# perc.v2.1.0.mcmc.pop.model -- Updated PERC Risk Assessment Model
# perc.v2.1.0.risk.pop.model
#
# Based on Chiu et al. (2009) TCE model
# Replaced TCE with PERC
# Removed TCOH, TCOG compartments
# Replaced DCVG, DCVC, NAcDCVC with TCVG, TCVC, and NAcTCVC
# Used PERC in vitro data for distribution and metabolism parameters
#
# TCVG compartment removed (no TCVG blood data) by setting
# lnFracKidTCVCC = 30;
# lnkTCVGC = 30;
#
# version 1.2
# TCVG kidney metabolism scaled from liver
#
# version 1.3
# added hyper-population parameters (see comments)
# fixed "0" errors in some outputs
#
# version 1.4
# checked and revised baseline values
#
# version 1.5
# Revised kidney oxidation parameters/model
#
# version 1.7.1
# Revised lung oxidation
# Removed FracLungSys (Fraction of respiratory metabolism to systemic circ.)
# because non-identifiable relative to "FracOther" (fraction of oxidation
# NOT to TCA)
# Placed TCA produced from lung oxidation in TCA body compartment
# Removed TCVG from model code
#
# version 1.8
# Removed KTD (fecal excretion of perc)
# Separate perc absorption routes for oil and aqueous gavage
# Pdose = oil, PDoseAq = aqueous
# AStomAq, ADuodAq, kASAq, kTSDAq, kADAq
# Added TCA plasma fraction bound as an output
# Added Male/Female difference in baseline oxidation and conjugation
# Added TCA fractional absorption from Drinking water
# Updated TCVC model to include separate beta-lyase pathway and DCA in urine
# Updated baseline values
#
# version 1.9
# Moved Male/Female scaling to baseline values
# Added scaling of KMCla to KM, adjusted using partition coefficients
#
# version 1.9.1
# Removed TCVC sub-model to improve parameter identifiability
# GSH conjugation goes directly to NAcTCVC and DCA, with delay parameter
# for urinary excretion
#
# NOTE -- lines with comment "(vrisk)" are used only for
# calculating dose metrics, and are commented out
# when doing MCMC runs.
#
# version 2.0.0
# - Additional linear pathway to oxidation
# - Remove male/female scaling for GSH pathway
# - Add total clearance scaling of TCA excretion
# version 2.1.0
# - Additional saturable pathway to oxidation
# - Remove male/female scaling for GSH pathway
# - Add total clearance scaling of TCA excretion
#
#******************************************************************************
#***                  State Variable Specifications                         ***
#******************************************************************************

States = {
    #-- PERC uptake
    AStom, # Amount of PERC in stomach (oil)
    ADucd, # oral gavage absorption (oil) -- mice and rats only
    AStomAq, # Amount of PERC in stomach (aqueous)
    ADucdAq, # oral gavage absorption (aqueous) -- mice and rats only
    # AO, #vrisk) total absorbed
    InhDose, # Amount inhaled
    #-- PERC in the body
    ARap, # Amount in rapidly perfused tissues
    ASlw, # Amount in slowly perfused tissues
    AFat, # Amount in fat
    AGut, # Amount in gut
    ALiv, # Amount in liver
    AKid, # Amount in Kidney -- previously in Rap tissue
    ABld, # Amount in Blood -- previously in Rap tissue
    AInhResp, # Amount in respiratory lumen during inhalation
    AResp, # Amount in respiratory tissue
    AEhxResp, # Amount in respiratory lumen during exhalation
    #-- TCA in the body
    # AOTCA, #vrisk)
    AStomTCA, # Amount of TCA in stomach
    APlasTCA, # Amount of TCA in plasma #comment out for
    ABodTCA, # Amount of TCA in lumped body compartment
    ALivTCA, # Amount of TCA in liver
    #-- TCA metabolized
    AUrnTCA, # Cumulative Amount of TCA excreted in urine
    AUrnTCA_sat, # Amount of TCA excreted that during times that had
    # saturated measurements (for lower bounds)
    AUrnTCA_collect,# Cumulative Amount of TCA excreted in urine during
    # collection times (for intermittent collection)
    #-- NAcTCVC and DCA excreted
    ANTVCVC, # Amount of NAcTCVC formed that is ultimately excreted in urine
    ADCA, # Amount of DCA formed that is ultimately excreted in urine
    # AGSHOther, #vrisk) # Amount of untracked GSH conjugation
    AUrnNTCVC, # Amount of NAcTCVC excreted
    AUrnDCA, # Amount of DCA excreted
    # ANTCVCIn, #vrisk)
    # ADCAIn, #vrisk)
    #-- Other states for PERC
    ACh, # Amount in closed chamber -- mice and rats only
    AExh, # Amount exhaled
    AExhExp, # Amount exhaled during expos [to calc. retention]
    #-- Metabolism
    AMetLiv1, # Amount metabolized by P450 in liver
    AMetLiv2, # Amount metabolized by GSH conjugation in liver
    AMetLng, # Amount metabolized in the lung
    AMetKid1, # Amount metabolized by P450 in kidney
    AMetKid2, # Amount metabolized by GSH conjugation kidney
    # AMetTCA, #vrisk) Amount of TCA metabolized
    #-- Other Dose metrics
    # AUCCBld, #vrisk)
    # AUCCLiv, #vrisk)
}
### Input Variable Specifications

Inputs = {
##-- PERC dosing
Conc, # Inhalation exposure conc. (ppm)
IVDose, # IV dose (mg/kg)
PDose, # Oral gavage dose (mg/kg) - oil
PDoseAq, # Oral gavage dose (mg/kg) - aqueous
Drink, # Drinking water dose (mg/kg/day)
IADose, # Inter-arterial
PVDose, # Portal Vein
##-- TCA dosing
IVDoseTCA, # IV dose (mg/kg) of TCA
P DoddoseTCA, # Oral gavage dose (mg/kg) of TCA
DrinkTCA, # Oral drinking water dose (mg/kg/d) of TCA
##-- Potentially time-varying parameters
QPmeas, # Measured value of Alveolar ventilation QP
TCAUrnSat, # Flag for saturated TCA urine
UrnMissing # Flag for missing urine collection times
};

### Output Variable Specifications

Outputs = {
*** Outputs for mass balance check
MassBalPERC,
TotDose,
TotTissue,
MassBalTCA,
TotTCAIn,
TotTissueTCA,
MassBalNTCVC,#
MassBalDCA,#
TotMetab, # Total metabolism

