_and_invitro.data that includes data predicted with Support Vector Machine and Random Forest models developed and presented in Pradeep et al. 2020, included in pradeep2020.

### Usage

```
load_pradeep2020(overwrite = FALSE, target.env = .GlobalEnv)
```

### Arguments

| | |
|---|---|
| overwrite | Only matters if load.image=FALSE. If overwrite=TRUE then existing data in chem.physical_and_invitro.data will be replaced by any data/predictions in 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. |
| target.env | The environment where the new chem.physical_and_invitro.data is loaded. Defaults to global environment. |

### Value

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

### Author(s)

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, https://www.sciencedirect.com/science/article/pii/S2468111320300463.

### Examples

```
## Not run:
chem.physical_and_invitro.data <- load_pradeep2020()
chem.physical_and_invitro.data <- load_pradeep2020(overwrite=TRUE)

## End(Not run)
```

---

## load_sipes2017 *Load data from Sipes et al 2017.*

---

### Description

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

### Usage

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

### Arguments

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

### Value

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

### Author(s)

Robert Pearce and John Wambaugh

### References

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

### Examples

```
num.chems <- length(get_cheminfo())
load_sipes2017()

#We should have the ADMet Predicted chemicals from Sipes et al. (2017),
#this one is a good test since the logP is nearly 10
calc_css(chem.cas="26040-51-7")

#Let's see how many chemicals we have now with the Sipes (2017) data loaded:
length(get_cheminfo())

#Now let us reset
reset_httk()

# We should be back to our original number:
num.chems == length(get_cheminfo())
```

---

## lump_tissues *Lump tissue parameters into model compartments 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.*

---

## Description

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.

## 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. |

## Details

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.

## Value

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

## Author(s)

John Wambaugh and Robert Pearce

## References

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

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

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

### Description

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

---

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

---

`metabolism_data_Linakis2020`

*Metabolism data involved in Linakis 2020 vignette analysis.*

---

## Description

Metabolism data involved in Linakis 2020 vignette analysis.

## Usage

```
metabolism_data_Linakis2020
```

## Format

A data.frame containing x rows and y columns.

## Author(s)

Matt Linakis

## Source

Matt Linakis

## References

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

---

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

---

`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
)
```

## 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).

## 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.

## Value

Vdist
: Volume of distribution, units of L/kg BW.

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

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

kelim
: Elimination rate, units of 1/h.

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

kgutabs
: Rate chemical is absorbed, 1/h.

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

MW
: Molecular Weight, g/mol.

Rblood2plasma
: The ratio of the concentration of the chemical in the blood to the concentration in the plasma. Not used in calculations but included for the conversion of plasma outputs.

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

BW
: Body Weight, kg.

### Author(s)

John Wambaugh and Robert Pearce

### References

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

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

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

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

### See Also

solve_1comp

calc_analytic_css_1comp

calc_vdist

parameterize_steadystate

apply_clint_adjustment

tissue.data

physiology.data

### Examples

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

---

## parameterize_3comp *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,
  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
)
```

## Arguments

| | |
|---|---|
| chem.cas | Chemical Abstract Services Registry Number (CAS-RN) – the chemical must be identified by either CAS, name, or DTXISD |
| chem.name | Chemical name (spaces and capitalization ignored) – the chemical must be identified by either CAS, name, or DTXISD |
| dtxsid | EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) – the chemical must be identified by either CAS, name, or DTXSIDs |
| species | Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human"). |
| default.to.human | Substitutes missing animal values with human values if true. |
| force.human.clint.fup | Forces use of human values for hepatic intrinsic clearance and fraction of unbound plasma if true. |
| clint.pvalue.threshold | Hepatic clearances with clearance assays having p-values greater than the threshold are set to zero. |
| adjusted.Funbound.plasma | 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). |

## Value

| | |
|---|---|
| BW | Body Weight, kg. |
| Clmetabolismc | Hepatic Clearance, L/h/kg BW. |
| Fgutabs | Fraction of the oral dose absorbed, i.e. the fraction of the dose that enters the gutlumen. |
| Funbound.plasma | Fraction of plasma that is not bound. |
| Fhep.assay.correction | The fraction of chemical unbound in hepatocyte assay using the method of Kilford et al. (2008) |
| hematocrit | Percent volume of red blood cells in the blood. |
| Kgut2pu | Ratio of concentration of chemical in gut tissue to unbound concentration in plasma. |
| Kliver2pu | Ratio of concentration of chemical in liver tissue to unbound concentration in plasma. |
| Krbc2pu | Ratio of concentration of chemical in red blood cells to unbound concentration in plasma. |
| Krest2pu | Ratio of concentration of chemical in rest of body tissue to unbound concentration in plasma. |
| million.cells.per.gliver | Millions cells per gram of liver tissue. |
| MW | Molecular Weight, g/mol. |
| Qcardiacc | Cardiac Output, L/h/kg BW^3/4. |
| Qgfrc | Glomerular Filtration Rate, L/h/kg BW^3/4, volume of fluid filtered from kidney and excreted. |
| Qgutf | Fraction of cardiac output flowing to the gut. |
| Qliverf | Fraction of cardiac output flowing to the liver. |
| Rblood2plasma | The ratio of the concentration of the chemical in the blood to the concentration in the plasma. |
| Vgutc | Volume of the gut per kg body weight, L/kg BW. |
| Vliverc | Volume of the liver per kg body weight, L/kg BW. |
| Vrestc | Volume of the rest of the body per kg body weight, L/kg BW. |

## Author(s)

Robert Pearce and John Wambaugh

## References

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

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

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

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

## See Also

solve_3comp

calc_analytic_css_3comp

parameterize_pbtk

apply_clint_adjustment

tissue.data

physiology.data

## Examples

```
parameters <- parameterize_3comp(chem.name='Bisphenol-A',species='Rat')
parameters <- parameterize_3comp(chem.cas='80-05-7',
                                 species='rabbit',default.to.human=TRUE)
out <- solve_3comp(parameters=parameters,plots=TRUE)
```

---

# parameterize_fetal_pbtk

*Parameterize_fetal_PBTK*

---

## Description

This function initializes the parameters needed in the functions solve_fetal_pbtk by calling solve_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 (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 narrow human model is supported. |

`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.

## Value

`pre_pregnant_BW`
: Body Weight before pregnancy, kg.

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

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

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

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

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

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

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

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

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

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

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

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

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

`MW`
: Molecular Weight, g/mol.

`Qgfrc`
: 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. |
| 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. |
| Kthyroid2pu | Ratio of concentration of chemical in fetal thyroid 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. |

## Author(s)

Robert Pearce, Mark Sfeir, John Wambaugh, and Dustin Kapraun

Mark Sfeir, Dustin Kapraun, John Wambaugh

## References

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

McNamara PJ, Alcorn J. Protein binding predictions in infants. AAPS PharmSci. 2002;4(1):E4. doi: 10.1208/ps040104. PMID: 12049488.