### Outputs that are potential dose metrics
# TotTCA SysIn, #(vrisk) total systemic TCA dose (not incl. direct to urine)
# TotMetabBW34, #(vrisk) Total metabolism/BW^3/4
# ATotBioactTCVC, # (vrisk)
# ATotMetLiv, # (vrisk) Total metabolism in liver
# AMetLiv1Liv, # (vrisk) Total oxidation in liver/liver volume
# AMetLivOther, # (vrisk) Total "other" oxidation in liver
# AMetLivOtherLiv, # (vrisk) Total "other" oxidation in liver/liver vol
# AMetLngResp, # (vrisk) oxidation in lung/respiratory tissue volume
# AMetGSH, # (vrisk) total GSH conjugation
# AMetGSHKid, # (vrisk)# Amount of GSH conjugation/kidney volume
# AMetGSHBW34, # (vrisk) total GSH conjugation/BW^3/4
# ADAKId, # (vrisk)# Amount of urinary DCA formed/kidney volume
# ANATKid, # (vrisk)# Amount of urinary NAcTCVC formed/kidney volume
# AGSHOtherKid, # (vrisk)# Amount of other GSH conjugates/kidney volume
# TotDoseBW34, # (vrisk) mg intake / BW^3/4
# AMetLiv1BW34, #(vrisk) mg hepatic oxidative metabolism / BW^3/4
# TotOxMetaBW34, #(vrisk) mg oxidative metabolism / BW^3/4
# TotTCAInBW, #(vrisk) TCA production / BW
# TotTCAsysInBW, #(vrisk) TCA production / BW
# AMetLngBW34, #(vrisk) oxidation in lung/BW^3/4
# ADCA34, #(vrisk)# Amount of urinary DCA formed/BW^3/4
# AGSHOtherBW34, #(vrisk)# Amount of other GSH conjugates/BW^3/4
# AMetLivOtherBW34, #(vrisk) Total "other" oxidation in liver/BW^3/4

**************************************************************************
*** Outputs for comparison to in vivo data
# PERC
RetDose, # mouse, human - = (InhDose - AExhExp)
FracRetMetab, # mouse - fraction of retained dose metabolized
FracRetExh, # mouse - fraction of retained dose exhaled (post-exposure)
CAlv, # needed for CA1vPPM
CA1vPPM, # human
CInhPPM, # mouse, rat
CInh, # needed for CMixExh
CMixExh, # rat - Mixed exhaled breath (mg/l)
CArt, # rat, human - Arterial blood concentration
CVen, # mouse, rat, human
CBldMix, # rat - Concentration in mixed arterial+venous blood
# (used for cardiac puncture)
CFat, # mouse, rat - Concentration in fat
CGut, # rat
CRap, # needed for unlumped tissues
CSlw, # needed for unlumped tissues
CHrt, # rat - Concentration in heart tissue [use CRap]
CKid, # mouse, rat - Concentration in kidney
CLiv, # mouse, rat - Concentration in liver
CLung, # mouse, rat - Concentration in lung [use CRap]
CMus, # rat - Concentration in muscle [use CSLw]
CSpl, # rat - Concentration in spleen [use CRap]
CBrn, # rat - Concentration in brain [use CRap]
zAExh, # mouse
zAExhpost, # mouse, rat - Amount exhaled post-exposure (mg)
RAExh, # zRAExh, # mouse and rat - rate of Perc exhalation (mg/hr)

# TCA
CPlasTCA, # mouse, rat, human - TCA concentration in plasma
CBldTCA, # mouse, rat, human - TCA concentration in blood
CBodTCA, # needed for CKidTCA and CLungTCA
CKidTCA, # mouse - TCA concentration in kidney
CLivTCA, # mouse, rat - TCA concentration in liver
CLungTCA, # mouse - TCA concentration in lung
zAUrnTCA, # human - Cumulative Urinary TCA
zAUrnTCA_collect, # human - TCA measurements for intermittent collection
zAUrnTCA_sat, # human - Saturated TCA measurements
FracBndPlasTCA, # mouse - TCA fraction bound

# Other
zAUrnNTCVC, # rat, human - Cumulative urinary NAcTCVC
zAUrnDCA, # rat, human - Cumulative urinary DCA
QPsamp, # human - sampled value of alveolar ventilation rate

# Resp tract#(vrisk)
# CResp, #(vrisk)
# CInhResp, #(vrisk)
# CExhResp, #(vrisk)

### PARAMETERS #(vrisk)
# Qcnow, # (vrisk) #Cardiac output (L/hr)
# Qp, # (vrisk) #Alveolar ventilation (L/hr)
# QFatCtmp, # (vrisk) #Scaled fat blood flow
# QGutCtmp, # (vrisk) #Scaled gut blood flow
# QLivCtmp, # (vrisk) #Scaled liver blood flow
# QslwCtmp, # (vrisk) #Scaled slowly perfused blood flow
# QrapCtmp, # (vrisk) #Scaled rapidly perfused blood flow
# QkidCtmp, # (vrisk) #Scaled kidney blood flow
# Dresp, # (vrisk) #Respiratory lumen:tissue diffusive clearance rate
# VfatCtmp, # (vrisk) #Fat fractional compartment volume
# VGutCtmp, # (vrisk) #Gut fractional compartment volume
# vLivCtmp, # (vrisk) #Liver fractional compartment volume
# VRapCtmp, # (vrisk) #Rapidly perfused fractional compartment volume
# VrespLumCtmp, # (vrisk) #Fractional volume of respiratory lumen
# VrespEffCtmp, # (vrisk) #Effective fractional volume of respiratory tissue
# VKidCtmp, # (vrisk) #Kidney fractional compartment volume
# VBldCtmp, # (vrisk) #Blood fractional compartment volume
# VslwCtmp, # (vrisk) #Slowly perfused fractional compartment volume
# VplasCtmp, # (vrisk) #Plasma fractional compartment volume
# VBodCtmp, # (vrisk) #TCA body fractional compartment volume [not incl.
# blood+liver]
# PB, # (vrisk) #PERC Blood/air partition coefficient
# PFat, # (vrisk) #PERC Fat/Blood partition coefficient
# PGut, # (vrisk) #PERC Gut/Blood partition coefficient
# PLiv, # (vrisk) #PERC Liver/Blood partition coefficient
# PRap, # (vrisk) #PERC Rapidly perfused/Blood partition coefficient
# Presp, # (vrisk) #PERC Respiratory tissue:air partition coefficient
# PKid, # (vrisk) #PERC Kidney/Blood partition coefficient
# Pslw, # (vrisk) #PERC Slowly perfused/Blood partition coefficient
# TCAPlas, # (vrisk) #TCA blood/plasma concentration ratio
# PBodTCA, # (vrisk) #Free TCA Body/blood plasma partition coefficient
# PLivTCA, # (vrisk) #Free TCA Liver/blood plasma partition coefficient
# kDissoc, # (vrisk) #Protein/TCA dissociation constant (umole/L)
# BMax, # (vrisk) #Maximum binding concentration (umole/L)
# kAS, # (vrisk) #PERC Stomach absorption coefficient (oil) (/hr)
# kTSD, # (vrisk) #PERC Stomach-duodenum transfer coefficient (oil) (/hr)
# kAD, # (vrisk) #PERC Duodenum absorption coefficient (oil) (/hr)
# kASaq, # (vrisk) #PERC Stomach absorption coefficient (aqueous) (/hr)
# kTSDaq, # (vrisk) #PERC Stomach-duodenum transfer coefficient (aqueous) (/hr)
# kADAq, # (vrisk) #PERC Duodenum absorption coefficient (aqueous) (/hr)
# kATCA, # (vrisk) #TCA Stomach absorption coefficient (/hr)
# FracAbsTCA, # (vrisk) #TCA Fraction absorbed from drinking water
# VMax, # (vrisk) #VMax for hepatic PERC oxidation (mg/hr)
# KM, # (vrisk) #KM for hepatic PERC oxidation (mg/L)
# VMax2, # (vrisk) (#2.1.0) #VMax2 for hepatic PERC oxidation (mg/hr)
# KM2, # (vrisk) (#2.1.0) #KM2 for hepatic PERC oxidation (mg/L)
# FracOther, # (vrisk) #Fraction of hepatic PERC oxidation not to TCA
# VMaxTCVG, # (vrisk) #VMax for hepatic PERC GSH conjugation (mg/hr)
# KMTCVG, # (vrisk) #KM for hepatic PERC GSH conjugation (mg/L)
# VMaxKid, # (vrisk) #VMax for renal PERC oxidation (mg/hr)
# KMKid, # (vrisk) #KM for renal PERC oxidation (mg/L)
# FracKidTCA, # (vrisk) #Fraction of renal PERC TCA production "directly"
# to urine (i.e., via first pass)
# VMaxKidTCVG, # (vrisk) #VMax for renal PERC GSH conjugation (mg/hr)
# KMKidTCVG, # (vrisk) #KM for renal PERC GSH conjugation (mg/L)
# VMaxClar, # (vrisk) #VMax for Tracheo-bronchial PERC oxidation (mg/hr)
# KMClar, # (vrisk) #KM for Tracheo-bronchial PERC oxidation (mg/L)
# kUrntCA, # (vrisk) #Rate constant for TCA plasma->urine (/hr)
# kMetTCA, # (vrisk) #Rate constant for hepatic TCA->other (/hr)
# FracNATurn, # (vrisk) #Fraction of GSH conjugation to NAcTCVC in urine#
# FracDCAUrtn, # (vrisk) #Fraction of GSH conjugation to DCA in urine#
# kNAT, # (vrisk) #Delay rate constant for NAcTCVC excretion in urine (/hr)
# kDCA, #(vrisk) # Delay rate constant for DCA excretion in urine (/hr)?
### Misc
# RUrnTCA, #(vrisk)
# RUrnNTCVC, #(vrisk)
# RUrnDCA, #(vrisk)#
RAO,
CVenMole,
CPlasTCA Mole,
CPlasTCA Free Mole
}

#**************************************************************************
#***                  Global Constants                                      ***
#**************************************************************************
# Molecular Weights
MWPerc = 165.83;        # PERC
MWTCVC = 250.53;        # TCVC
MWTCA = 163.39;        # TCA
MWDCA = 128.94;        # DCA
MNATCVC = 292.57;        # N Acetyl TCVC

# Stoichiometry
StochTCAPERC = MWTCA / MWPerc;
StochTCVCPERC = MWTCVC / MWPerc;
StochN = MNATCVC / MWTCVC;
StochDCATCVC = MWDCA / MWTCVC;

#**************************************************************************
#***                  Global Model Parameters                               ***
#**************************************************************************
# These are the actual model parameters used in "dynamics."
# Values that are assigned in the "initialize" section,
# are all set to 1 to avoid confusion.

#**************************************************************************
# Flow Rates
QC = 1; # Cardiac output (L/hr)
VPR = 1; # Alveolar ventilation-perfusion ratio
QPsamp = 1; # Alveolar ventilation (L/hr)
# Fractional Blood flows
QFatCtmp = 1; # Scaled fat blood flow
QGutCtmp = 1; # Scaled gut blood flow
QLivCtmp = 1; # Scaled liver blood flow
QSlwCtmp = 1; # Scaled slowly perfused blood flow
QKidCtmp = 1; # Scaled kidney blood flow
FracPlas = 1; # Fraction of blood that is plasma (1-hematocrit)
DResptmp = 1; # Respiratory lumen:tissue diffusive clearance rate (L/hr)
[scaled to QP]

#**************************************************************************
# Volumes
VFat = 1; # Fat compartment volume (L)
VGut = 1; # Gut compartment volume (L)
VLiv = 1; # Liver compartment volume (L)
VRap = 1; # Rapidly perfused compartment volume (L)
VRespLum = 1; # Volume of respiratory lumen (L air)
# VRespEfftmp = 1; #(vrisk) volume for respiratory tissue (L)
VRespEff = 1; # Effective volume for respiratory tissue (L air) = V(tissue) * Resp:Air partition coefficient
VKid = 1; # Kidney compartment volume (L)
VBld = 1; # Blood compartment volume (L)
VSlw = 1; # Slowly perfused compartment volume (L)
VPlas = 1; # Plasma compartment volume [fraction of blood] (L)
VBod = 1; # TCA Body compartment volume [not incl. blood+liver] (L)

# Distribution/partitioning
PB = 1; # PERC Blood/air partition coefficient
PFat = 1; # PERC Fat/Blood partition coefficient
PGut = 1; # PERC Gut/Blood partition coefficient
PLiv = 1; # PERC Liver/Blood partition coefficient
PRap = 1; # PERC Rapidly perfused/Blood partition coefficient
PResp = 1; # PERC Respiratory tissue:air partition coefficient
PKid = 1; # PERC Kidney/Blood partition coefficient
PSlw = 1; # PERC Slowly perfused/Blood partition coefficient

# TCA
TCAPlas = 1; # TCA blood/plasma concentration ratio
PBodTCA = 1; # Free TCA Body/blood plasma partition coefficient
PLivTCA = 1; # Free TCA Liver/blood plasma partition coefficient

# TCA plasma binding
kDissoc = 1; # Protein/TCA dissociation constant (umole/L)
BMax = 1; # Protein concentration (UNITS?)