## See Also

solve_fetal_pbtk

parameterize_pbtk

predict_partitioning_schmitt

apply_clint_adjustment

tissue.data

physiology.data

kapraun2019

## Examples

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

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

---

`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,
  ...
)
```

## 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).

... — Other parameters

## Value

BW — Body Weight, kg.

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

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

| | |
|---|---|
| Clmetabolismc | Hepatic Clearance, L/h/kg BW. |
| Fgutabs | Fraction of the oral dose absorbed, i.e. the fraction of the dose that enters the gut lumen. |
| Fhep.assay.correction | The fraction of chemical unbound in hepatocyte assay using the method of Kilford et al. (2008) |
| Funbound.plasma | Fraction of chemical unbound to plasma. |
| Funbound.plasma.adjustment | Fraction unbound to plasma adjusted as described in Pearce et al. 2017 |
| Funbound.plasma.dist | Distribution of fraction unbound to plasma (median, lower 95th, upper 95th) |
| hematocrit | Percent volume of red blood cells in the blood. |
| Kblood2air | Ratio of concentration of chemical in blood to air |
| Kgut2pu | Ratio of concentration of chemical in gut tissue to unbound concentration in plasma. |
| kgutabs | Rate that chemical enters the gut from gutlumen, 1/h. |
| Kkidney2pu | Ratio of concentration of chemical in kidney tissue to unbound concentration in plasma. |
| Kliver2pu | Ratio of concentration of chemical in liver tissue to unbound concentration in plasma. |
| Klung2pu | Ratio of concentration of chemical in lung tissue to unbound concentration in plasma. |
| km | Michaelis-Menten concentration of half-maximal activity |
| Kmuc2air | Mucus to air partition coefficient |
| Krbc2pu | Ratio of concentration of chemical in red blood cells to unbound concentration in plasma. |
| Krest2pu | Ratio of concentration of chemical in rest of body tissue to unbound concentration in plasma. |
| kUrtc | Unscaled upper respiratory tract uptake parameter (L/h/kg^0.75) |
| liver.density | Density of liver in g/mL |
| MA | phospholipid:water distribution coefficient, membrane affinity |
| million.cells.per.gliver | Millions cells per gram of liver tissue. |
| MW | Molecular Weight, g/mol. |
| pKa_Accept | compound H association equilibrium constant(s) |
| pKa_Donor | compound H dissociation equilibirum constant(s) |
| Pow | octanol:water partition coefficient (not log transformed) |
| Qalvc | Unscaled alveolar ventilation rate (L/h/kg^0.75) |
| Qcardiacc | Cardiac Output, L/h/kg BW^3/4. |
| Qgfrc | Glomerular Filtration Rate, L/h/kg BW^0.75, volume of fluid filtered from kidney and excreted. |
| Qgutf | Fraction of cardiac output flowing to the gut. |
| Qkidneyf | Fraction of cardiac output flowing to the kidneys. |

| | |
|---|---|
| Qliverf | Fraction of cardiac output flowing to the liver. |
| Qlungf | Fraction of cardiac output flowing to lung tissue. |
| Qrestf | Fraction of blood flow to rest of body |
| Rblood2plasma | The ratio of the concentration of the chemical in the blood to the concentration in the plasma from available_rblood2plasma. |
| Vartc | Volume of the arteries per kg body weight, L/kg BW. |
| Vgutc | Volume of the gut per kg body weight, L/kg BW. |
| Vkidneyc | Volume of the kidneys per kg body weight, L/kg BW. |
| Vliverc | Volume of the liver per kg body weight, L/kg BW. |
| Vlungc | Volume of the lungs per kg body weight, L/kg BW. |
| vmax | Michaelis-Menten maximum reaction velocity (1/min) |
| Vmucc | Unscaled mucosal volume (L/kg BW^0.75 |
| Vrestc | Volume of the rest of the body per kg body weight, L/kg BW. |
| Vvenc | Volume of the veins per kg body weight, L/kg BW. |

## Author(s)

Matt Linakis, Robert Pearce, John Wambaugh

## References

Linakis, Matthew W., et al. "Development and evaluation of a high throughput inhalation model for organic chemicals." Journal of exposure science & environmental epidemiology 30.5 (2020): 866-877.

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

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

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

## 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,
  million.cells.per.gliver = 110,
  liver.density = 1.05,
  kgutabs = 2.18
)
```

## 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). |
| 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 (defaults to 2.18 1/h from Wambaugh et al. (2018)) |

## 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).

## Value

| | |
|---|---|
| BW | Body Weight, kg. |
| Clmetabolismc | Hepatic Clearance, L/h/kg BW. |

| | |
|---|---|
| Fgutabs | Fraction of the oral dose absorbed, i.e. the fraction of the dose that enters the gutlumen. |
| Funbound.plasma | Fraction of plasma that is not bound. |
| Fhep.assay.correction | The fraction of chemical unbound in hepatocyte assay using the method of Kilford et al. (2008) |
| hematocrit | Percent volume of red blood cells in the blood. |
| Kgut2pu | Ratio of concentration of chemical in gut tissue to unbound concentration in plasma. |
| kgutabs | Rate that chemical enters the gut from gutlumen, 1/h. |
| Kkidney2pu | Ratio of concentration of chemical in kidney tissue to unbound concentration in plasma. |
| Kliver2pu | Ratio of concentration of chemical in liver tissue to unbound concentration in plasma. |
| Klung2pu | Ratio of concentration of chemical in lung tissue to unbound concentration in plasma. |
| Krbc2pu | Ratio of concentration of chemical in red blood cells to unbound concentration in plasma. |
| Krest2pu | Ratio of concentration of chemical in rest of body tissue to unbound concentration in plasma. |
| million.cells.per.gliver | Millions cells per gram of liver tissue. |
| MW | Molecular Weight, g/mol. |
| Qcardiacc | Cardiac Output, L/h/kg BW^3/4. |
| Qgfrc | Glomerular Filtration Rate, L/h/kg BW^3/4, volume of fluid filtered from kidney and excreted. |
| Qgutf | Fraction of cardiac output flowing to the gut. |
| Qkidneyf | Fraction of cardiac output flowing to the kidneys. |
| Qliverf | Fraction of cardiac output flowing to the liver. |
| Rblood2plasma | The ratio of the concentration of the chemical in the blood to the concentration in the plasma from available_rblood2plasma. |
| Vartc | Volume of the arteries per kg body weight, L/kg BW. |
| Vgutc | Volume of the gut per kg body weight, L/kg BW. |
| Vkidneyc | Volume of the kidneys per kg body weight, L/kg BW. |
| Vliverc | Volume of the liver per kg body weight, L/kg BW. |
| Vlungc | Volume of the lungs per kg body weight, L/kg BW. |
| Vrestc | Volume of the rest of the body per kg body weight, L/kg BW. |
| Vvenc | Volume of the veins per kg body weight, L/kg BW. |

## Author(s)

John Wambaugh and Robert Pearce

## References

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

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

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

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

Carlile, David J., Katayoun Zomorodi, and J. Brian Houston. "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 (1997): 903-911.

International Commission on Radiological Protection. Report of the task group on reference man. Vol. 23. Pergamon, Oxford. 1975.

Wambaugh, John F., et al. "Evaluating in vitro-in vivo extrapolation of toxicokinetics." Toxicological Sciences 163.1 (2018): 152-169.

## See Also

solve_pbtk

calc_analytic_css_pbtk

predict_partitioning_schmitt

apply_clint_adjustment

tissue.data

physiology.data

## Examples

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

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

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

---

# parameterize_schmitt *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) method for predicting tissue:plasma partition coefficients as modified by Pearce et al. (2017). The modifications include approaches adapted from Peyret et al. (2010).

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

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

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

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

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

## See Also

predict_partitioning_schmitt

tissue.data

calc_ma

apply_fup_adjustment

## Examples

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

---

# 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,
  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
)
```

## 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). |
| 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). |

## Value

| | |
|---|---|
| `Clint` | Hepatic Intrinsic Clearance, uL/min/10^6 cells. |
| `Fgutabs` | Fraction of the oral dose absorbed, i.e. the fraction of the dose that enters the gutlumen. |
| `Funbound.plasma` | Fraction of plasma that is not bound. |
| `Qtotal.liverc` | Flow rate of blood exiting the liver, L/h/kg BW^3/4. |
| `Qgfrc` | Glomerular Filtration Rate, L/h/kg BW^3/4, volume of fluid filtered from kidney and excreted. |
| `BW` | Body Weight, kg |
| `MW` | Molecular Weight, g/mol |
| `million.cells.per.gliver` | Millions cells per gram of liver tissue. |
| `Vliverc` | Volume of the liver per kg body weight, L/kg BW. |
| `liver.density` | Liver tissue density, kg/L. |
| `Fhep.assay.correction` | The fraction of chemical unbound in hepatocyte assay using the method of Kilford et al. (2008) |
| `hepatic.bioavailability` | Fraction of dose remaining after first pass clearance, calculated from the corrected well-stirred model. |

## Author(s)

John Wambaugh

## References

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

---

## physiology.data *Species-specific physiology parameters*

---

### Description

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

### Usage

```
physiology.data
```

### Format

A data.frame containing 11 rows and 7 columns.

### Author(s)

John Wambaugh and Nisha Sipes

### Source

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

### References

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

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

## 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 et al. 2021 (submitted)

### 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.

## 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-centur

### Usage

```
pradeep2020
```

### Format

data.frame

### Details

Prediction were made with Support Vector Machine and Random Forest models, as reported in Pradeep et al. (2020).

## Source

Pradeep et al. 2020 Chemical Structure Predictive Models for HTTK

## 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, https://www.sciencedirect.com/science/article/pii/S2468111320300463.

---

`predict_partitioning_schmitt`

*Predict partition coefficients using the method from Schmitt (2008). #' 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 modifed by Pearce et al. (2017) based on an evalaution using in vivo measured partition coefficients.*

---

## Description

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.

## 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. |

## Details

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.

## Value

Returns tissue to unbound plasma partition coefficients for each tissue.

## Author(s)

Robert Pearce

## References

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

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

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

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

## See Also

parameterize_schmitt

tissue.data

## Examples

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

---

# 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 et al. 2021 (submitted)

## 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.

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

`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 et al., in preparation

## 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 Fgutabs, 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
)
```

### 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". |

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

---

`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

`skeletal_muscle_mass` *Predict skeletal muscle mass*

## Description

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

## Usage

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

## Arguments

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

## Details

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

## Value

Vector of skeletal muscle masses in kg.

## Author(s)

Caroline Ring

## References

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

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

## See Also

`skeletal_muscle_mass_children`

## skeletal_muscle_mass_children *Predict skeletal muscle mass for children*

### Description

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

### Usage

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

### Arguments

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

### Value

Vector of skeletal muscle masses in kg.

### Author(s)

Caroline Ring

### References

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

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

## skin_mass_bosgra *Predict skin mass*

### Description

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

### Usage

```
skin_mass_bosgra(BSA)
```

### Arguments

| | |
|---|---|
| BSA | Vector of body surface areas in cm^2. |

## Value

Vector of skin masses in kg.

## Author(s)

Caroline Ring

## References

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

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

---

# solve_1comp *Solve one compartment TK model*

---

## Description

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

## Usage

```
solve_1comp(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  times = NULL,
  parameters = NULL,
  days = 10,
  tsteps = 4,
  daily.dose = NULL,
  dose = NULL,
  doses.per.day = NULL,
  initial.values = NULL,
  plots = FALSE,
  suppress.messages = FALSE,
  species = "Human",
  iv.dose = FALSE,
  input.units = "mg/kg",
  output.units = NULL,
  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 = TRUE,
  minimum.Funbound.plasma = 1e-04,
  monitor.vars = NULL,
  ...
)
```

## Arguments

| | |
|---|---|
| chem.name | Either the chemical name, CAS number, or the parameters must be specified. |
| chem.cas | Either the chemical name, CAS number, or the parameters must be specified. |
| dtxsid | EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs |
| times | Optional time sequence for specified number of days. |
| parameters | Chemical parameters from parameterize_1comp function, overrides chem.name and chem.cas. |
| days | Length of the simulation. |
| tsteps | The number time steps per hour. |
| daily.dose | Total daily dose, 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. |
| method | Method used by integrator (deSolve). |
| rtol | Argument passed to integrator (deSolve). |
| atol | Argument passed to integrator (deSolve). |
| default.to.human | Substitutes missing rat values with human values if true. |
| recalc.blood2plasma | Whether or not to recalculate the blood:plasma chemical concentrationr ratio |
| recalc.clearance | Whether or not to recalculate the elimination rate. |
| dosing.matrix | Vector of dosing times or a matrix consisting of two columns or rows named "dose" and "time" containing the time and amount, in mg/kg BW 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"