# Oral absorption
kAS = 1.4; # PERC Stomach absorption coefficient (oil) (/hr)
kTSD = 1.4; # PERC Stomach-duodenum transfer coefficient (oil) (/hr)
kJAS = 0.75; # PERC Duodenum absorption coefficient (oil) (/hr)
kJTSD = 1.4; # PERC Stomach-duodenum transfer coefficient (aqueous) (/hr)
kJADAq = 0.75; # PERC Duodenum absorption coefficient (aqueous) (/hr)
kASTCA = 0.75; # TCA Stomach absorption coefficient (/hr)
FracAbsTCA = 1.0; # TCA drinking water fractional absorption

# PERC Metabolism
VMax = 1; # VMax for hepatic PERC oxidation (mg/hr)
KM = 1; # KM for hepatic PERC oxidation (mg/L)
VMax2 = 1; # VMax2 for hepatic PERC oxidation (mg/hr)#(v2.1.0)
KM2 = 1; # KM2 for hepatic PERC oxidation (mg/L)#(v2.1.0)

# FracOther = 1; # Fraction of hepatic PERC oxidation not to TCA
VMaxTCVG = 1; # VMax for hepatic PERC GSH conjugation (mg/hr)
KMTVCVG = 1; # KM for hepatic PERC GSH conjugation (mg/L)

# VMaxKid = 1; # VMax for renal PERC oxidation (mg/hr)
KMKid = 1; # KM for renal PERC oxidation (mg/L)

# FracKidTCA = 1; # Fraction of renal PERC TCA "directly" to urine(i.e., via first pass)
VMaxKidTVCVG = 1; # VMax for renal PERC GSH conjugation (mg/hr)
KMKidTVCVG = 1; # KM for renal PERC GSH conjugation (mg/L)

# VMaxClara = 1; # VMax for Tracheo-bronchial PERC oxidation (mg/hr)
KMClara = 1; # KM for Tracheo-bronchial PERC oxidation (mg/L) but in units of air concentration

# TCA metabolism/clearance
kUrnTCA = 1; # Rate constant for TCA plasma->urine (/hr)
kMetTCA = 1;  # Rate constant for hepatic TCA->other (/hr)

# TCVC metabolism/clearance
FracNATUrn = 1; # Fraction of GSH conjugation to NAcTCVC in urine#
FracDCAUrn = 1; # Fraction of GSH conjugation to DCA urine#
kNAT = 1;  # Delay rate constant for NAcTCVC excretion in urine (/hr)#
kDCA = 1;  # Delay rate constant for DCA excretion in urine (/hr)#

# Closed chamber and other exposure parameters
Rodents = 1;  # Number of rodents in closed chamber data
VCh = 1;  # Chamber volume for closed chamber data
kLoss = 1; # Rate constant for closed chamber air loss
CC = 0.0; # Initial chamber concentration (ppm)
TChng = 0.003;  # IV infusion duration (hour)

# Flag for species, sex -- these are global parameters
BW = 0.0;  # Species-specific defaults during initialization
#BW75 = 0.0; #(vrisk) Variable for BW^3/4
Male = 0.5; # 1 = male, 0 = female, 0.5 = unknown or mixed
Species = 1.0; # 1 = human, 2 = rat, 3 = mouse

# These parameters are potentially sampled/calibrated in the MCMC or MC # analyses. The default values here are used if no sampled value is given. # M_ indicates population mean parameters used only in MC sampling # V_ indicates a population variance parameter used in MC and MCMC sampling

# Flow Rates
lnQCC = 0.0; # Scaled by BW^-0.75 and species-specific central estimates
lnVPRC = 0.0; # Scaled to species-specific central estimates

# Fractional Blood Flows to Tissues (fraction of cardiac output)
QFatC = 1.0; # Scaled to species-specific central estimates
QGutC = 1.0; # Scaled to species-specific central estimates
QLivC = 1.0; # Scaled to species-specific central estimates
QSLwC = 1.0; # Scaled to species-specific central estimates
QKidC = 1.0; # Scaled to species-specific central estimates
FracPlasC = 1.0; # Scaled to species-specific central estimates
lnDRespC = 0.0; # Scaled to alveolar ventilation rate in dynamics

# Fractional Tissue Volumes (fraction of BW)
VFatC = 1.0; # Scaled to species-specific central estimates
VQutC = 1.0; # Scaled to species-specific central estimates
VLivC = 1.0; # Scaled to species-specific central estimates
VRapC = 1.0; # Scaled to species-specific central estimates
VRespLumC = 1.0; # Scaled to species-specific central estimates
VRespEffC = 1.0; # Scaled to species-specific central estimates
VKidC = 1.0; # Scaled to species-specific central estimates
VBldC = 1.0; # Scaled to species-specific central estimate

# Total perfused fractional volume (used to derive VSlw)
# Partition Coefficients for PERC

\[ PBC = 1.0; \] # Scaled to species-specific central estimates
\[ PFatC = 1.0; \] # Scaled to species-specific central estimates and by Blood:air
\[ \ln PGutC = 0.0; \] # Scaled to species-specific central estimates and by Blood:air
\[ \ln PLivC = 0.0; \] # Scaled to species-specific central estimates and by Blood:air
\[ \ln PRapC = 0.0; \] # Scaled to species-specific central estimates and by Blood:air
\[ \ln PrespC = 0.0; \] # Scaled to species-specific central estimates and by Blood:air
\[ \ln PKidC = 0.0; \] # Scaled to species-specific central estimates and by Blood:air
\[ \ln PSlwC = 0.0; \] # Scaled to species-specific central estimates and by Blood:air

# Partition Coefficients for TCA

\[ \ln PRBCPlasTCAC = 0.0; \] # Scaled to species-specific central estimates
\[ \ln PBodTCAC = 0.0; \] # Scaled to species-specific central estimates
\[ \ln PLivTCAC = 0.0; \] # Scaled to species-specific central estimates

# Plasma Binding for TCA

\[ \ln kDissocC = 0.0; \] # Scaled to species-specific central estimates
\[ \ln bMaxkDC = 0.0; \] # Scaled to species-specific central estimates