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

## Details

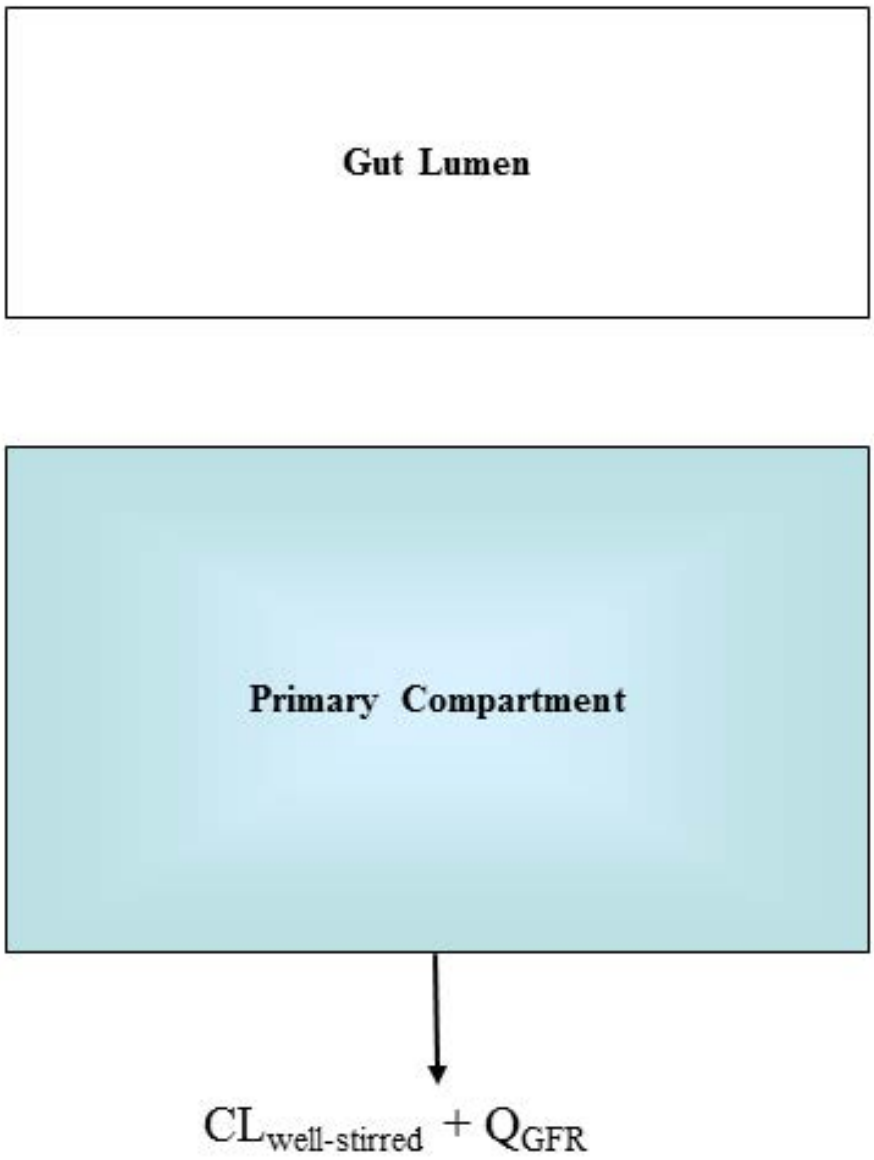
Note that the timescales for the model parameters have units of hours while the model output is in days.

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.

AUC is area under plasma concentration curve.

Model Figure




altalt

## Value

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

## Author(s)

Robert Pearce

## References

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

## 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)
```

---

solve_3comp *Solve_3comp*

---

## Description

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

## Usage

```
solve_3comp(
  chem.name = NULL,
  chem.cas = NULL,
  dtxsid = NULL,
  times = NULL,
  parameters = NULL,
  days = 10,
  tsteps = 4,
  daily.dose = NULL,
  dose = NULL,
  doses.per.day = NULL,
  initial.values = NULL,
  plots = FALSE,
```

```
  suppress.messages = FALSE,
  species = "Human",
  iv.dose = FALSE,
  input.units = "mg/kg",
  output.units = NULL,
  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 = TRUE,
  minimum.Funbound.plasma = 1e-04,
  monitor.vars = NULL,
  ...
)
```

## Arguments

| | |
|---|---|
| chem.name | Either the chemical name, CAS number, or the parameters must be specified. |
| chem.cas | Either the chemical name, CAS number, or the parameters must be specified. |
| dtxsid | EPA's 'DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs |
| times | Optional time sequence for specified number of days. The dosing sequence begins at the beginning of times. |
| parameters | Chemical parameters from parameterize_3comp function, overrides chem.name and chem.cas. |
| days | Length of the simulation. |
| tsteps | The number time steps per hour. |
| daily.dose | Total daily dose, mg/kg BW. |
| dose | Amount of a single dose, mg/kg BW. |
| doses.per.day | Number of doses per day. |
| initial.values | Vector containing the initial concentrations or amounts of the chemical in specified tissues with units corresponding to output.units. Defaults are zero. |
| plots | Plots all outputs if true. |
| suppress.messages | Whether or not the output message is suppressed. |
| species | Species desired (either "Rat", "Rabbit", "Dog", "Mouse", or default "Human"). |
| iv.dose | Simulates a single i.v. dose if true. |
| 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. |
| method | Method used by integrator (deSolve). |
| rtol | Argument passed to integrator (deSolve). |

`atol` Argument passed to integrator (deSolve).

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

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

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

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

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

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

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

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

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

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

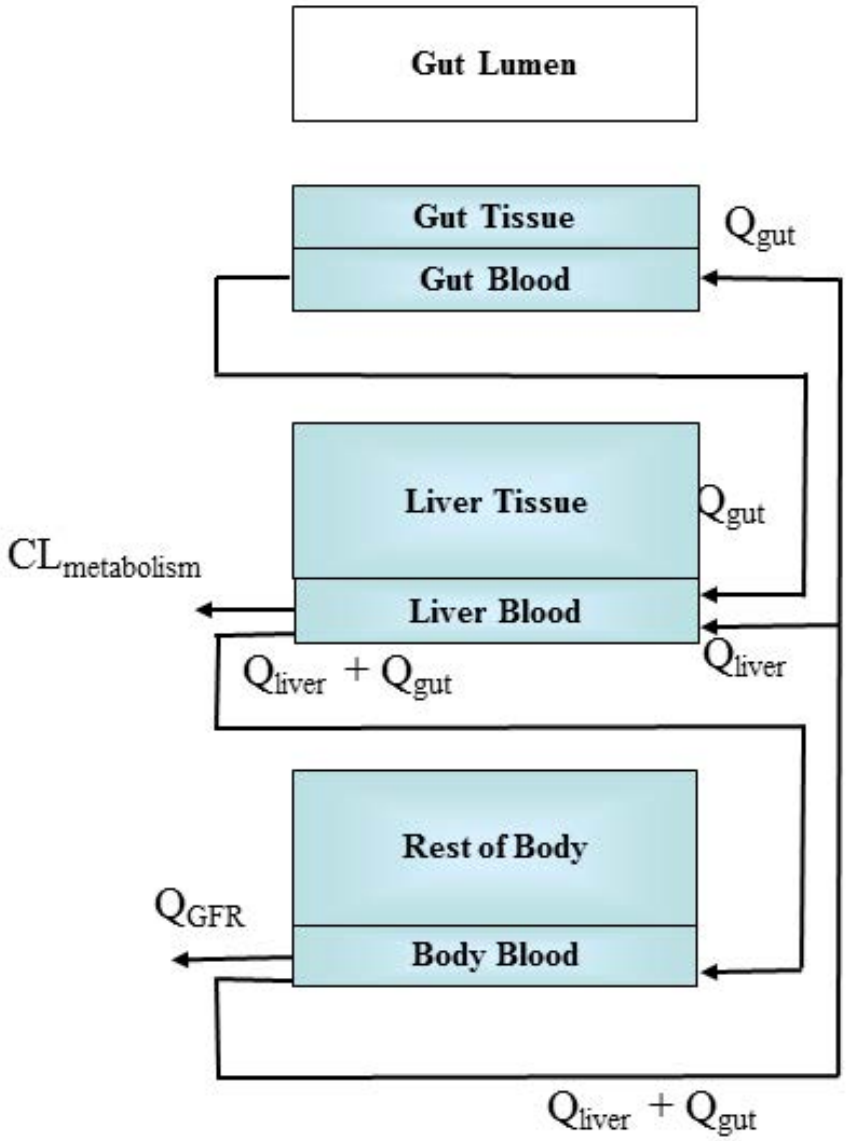
## Details

Note that the 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 equivalent to the liver plasma.

Model Figure




altalt

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

## Value

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

## Author(s)

John Wambaugh and Robert Pearce

## References

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

## 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)
```

---

# 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 = 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,
  method = "lsoda",
  rtol = 1e-08,
  atol = 1e-12,
  default.to.human = FALSE,
  recalc.blood2plasma = FALSE,
  recalc.clearance = FALSE,
  adjusted.Funbound.plasma = TRUE,
  regression = TRUE,
  restrictive.clearance = TRUE,
  minimum.Funbound.plasma = 1e-04,
  monitor.vars = NULL,
  ...
)
```

## Arguments

| | |
|---|---|
| chem.name | Either the chemical name, CAS number, or the parameters must be specified. |
| chem.cas | Either the chemical name, CAS number, or the parameters must be specified. |
| dtxsid | EPA's DSSTox Structure ID (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. |
| method | Method used by integrator (deSolve). |
| rtol | Argument passed to integrator (deSolve). |
| atol | Argument passed to integrator (deSolve). |
| default.to.human | Substitutes missing animal values with human values if true (hepatic intrinsic clearance or fraction of unbound plasma). |
| recalc.blood2plasma | Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters, calculated with hematocrit, Funbound.plasma, and Krbc2pu. |
| recalc.clearance | Recalculates the the hepatic clearance (Clmetabolism) with new million.cells.per.gliver parameter. |
| 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 |
| ... | 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.

## 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

## 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 = 'perfluorooctane sulfonic acid')
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 = 'perfluorooctane sulfonic acid',
                                fetal_fup_adjustment = FALSE)
head(solve_fetal_pbtk(parameters = fetal_parms_fup_unadjusted))
```

---

# 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.

## 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,
  method = "lsoda",
  rtol = 1e-08,
  atol = 1e-12,
  default.to.human = FALSE,
  recalc.blood2plasma = FALSE,
  recalc.clearance = FALSE,
  adjusted.Funbound.plasma = TRUE,
  regression = TRUE,
  restrictive.clearance = TRUE,
  minimum.Funbound.plasma = 1e-04,
  monitor.vars = NULL,
  vmax = 0,
  km = 1,
  exercise = FALSE,
  fR = 12,
  VT = 0.75,
  VD = 0.15,
  ...
)
```

## Arguments

| | |
|---|---|
| chem.name | Either the chemical name, CAS number, or the parameters must be specified. |
| chem.cas | Either the chemical name, CAS number, or the parameters must be specified. |
| dtxsid | EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs |
| parameters | Chemical parameters from parameterize_gas_pbtk (or other bespoke) function, overrides chem.name and chem.cas. |
| times | Optional time sequence for specified number of days. Dosing sequence begins at the beginning of times. |
| days | Length of the simulation. |
| tsteps | The number of time steps per hour. |

| | |
|---|---|
| daily.dose | Total daily dose |
| 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. |
| method | Method used by integrator (deSolve). |
| rtol | Argument passed to integrator (deSolve). |
| atol | Argument passed to integrator (deSolve). |
| default.to.human | Substitutes missing animal values with human values if true (hepatic intrinsic clearance or fraction of unbound plasma). |
| recalc.blood2plasma | Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters, calculated with hematocrit, Funbound.plasma, and Krbc2pu. |
| recalc.clearance | Recalculates the hepatic clearance (Clmetabolism) with new million.cells.per.gliver parameter. |
| adjusted.Funbound.plasma | Uses adjusted Funbound.plasma when set to TRUE along with partition coefficients calculated with this value. |
| regression | Whether or not to use the regressions in calculating partition coefficients. |

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

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

`monitor.vars`
: Which variables are returned as a function of time. Defaults value of NULL provides "Cgut", "Cliver", "Cven", "Clung", "Cart", "Crest", "Ckidney", "Cplasma", "Calv", "Cendexh", "Cmixexh", "Cmuc", "Atubules", "Ametabolized", "AUC"

`vmax`
: Michaelis-Menten vmax value in reactions/min

`km`
: Michaelis-Menten concentration of half-maximal reaction velocity in desired output concentration units.

`exercise`
: Logical indicator of whether to simulate an exercise-induced heightened respiration rate

`fR`
: Respiratory frequency (breaths/minute), used especially to adjust breathing rate in the case of exercise. This parameter, along with VT and VD (below) gives another option for calculating Qalv (Alveolar ventilation) in case pulmonary ventilation rate is not known

`VT`
: Tidal volume (L), to be modulated especially as part of simulating the state of exercise

`VD`
: Anatomical dead space (L), to be modulated especially as part of simulating the state of exercise

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

## Details

The default dosing scheme involves 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.

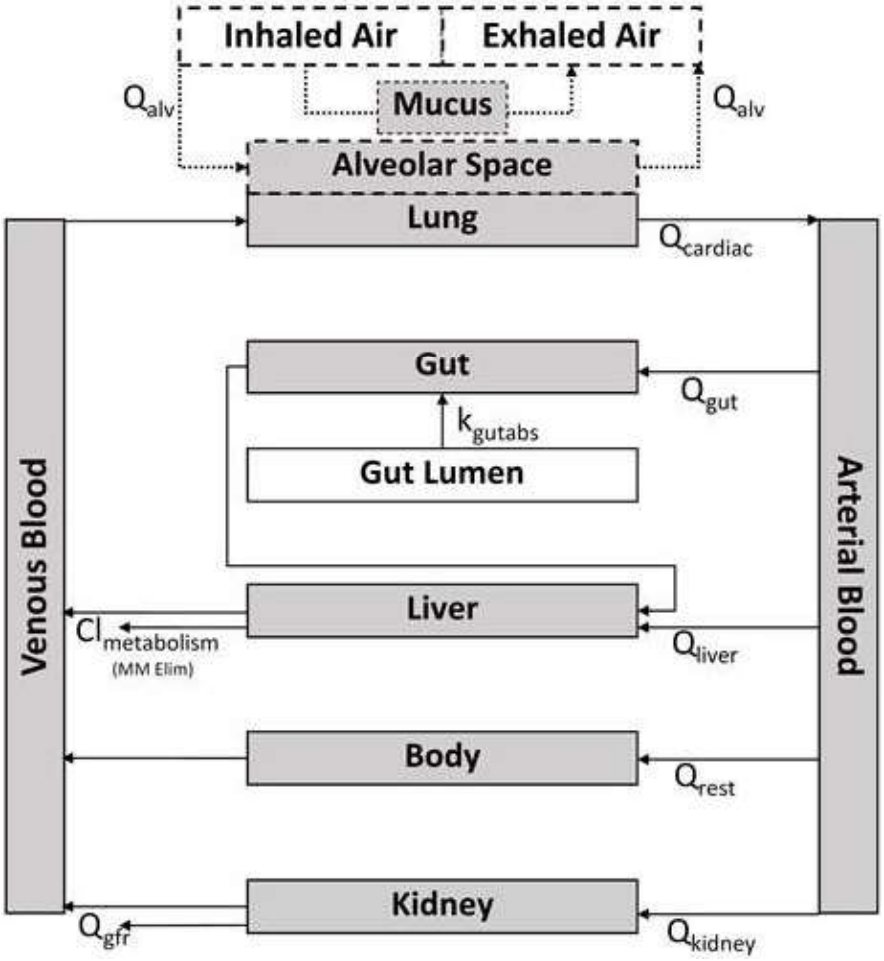
Default NULL value for doses.per.day solves for a single dose.

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.

## 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.

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.

## 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")))
```