# Oral Absorption rates

\[ \ln kAS = 0.336; \]
\[ \ln kTSD = 0.336; \]
\[ \ln kAD = -0.288; \]
\[ \ln kASAg = 0.336; \]
\[ \ln kTSDAg = 0.336; \]
\[ \ln kADAg = -0.288; \]
\[ \ln kASTCA = -0.288; \]
\[ \ln FracAbsTCAC = 2.94; \]

# PERC Metabolism

\[ \ln VMaxC = 0.0; \] # Scaled by liver weight and species-specific central estimates
\[ \ln KMC = 0.0; \] # Scaled to species-specific central estimates
\[ \ln ClC = 0.0; \] # Scaled to KM of first pathway\(^{(v2.1.0)}\)
\[ \ln Cl2OxC = 0.0; \] # Scaled to clearance of first pathway\(^{(v2.0.0)}\)
\[ \ln FracOtherC = -2.197; \] # Ratio of oxidation of non-TCA to TCA
\[ \ln VMaxTVGC = 0.0; \] # Scaled by liver weight and species-specific central estimates
\[ \ln KMTCVGC = 0.0; \] # Scaled to species-specific central estimates
\[ \ln ClTCVGC = 0.0; \] # Scaled to species-specific central estimates
\[ \ln VMaxKidLivC = 0.0; \] # Ratio of kidney VMax to Liver VMax, Scaled by kidney weight and species-specific central estimates
\[ \ln KMKidLivC = 0.0; \] # Ratio of kidney KM to liver KM, Scaled to species-specific central estimates
\[ \ln ClKidLivC = 0.0; \] # Ratio of kidney Cl to liver Cl, Scaled to species-specific central estimates
\[ \ln FracKidTCAC = 0.0; \] # Ratio of "directly" to urine to systemic TCA
\[ \ln VMaxKidLivTCVGC = 0.0; \] # Ratio of kidney Vmax to liver Vmax, Scaled by kidney weight and species-specific central estimates
\[ \ln KMKidTCVGC = 0.0; \] # Scaled to species-specific central estimates
\[ \ln ClKidLivTCVGC = 0.0; \] # Ratio of kidney Cl to liver Cl, Scaled to species-specific central estimates
\[ \ln VMaxLungLivC = 0.0; \] # Ratio of lung Vmax to liver Vmax, scaled to species-specific central estimates
\[ \ln KMRespLivC = 0.0; \] # Ratio of lung to liver KM

# TCA Metabolism/clearance

\[ \ln UrnTCAC = 0.0; \] # Scaled by (plasma volume)^\(-1\) and species-specific central estimates
\[ \ln MetTCAC = 0.0; \] # Scaled by BW\(^{-0.25}\)
\[ \ln TotTCAC = 0.0; \] # Scaling of both urine and other metabolism\(^{(v2.0.0)}\)
# TCVC metabolism
lnFracNATurnC = 0.0;  #
lnFracDCAUrnC = 0.0;  # # This is logit of fraction remaining after NAT
lnkNATC = 0.0;  # Scaled by BW^-0.25 #
lnkDCAC = 0.0;  # Scaled by BW^-0.25 #

# Closed chamber parameters
NRodents = 1;  #
VChC = 1;  #
lnkLossC = 0;  #

#****************************************************************************
# Hyper-Population means
#
# These are "species-independent" parameters, defining the central estimate
# of the "population of species." Species-specific parameter are
# drawn from a distribution with these as central estimates.
#
# Some of these priors for these are based on in vitro data, and for these
# it is assumed that the in-vitro-to-in-vivo scaling is similar across
# species (with scatter)
# For the priors which are uninformative, use of these parameters penalizes
# large inter-species differences (parameters are all scaled, e.g.,
# allometrically if appropriate).
#
M_M_lnKMC = 1.0;
M_M_lnClC = 1.0;
M_M_lnKM2C = 1.0;#{v2.1.0}
M_M_lnCl2OxC = 1.0;#{v2.0.0}
M_M_lnFracOtherC = 1.0;
M_M_lnVMaxTCVGC = 1.0;
M_M_lnClTCVGC = 1.0;
M_M_lnCMKidLivC = 1.0;
M_M_lnClKidLivC = 1.0;
M_M_lnFracKidTCAC = 1.0;
M_M_lnVMaxKidLivTCVGC = 1.0;
M_M_lnClKidLivTCVGC = 1.0;
M_M_lnVMaxLungLivC = 1.0;
M_M_lnKMRespLivC = 1.0;
M_M_lnFracNATUrnC = 1.0;
M_M_lnFracDCAUrnC = 1.0;
M_M_lnkNATC = 1.0;
M_M_lnkDCAC = 1.0;

#****************************************************************************
# Population means
#
# These are given truncated normal or uniform distributions, depending on
# what prior information is available. Note that these distributions
# reflect uncertainty in the population mean, not inter-individual
variability. Normal distributions are truncated at 2, 3, or 4 SD.
For fractional volumes and flows, 2xSD
For plasma fraction, 3xSD
For cardiac output and ventilation-perfusion ratio, 4xSD
For all others, 3xSD
For uniform distributions, range of 1e2 to 1e8 fold, centered on
central estimate.

# Population Mean Parameter
M_lnQCC = 1.0;
M_lnVPRC = 1.0;

M_QFatC = 1.0;
M_QGutC = 1.0;
M_QLivC = 1.0;
M_QSlwC = 1.0;
M_QKidC = 1.0;
M_FracPlasC = 1.0;
M_inDRespC = 1.0;

M_VFatC = 1.0;
M_VGutC = 1.0;
M_VLivC = 1.0;
M_VRapC = 1.0;
M_VRespLumC = 1.0;
M_VRespEffC = 1.0;

M.VKidC = 1.0;
M.VBldC = 1.0;

M_PB = 1.0;
M_PFatC = 1.0;
M_inPGutC = 1.0;
M_inPLivC = 1.0;
M_inPRapC = 1.0;
M_inPRespC = 1.0;
M_inPKidC = 1.0;
M_inPSlwC = 1.0;

M_lnPRBCPlasTCAC = 1.0;
M_lnPBodTCAC = 1.0;
M_lnPLivTCAC = 1.0;

M_lnkDissocC = 1.0;
M_lnkBMaxkDC = 1.0;

M_lnkAS = 1.0;
M_lnkTSD = 1.0;
M_lnkAD = 1.0;
M_lnkASAq = 1.0;
M_lnkTSDAq = 1.0;
M_lnkADAq = 1.0;
M_lnkASTCA = 1.0;
M\_lnFracAbsTCAC = 1.0;