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 = "lsoda",
  rtol = 1e-08,
  atol = 1e-12,
  recalc.blood2plasma = FALSE,
  recalc.clearance = FALSE,
  restrictive.clearance = TRUE,
  adjusted.Funbound.plasma = TRUE,
  minimum.Funbound.plasma = 1e-04,
  parameterize.arg.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 (http://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs |

`times` Optional time sequence for specified number of days. Dosing sequence begins at the beginning of times.

`parameters` List of chemical parameters, as output by parameterize_pbtk function. Overrides chem.name and chem.cas.

`model` Specified model to use in simulation: "pbtk", "3compartment", "3compartmentss", "1compartment", "schmitt", ...

`route` String specification of route of exposure for simulation: "oral", "iv", "inhalation", ...

`dosing` List of dosing metrics 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 dose of 1 mg/kg BW along with the dose type (add/multiply) specified for a given route (e.g. add the dose to gut lumen for oral route)

`days` Simulated period. Default 10 days.

`tsteps` The number of time steps per hour. Default of 4.

`initial.values` Vector 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` Argument passed to integrator (deSolve).

`atol` Argument passed to integrator (deSolve).

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

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

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

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

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

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

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

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

## Examples

```
# The varrious "solve_x" functions are wrappers for solve_model:
head(solve_pbtk(chem.name="Terbufos", days=1))

head(solve_model(chem.name="Terbufos",model="pbtk",dosing=list(
                 initial.dose = 1, # Assume dose is in mg/kg BW/day
                 doses.per.day=NULL,
                 dosing.matrix = NULL,
                 days=1,
                 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",dosing=list(
            initial.dose =NULL,
            doses.per.day=NULL,
            daily.dose=NULL,
            days=2.5,
            dosing.matrix=dm))

solve_model(chem.name="Besonprodil",model="pbtk",dosing=list(
            initial.dose =NULL,
            doses.per.day=4,
            daily.dose=1,
            days=2.5,
            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.

## 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,
  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 = TRUE,
  minimum.Funbound.plasma = 1e-04,
  monitor.vars = NULL,
  ...
)
```

## Arguments

| | |
|---|---|
| chem.name | Either the chemical name, CAS number, or the parameters must be specified. |
| chem.cas | Either the chemical name, CAS number, or the parameters must be specified. |
| dtxsid | EPA's DSSTox Structure ID (https://comptox.epa.gov/dashboard) the chemical must be identified by either CAS, name, or DTXSIDs |
| times | Optional time sequence for specified number of days. Dosing sequence begins at the beginning of times. |
| parameters | Chemical parameters from parameterize_pbtk function, overrides chem.name and chem.cas. |
| days | Length of the simulation. |
| tsteps | The number of time steps per hour. |
| daily.dose | Total daily dose, 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. |
| method | Method used by integrator (deSolve). |
| rtol | Argument passed to integrator (deSolve). |
| atol | Argument passed to integrator (deSolve). |
| default.to.human | Substitutes missing animal values with human values if true (hepatic intrinsic clearance or fraction of unbound plasma). |
| recalc.blood2plasma | Recalculates the ratio of the amount of chemical in the blood to plasma using the input parameters, calculated with hematocrit, Funbound.plasma, and Krbc2pu. |
| recalc.clearance | Recalculates the the hepatic clearance (Clmetabolism) with new million.cells.per.gliver parameter. |
| dosing.matrix | Vector of dosing times or a matrix consisting of two columns or rows named "dose" and "time" containing the time and amount, in mg/kg BW, of each dose. |
| adjusted.Funbound.plasma | Uses adjusted Funbound.plasma when set to TRUE along with partition coefficients calculated with this value. |
| regression | Whether or not to use the regressions in calculating partition coefficients. |
| restrictive.clearance | Protein binding not taken into account (set to 1) in liver clearance if FALSE. |
| minimum.Funbound.plasma | Monte Carlo draws less than this value are set equal to this value (default is 0.0001 – half the lowest measured Fup in our dataset). |
| monitor.vars | Which variables are returned as a function of time. The default value of NULL provides "Cgut", "Cliver", "Cven", "Clung", "Cart", "Crest", "Ckidney", "Cplasma", "Atubules", "Ametabolized", and "AUC" |
| ... | Additional arguments passed to the integrator. |