M\_lnVMaxC = 1.0;
M\_lnKM2C = 1.0;
M\_lnClC = 1.0;
M\_lnCl2OxC = 1.0;
M\_lnVMaxKidLivC = 1.0;
M\_lnClKidLivC = 1.0;
M\_lnKMKidLivC = 1.0;
M\_lnClKidLivTCVGC = 1.0;
M\_lnVMaxKidTCAC = 1.0;
M\_lnClKidTCVGC = 1.0;
M\_lnKMKidTCVGC = 1.0;
M\_lnClKidLivTCVGC = 1.0;
M\_lnVMaxLungLivC = 1.0;
M\_lnKMRespLivC = 1.0;

M\_lnUrncTCAC = 1.0;
M\_lnMetTCAC = 1.0;
M\_lnTotTCAC = 1.0;

M\_lnFracNATUrnc = 1.0;
M\_lnFracDCAUrnc = 1.0;
M\_lnNatC = 1.0;
M\_lnDCAC = 1.0;

#******************************************************************************
# Population Variances
#
# These are given InvGamma(alpha,beta) distributions. The parameterization
# for alpha and beta is given by:
#  alpha = (n-1)/2
#  beta = s^2*(n-1)/2
# where n = number of data points, and s^2 is the sample variance
#  Sum(x_i^2)/n - <x>^2.
# Generally, for parameters for which there is no direct data,
# a population coefficient of variation (CV) of 0.5 was assumed,
# with a coefficient of uncertainty (CU) of 2. This corresponds
# to alpha=2+1/CU^2=2.25 and beta=(alpha-1)CV^2=0.3125.
# Matching with the above gives and effective n = 5.5.
#
#
# Population Variance Parameter
V\_lnQCC = 1.0;
V\_lnVPRC = 1.0;

V\_QFatC = 1.0;
V\_QOutC = 1.0;
V\_QLivC = 1.0;
V\_QLwC = 1.0;
V\_QKidC = 1.0;
V\_FracPlasC = 1.0;
V\_lnDRespC = 1.0;
V_VFatC = 1.0;
V_VGutC = 1.0;
V_VLivC = 1.0;
V_VRapC = 1.0;
V_VRespLumC = 1.0;
V_VRespEffC = 1.0;
V.VKidC = 1.0;
V.VBldC = 1.0;
V_PBC = 1.0;
V_PFatC = 1.0;
V_lnPGutC = 1.0;
V_lnPLivC = 1.0;
V_lnPRapC = 1.0;
V_lnPRespC = 1.0;
V_lnPKidC = 1.0;
V_lnPSlwC = 1.0;
V_lnPBCPlasTCAC = 1.0;
V_lnPBodTCAC = 1.0;
V_lnPLivTCAC = 1.0;
V_lnkDissocC = 1.0;
V_lnBMaxkDC = 1.0;
V_lnkAS = 1.0;
V_lnkTSD = 1.0;
V_lnkAD = 1.0;
V_lnkASAq = 1.0;
V_lnkTSDAq = 1.0;
V_lnkADAq = 1.0;
V_lnkASTCA = 1.0;
V_lnFracAbsTCAC = 1.0;
V_lnVMaxC = 1.0;
V_lnKMC = 1.0;
V_lnClC = 1.0;
V_lnKM2C = 1.0; (#(v2.1.0)
V_lnCl2OxC = 1.0; (#(v2.0.0)
V_lnFracOtherC = 1.0;
V_lnVMaxTCVGC = 1.0;
V_lnKMTCVGC = 1.0;
V_lnClTCVGC = 1.0;
V_lnVMaxKidLivC = 1.0;
V_lnKMKidLivC = 1.0;
V_lnClKidLivC = 1.0;
V_lnFracKidTCAC = 1.0;
V_lnVMaxKidLivTCVGC = 1.0;
V_lnKMKidTCVGC = 1.0;
V_lnClKidLivTCVGC = 1.0;
V_lnVMaxLungLivC = 1.0;
V\_lnKMRespLivC = 1.0; 
V\_lnkUrnTCAC = 1.0; 
V\_lnkMetTCAC = 1.0; 
V\_lnkTotTCAC = 1.0;#(v2.0.0)

V\_lnFracNATurnC = 1.0; 
V\_lnFracDCAUrnC = 1.0; 
V\_lnkNATC = 1.0; 
V\_lnkDCAC = 1.0; 

#*****************************************************************************
# Measurement error variances for output 
#*****************************************************************************

Ve\_RetDose = 1; 
Ve\_FracRetMetab = 1; 
Ve\_FracRetExh = 1; 
Ve\_CAlv = 1; 
Ve\_CAlvPPM = 1; 
Ve\_CInhPPM = 1; 
Ve\_CInh = 1; 
Ve\_CMixExh = 1; 
Ve\_CArt = 1; 
Ve\_CVen = 1; 
Ve\_CBldMix = 1; 
Ve\_CFat = 1; 
Ve\_CGut = 1; 
Ve\_CRap = 1; 
Ve\_CSlw = 1; 
Ve\_CHrt = 1; 
Ve\_CKid = 1; 
Ve\_CLiv = 1; 
Ve\_CLung = 1; 
Ve\_CMus = 1; 
Ve\_CSp1 = 1; 
Ve\_CBrn = 1; 
Ve\_zABExh = 1; 
Ve\_zAExhpost = 1; 
Ve\_zRAExh = 1; 
Ve\_TotMetab = 1; 
Ve\_CPlasTCA = 1; 
Ve\_CBldTCA = 1; 
Ve\_CBodTCA = 1; 
Ve\_CKidTCA = 1; 
Ve\_CLivTCA = 1; 
Ve\_CLungTCA = 1; 
Ve\_zAUrnTCA = 1; 
Ve\_zAUrnTCA\_collect = 1; 
Ve\_zAUrnTCA\_sat = 1; 
Ve\_zAUrnNTCVC = 1; 
Ve\_zAUrnDCA = 1;
Ve_QPsamp = 1;

******************************************************************************
**                      Defaults for input parameters                        **
******************************************************************************
##-- PERC dosing
Conc = 0.0;  # Inhalation exposure conc. (ppm)
IVDose = 0.0;  # IV dose (mg/kg)
PDose = 0.0;  # Oral gavage dose (mg/kg) - oil
PDoseAq = 0.0;  # Oral gavage dose (mg/kg) - aqueous
Drink = 0.0;  # Drinking water dose (mg/kg/day)
IADose = 0.0;  # Intraarterial dose (mg/kg)
PVDose = 0.0;  # Portal vein dose (mg/kg)