## Details

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

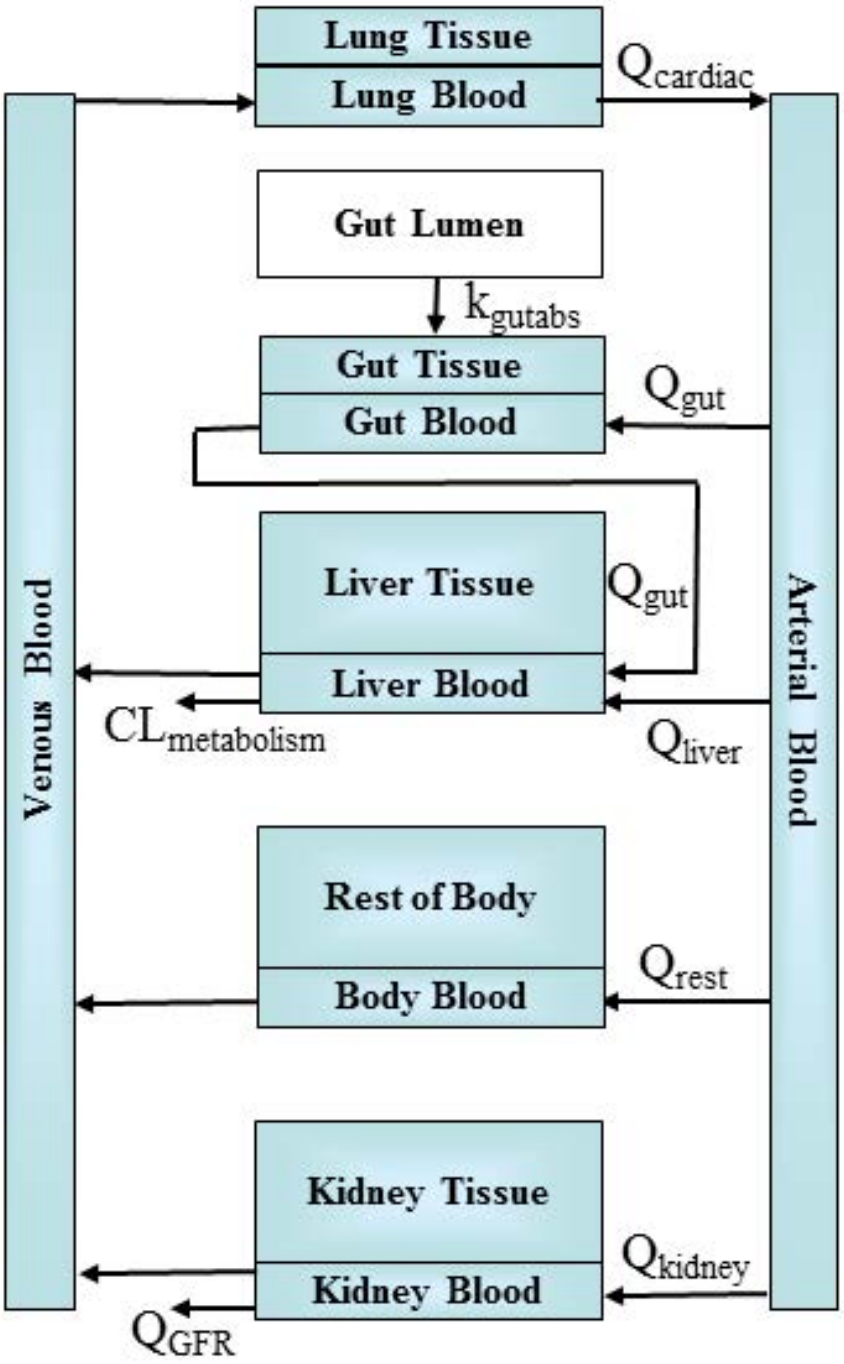
Default NULL value for doses.per.day solves for a single dose.

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

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

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

Model Figure




altalt

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

## Value

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

## Author(s)

John Wambaugh and Robert Pearce

## References

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

## 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)
```

---

`spleen_mass_children` *Predict spleen mass for children*

---

## Description

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

## Usage

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

## Arguments

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

## Value

A vector of spleen masses in kg.

## Author(s)

Caroline Ring

## References

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

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

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

## supptab1_Linakis2020 *Supplementary output from Linakis 2020 vignette analysis.*

### Description

Supplementary output from Linakis 2020 vignette analysis.

### Usage

```
supptab1_Linakis2020
```

### Format

A data.frame containing x rows and y columns.

### Author(s)

Matt Linakis

### Source

Matt Linakis

### References

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

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

### Description

More supplementary output from Linakis 2020 vignette analysis.

### Usage

```
supptab2_Linakis2020
```

### Format

A data.frame containing x rows and y columns.

### Author(s)

Matt Linakis

### Source

Matt Linakis

### References

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

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

### Description

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

### Usage

```
Tables.Rdata.stamp
```

### Format

An object of class `character` of length 1.

### Author(s)

John Wambaugh

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

### Description

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

### Usage

```
tissue.data
```

### Format

A data.frame containing 13 rows and 20 columns.

### Details

New tissues can be added to this table to generate their partition coefficients.

The tissue data needed for calculating partition coefficients include: cellular and water fractions of total volume, lipid and protein fractions of cellular volume, lipid fractions of the total lipid volume, the pH of each tissue, and the fractional volume of protein in plasma.

### Author(s)

John Wambaugh, Robert Pearce, and Nisha Sipes

## Source

Pearce et al. (2017), in preparation,

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

## References

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

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

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

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

## 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)
```

---

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

---

## Description

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

### Usage

```
tissue_masses_flows(tmf_dt)
```

### Arguments

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

### Value

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

### Author(s)

Caroline Ring

### References

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

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

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

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

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

---

## tissue_scale *Allometric scaling.*

---

### Description

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

### Usage

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

### Arguments

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

### Value

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

## Author(s)

Caroline Ring

## References

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

---

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

---

## Description

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

## Usage

```
wambaugh2019
```

## Format

A data frame with 496 rows and 17 variables:

**Compound** The name of the chemical

**CAS** The Chemical Abstracts Service Registry Number

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

**Human.Clint.pValue** Probability that there is no clearance

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

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

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

**DSSTox_Substance_Id** Identifier for CompTox Chemical Dashboard

**SMILES** Simplified Molecular-Input Line-Entry System structure description

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

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

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

**Human.Funbound.plasma.Low95** Lower 95th percentile of Bayesian credible interval for fraction of chemical free in the presence of plasma

**Human.Funbound.plasma.High95** Upper 95th percentile of Bayesian credible interval for fraction of chemical free in the presence of plasma

**Human.Funbound.plasma.Point** Point estimate of the fraction of chemical free in the presence of plasma

**MW** Molecular weight (Daltons)

**logP** log base ten of octanol:water partiion coefficient

## Author(s)

John Wambaugh

## Source

Wambaugh et al. (2019)

## References

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

---

`wambaugh2019.nhanes` *NHANES Chemical Intake Rates for chemicals in Wambaugh et al. (2019)*

---

## Description

These data are a subset of the Bayesian inferrences reported by Ring et al. (2017) from the U.S. Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES). They reflect the populaton median intake rate (mg/kg body weight/day), with uncertainty.

## Usage

```
wambaugh2019.nhanes
```

## Format

A data frame with 20 rows and 4 variables:

**lP** The median of the Bayesian credible interval for median population intake rate (mg/kg bodyweight/day)

**lP.min** The lower 95th percentile of the Bayesian credible interval for median population intake rate (mg/kg bodyweight/day)

**lP.max** The upper 95th percentile of the Bayesian credible interval for median population intake rate (mg/kg bodyweight/day)

**CASRN** The Chemical Abstracts Service Registry Number

## Author(s)

John Wambaugh

## Source

Wambaugh et al. (2019)

## References

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

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

---

`wambaugh2019.raw` *Raw Bayesian in vitro Toxicokinetic Data Analysis from Wambaugh et al. (2019)*

---

## Description

These data are the new HTTK in vitro data for chemicals reported in Wambaugh et al. (2019) They are the output of different Bayesian models evaluated to compare using a single protein concentration vs. the new three concentration titration protocol. These data summarize the results of Bayesian analysis of the in vitro toxicokinetic experiments conducted by Cyprotex to characterize fraction unbound in the presence of pooled human plasma protein and the intrnsic hepatic clearance of the chemical by pooled human hepatocytes. This file includes replicates (diferent CompoundName id's but same chemical')