##-- TCA dosing
IVDoseTCA = 0.0;  # IV dose (mg/kg) of TCA
PODoseTCA = 0.0;  # Oral dose (mg/kg) of TCA
DrinkTCA = 0.0;  # Oral drinking water dose (mg/kg/d) of TCA

##-- Potentially time-varying parameters
QPmeas = 0.0;  # Measured value of Alveolar ventilation QP
TCAUrnsat = 0.0;  # Flag for saturated TCA urine
UrnMissing = 0.0;  # Flag for missing urine collection times

Initialize {

******************************************************************************
**                          Parameter Initialization and Scaling              **
******************************************************************************

# Model Parameters (used in dynamics):
#  QC Cardiac output (L/hr)
#  VPR Ventilation-perfusion ratio
#  QPsamp Alveolar ventilation (L/hr)
#  QFatCtmp Scaled fat blood flow
#  QGutCtmp Scaled gut blood flow
#  QLivCtmp Scaled liver blood flow
#  QSlwCtmp Scaled slowly perfused blood flow
#  DResptmp Respiratory lumen:tissue diffusive clearance rate
#  QKidCtmp Scaled kidney blood flow
#  FracPlas Fraction of blood that is plasma (1-hematocrit)
#  VFat Fat compartment volume (L)
#  VGut Gut compartment volume (L)
#  VLiv Liver compartment volume (L)
#  VLiv Liver compartment volume (L)
#  VRap Rapidly perfused compartment volume (L)
#  VRespLum Volume of respiratory lumen (L air)
#  VRespEff Effective volume of respiratory tissue (L air)
#  VKid Kidney compartment volume (L)
#  VBld Blood compartment volume (L)
#  VSlw Slowly perfused compartment volume (L)
#  VPlas Plasma compartment volume [fraction of blood] (L)
#  VBod TCA Body compartment volume [not incl. blood+liver] (L)
#  PB PERC Blood/air partition coefficient
#  PFat PERC Fat/Blood partition coefficient
#  PGut PERC Gut/Blood partition coefficient
#  PLiv PERC Liver/Blood partition coefficient
#  PRap PERC Rapidly perfused/Blood partition coefficient
#  PResp PERC Respiratory tissue:air partition coefficient
#  PKid PERC Kidney/Blood partition coefficient
#  PSlw PERC Slowly perfused/Blood partition coefficient
#  TCAPlas TCA blood/plasma concentration ratio
#  PBodTCA Free TCA Body/blood plasma partition coefficient
#  PLivTCA Free TCA Liver/blood plasma partition coefficient
#  kDissoc Protein/TCA dissociation constant (umole/L)
#  BMax Maximum binding concentration (umole/L)
#  kAS PERC Stomach absorption coefficient (oil) (/hr)
# kTSD  PERC Stomach-duodenum transfer coefficient (oil) (/hr)
# kAD  PERC Duodenum absorption coefficient (oil) (/hr)
# kASAq  PERC Stomach absorption coefficient (aqueous) (/hr)
# kTSDAq  PERC Stomach-duodenum transfer coeff (aqueous) (/hr)
# kADaq  PERC Duodenum absorption coefficient (aqueous) (/hr)
# kASTCA  TCA Stomach absorption coefficient (/hr)
# FracAbsTCA  TCA drinking water fractional absorption
# VMax  VMax for hepatic PERC oxidation (mg/hr)
# KM  KM for hepatic PERC oxidation (mg/L)
# FracOther  Fraction of hepatic PERC oxidation not to TCA
# VMaxTCVG  VMax for hepatic PERC GSH conjugation (mg/hr)
# KMTCVG  KM for hepatic PERC GSH conjugation (mg/L)
# VMaxKid  VMax for renal PERC oxidation (mg/hr)
# KMKid  KM for renal PERC oxidation (mg/L)
# FracKidTCA  Fraction of renal PERC TCA "directly" to urine
# VMaxKidTCVG  VMax for renal PERC GSH conjugation (mg/hr)
# KMKidTCVG  KM for renal PERC GSH conjugation (mg/L)
# VMaxClara  VMax for Tracheo-bronchial PERC oxidation (mg/hr)
# KMClara  KM for Tracheo-bronchial PERC oxidation (mg/L)
# kUrntCA  Rate constant for TCA plasma->urine (/hr)
# kMetTCA  Rate constant for hepatic TCA->other (/hr)
# FracNATurn  Fraction of GSH conjugation to NATCVC in urine#
# FracDCAurn  Fraction of GSH conjugation to DCA urine#
# kNAT  Delay rate constant for NATCVC excretion in urine (/hr)#
# kDCA  Delay rate constant for DCA excretion in urine (/hr)#
# Rodents  Number of rodents in closed chamber data
# VCh  Chamber volume for closed chamber data
# kLoss  Rate constant for closed chamber air loss
# Parameters used (not assigned here)
# BW  Body weight in kg
# Species  1 = human (default), 2 = rat, 3 = mouse
# Male  0 = female, 1 = male, 0.5 = unknown or mixed
# CC  Closed chamber initial concentration
# Sampling/scaling parameters (assigned or sampled)
# lnQCC
# lnVPRC
# lnDRespC
# QFatC
# QGutC
# QLivC
# QSlwC
# QKidC
# FracPlasC
# VFatC
# VGutC
# VLivC
# VRapC
# VRespLumC
# VRespEffC
# VKidC
# VBldC
# PBC
# PFatC
# lnPGutC
# lnPLivC
# lnPRapC
# lnPSlwC
# lnPRespC
# lnPKidC
# lnPRBCPlasTCAC
# lnPBodTCAC
# lnPLivTCAC
# lnkDissocC
# lnBMaxkDC
# lnkAS
# lnkTSD
# lnkAD
# lnkASAg
# lnkTSDAg
# lnkADAq
# lnkASTCA
# lnFracAbsTCAC
# lnVMaxC
# lnKMC
# lnClC
# lnKM2C#(v2.1.0)
# lnCl2OxC#(v2.0.0)
# lnFracOtherC
# lnVMaxTCVG
# lnClTCVG
# lnVMaxTCVG
# lnVMaxKidLivC
# lnClKidLivC
# lnKMKidLivC
# lnFracKidTCAC
# lnVMaxKidLivTCVG
# lnClKidTCVG
# lnKMKidLivTCVG
# lnVMaxLungLivC
# lnKMRespLivC
# lnUrnTCAC
# lnMetTCAC
# lnkTotTCAC#(v2.0.0)
# lnVMaxBetaLyaseC
# lnClBetaLyaseC
# lnFracDCAUrnC
# lnkNATC
# lnkKidBioactC
# NRodents
# VChC
# lnkLossC
# Input parameters
# none
# Notes:
#**************************************************************************
# use measured value of > 0, otherwise use 0.03 for mouse,
# 0.3 for rat, 60 for female human, 70 for male human
# BW = (BWmeas > 0.0 ? BWmeas : (Species == 3 ? 0.03 : (Species == 2 ? 0.3 :
# (Male == 0 ? 60.0 : 70.0) )));