## Usage

```
wambaugh2019.raw
```

## Format

A data frame with 530 rows and 28 variables:

**DTXSID** Identifier for CompTox Chemical Dashboard

**Name** The name of the chemical

**CAS** The Chemical Abstracts Service Registry Number

**CompoundName** Sample name provided by EPA to Cyprotex

**Fup.point** Point estimate of the fraction of chemical free in the presence of plasma

**Base.Fup.Med** Median of Bayesian credible interval for fraction of chemical free in the presence of plasma for analysis of 100 physiological plasma protein data only (base model)

**Base.Fup.Low** Lower 95th percentile of Bayesian credible interval for fraction of chemical free in the presence of plasma for analysis of 100 physiological plasma protein data only (base model)

**Base.Fup.High** Upper 95th percentile of Bayesian credible interval for fraction of chemical free in the presence of plasma for analysis of 100 physiological plasma protein data only (base model)

**Affinity.Fup.Med** Median of Bayesian credible interval for fraction of chemical free in the presence of plasma for analysis of protein titration protocol data (affinity model)

**Affinity.Fup.Low** Lower 95th percentile of Bayesian credible interval for fraction of chemical free in the presence of plasma for analysis of protein titration protocol data (affinity model)

**Affinity.Fup.High** Upper 95th percentile of Bayesian credible interval for fraction of chemical free in the presence of plasma for analysis of protein titration protocol data (affinity model)

**Affinity.Kd.Med** Median of Bayesian credible interval for protein binding affinity from analysis of protein titration protocol data (affinity model)

**Affinity.Kd.Low** Lower 95th percentile of Bayesian credible interval for protein binding affinity from analysis of protein titration protocol data (affinity model)

**Affinity.Kd.High** Upper 95th percentile of Bayesian credible interval for protein binding affinity from analysis of protein titration protocol data (affinity model)

**Decreases.Prob** Probability that the chemical concentration decreased systematiclally during hepatic clearance assay.

**Saturates.Prob** Probability that the rate of chemical concentration decrease varied between the 1 and 10 uM hepatic clearance experiments.

**Slope.1uM.Median** Estimated slope for chemcial concentration decrease in the 1 uM hepatic clearance assay.

**Slope.10uM.Median** Estimated slope for chemcial concentration decrease in the 10 uM hepatic clearance assay.

**CLint.1uM.Median** Median of Bayesian credible interval for intrinsic hepatic clearance at 1 uM inititial chemical concentration (uL/min/million hepatocytes)]

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

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

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

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

**CLint.10uM.High95th** Uppper 95th percentile of Bayesian credible interval for intrinsic hepatic clearance at 10 uM inititial chemical concentration(uL/min/million hepatocytes)

**CLint.1uM.Point** Point estimate of intrinsic hepatic clearance (uL/min/million hepatocytes) for 1 uM initial chemical concentration

**CLint.10uM.Point** Point estimate of intrinsic hepatic clearance (uL/min/million hepatocytes) for 10 uM initial chemical concentration

**Fit** Classification of clearance observed

**SMILES** Simplified Molecular-Input Line-Entry System structure description

## Author(s)

John Wambaugh

## Source

Wambaugh et al. (2019)

## References

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

## wambaugh2019.seem3 *ExpoCast SEEM3 Consensus Exposure Model Predictions for Chemical Intake Rates*

### Description

These data are a subset of the Bayesian inferrences reported by Ring et al. (2019) for a consensus model of twelve exposue predictors. The predictors were calibrated based upon their ability to predict intake rates inferred National Health and Nutrition Examination Survey (NHANES). They reflect the populaton median intake rate (mg/kg body weight/day), with uncertainty.

### Usage

```
wambaugh2019.seem3
```

### Format

A data frame with 385 rows and 38 variables:

### Author(s)

John Wambaugh

### Source

Wambaugh et al. (2019)

### References

Ring, Caroline L., et al. "Consensus modeling of median chemical intake for the US population based on predictions of exposure pathways." Environmental science & technology 53.2 (2018): 719-732.

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

## wambaugh2019.tox21 *Tox21 2015 Active Hit Calls (EPA)*

### Description

The ToxCast and Tox21 research programs employ batteries of high-throughput assays to assess chemical bioactivity in vitro. Not every chemical is tested through every assay. Most assays are conducted in concentration response, and each corresponding assay endpoint is analyzed statistically to determine if there is a concentration-dependent response or "hit" using the ToxCast Pipeline. Most assay endpoint-chemical combinations are non-responsive. Here, only the hits are treated as potential indicators of bioactivity. This bioactivity does not have a direct toxicological interpretation. The October 2015 release (invitrodb_v2) of the ToxCast and Tox21 data were used for this analysis. This object contains just the chemicals in Wambaugh et al. (2019) and only the quantiles across all assays for the ACC.

## Usage

```
wambaugh2019.tox21
```

## Format

A data.table with 401 rows and 6 columns

## Author(s)

John Wambaugh

## Source

ftp://newftp.epa.gov/COMPTOX/High_Throughput_Screening_Data/Previous_Data/ToxCast_Data_Release_Oct_2015/

## References

Kavlock, Robert, et al. "Update on EPA's ToxCast program: providing high-throughput decision support tools for chemical risk management." Chemical research in toxicology 25.7 (2012): 1287-1302.

Tice, Raymond R., et al. "Improving the human hazard characterization of chemicals: a Tox21 update." Environmental health perspectives 121.7 (2013): 756-765.

Richard, Ann M., et al. "ToxCast chemical landscape: paving the road to 21st century toxicology." Chemical research in toxicology 29.8 (2016): 1225-1251.

Filer, Dayne L., et al. "tcpl: the ToxCast pipeline for high-throughput screening data." Bioinformatics 33.4 (2016): 618-620.

Wambaugh, John F., et al. "Assessing Toxicokinetic Uncertainty and Variability in Risk Prioritization." Toxicological Sciences 172.2 (2019): 235-251.

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`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.*

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## 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 et al. 2021 (submitted)

### 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, https://ehp.niehs.nih.gov/doi/pdf/10.1289/EHP2920, https://ehp.niehs.nih.gov/doi/abs/10.1289/EHP2920.

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## 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

### Source

https://www.corning.com/catalog/cls/documents/application-notes/CLS-AN-209.pdf

### References

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

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

## Wetmore2012 — *Published toxicokinetic predictions based on in vitro data from Wetmore et al. 2012.*

### Description

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

### Usage

```
Wetmore2012
```

### Format

A data.frame containing 13 rows and 15 columns.

### References

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

## wfl — *WHO weight-for-length charts*

### Description

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

### Usage

```
wfl
```

### Format

a data.table 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.cdc.gov/growthcharts/who/boys_weight_head_circumference.htm and https://www.cdc.gov/growthcharts/who/girls_weight_head_circumference.htm

# Index