BW75 = pow(BW, 0.75);
BW25 = pow(BW, 0.25);

# Cardiac Output and alveolar ventilation (L/hr)
QC = exp(lnQCC) * BW75 * # Mouse, Rat, Human (default)
(Species == 3 ? 11.6 : (Species == 2 ? 13.3 : 16.0 ));
# Mouse: CO=13.98 +/- 2.85 ml/min, BW=30 g (Brown et al. 1997, Tab. 22)
# Uncertainty CV is 0.20
# Rat: CO=110.4 ml/min +/- 15.6, BW=396 g (Brown et al. 1997, Tab. 22,
# p 441). Uncertainty CV is 0.14.
# Human: Average of Male CO=6.5 l/min, BW=73 kg
# and female CO= 5.9 l/min, BW=60 kg (ICRP #89, sitting at rest)
# From Price et al. 2003, estimates of human perfusion rate were
# 4.7-6.5 for females and 5.5-7.1 l/min for males (note
# portal blood was double-counted, and subtracted off here)
Thus for uncertainty use CV of 0.2, truncated at 4xCV
Variability from Price et al. (2003) had CV of 0.14-0.20,
so use 0.2 as central estimate

\[ VPR = \exp(\ln VPRC) \]
\begin{align*}
\text{(Species } &= 3 \ ? 2.5 : \text{(Species } &= 2 \ ? 1.9 : 0.96 )); \\
\text{Mouse: } & \text{QP/BW}=116.5 \text{ ml/min/100 g (Brown et al. 1997, Tab. 31), VPR=2.5} \\
\text{Assume uncertainty CV of 0.2 similar to QC, truncated at 4xCV} \\
\text{Consistent with range of QP in Tab. 31} \\
\text{Rat: } & \text{QP/BW}=52.9 \text{ ml/min/100 g (Brown et al. 1997, Tab. 31), VPR=1.9} \\
\text{Assume uncertainty CV of 0.3 similar to QC, truncated at 4xCV} \\
\text{Used larger CV because Tab. 31 shows a very large range of QP} \\
\text{Human: Average of Male VE=9 l/min, resp. rate=12 /min,} \\
\text{dead space=0.15 l (QP=7.2 l/min), and Female} \\
\text{VE=6.5 l/min, resp. rate=14 /min, dead space=0.12 l} \\
\text{(QP=4.8 l/min), VPR = 0.96} \\
\text{Assume uncertainty CV of 0.2 similar to QC, truncated at 4xCV} \\
\text{Consistent with range of QP in Tab. 31} \\
\end{align*}

\[ QPsamp = QC \times VPR; \]

Respiratory diffusion flow rate
Will be scaled by QP in dynamics
Use log-uniform distribution from 1e-5 to 10
\[ DResptmp = \exp(\ln DRespC); \]

Fractional Flows scaled to the appropriate species
Fat = Adipose only
Gut = GI tract + pancreas + spleen (all drain to portal vein)
Liv = Liver, hepatic artery
Slw = Muscle + Skin
Kid = Kidney
Rap = Rapidly perfused (rest of organs, plus bone marrow, lymph, etc.),
derived by difference in dynamics

Mouse and rat data from Brown et al. (1997). Human data from
ICRP-89 (2002), and is sex-specific.

\[ QFatCtmp = QFatC \times (\text{Species } &= 3 \ ? 0.07 : \text{(Species } &= 2 \ ? 0.07 : \text{(Male } &= 0 \ ? \ 0.085 : \ 0.05 ))); \]
\[ QQutCtmp = QQutC \times (\text{Species } &= 3 \ ? 0.141 : \text{(Species } &= 2 \ ? 0.153 : \text{(Male } &= 0 \ ? \ 0.21 : \ 0.19 ))); \]
\[ QLivCtmp = QLivC \times (\text{Species } &= 3 \ ? 0.02 : \text{(Species } &= 2 \ ? 0.021 : \ 0.065 )); \]
\[ QSlwCtmp = QSlwC \times (\text{Species } &= 3 \ ? 0.217 : \text{(Species } &= 2 \ ? 0.336 : \text{(Male } &= 0 \ ? \ 0.17 : \ 0.22 )); \]
\[ QKidCtmp = QKidC \times (\text{Species } &= 3 \ ? 0.091 : \text{(Species } &= 2 \ ? 0.141 : \text{(Male } &= 0 \ ? \ 0.17 : \ 0.19 )); \]

Plasma Flows to Tissues (L/hr)
Mice and rats from Hejtmancik et al. 2002,
control F344 rats and B6C3F1 mice at 19 weeks of age
However, there appear to be significant strain differences in rodents, so
assume uncertainty CV=0.2 and variability CV=0.2.
Human central estimate from ICRP. Well measured in humans, from Price et al.,
human SD in hematocrit was 0.029 in females, 0.027 in males,
corresponding to FracPlas CV of 0.047 in females and
0.048 in males. Use rounded CV = 0.05 for both uncertainty and variability
Use measured 1-hematocrit if available
Truncate distributions at 3xCV to encompass clinical "normal range"
\[ FracPlas = \begin{cases} 
\text{Hematocritmeas} > 0.0 & \text{?(1-Hematocritmeas) \times (FracPlasC} & \text{(Species } &= 3 \ ? 0.52 : \text{(Species } &= 2 \ ? 0.53 : \text{(Male } &= 0 \ ? \ 0.615 : \ 0.567))); \end{cases} \]

Tissue Volumes (L)
# Fat = Adipose only
# Gut = GI tract (not contents) + pancreas + spleen (all drain to portal vein)
# Liv = Liver
# Rap = Brain + Heart + (Lungs-TB) + Bone marrow + "Rest of the body"
# VResp = Tracheobronchial region (trachea+bronchial basal+
#       bronchial secretory+bronchiolar)
# Kid = Kidney
# Bld = Blood
# Slw = Muscle + Skin, derived by difference
# residual (assumed unperfused) = (Bone-Marrow)+GI contents+other
#
# Mouse and rat data from Brown et al. (1997).  Human data from
# ICRP-89 (2002), and is sex-specific.

VFat = BW * (VFatCmeas > 0.0 ? VFatCmeas : (VFatC * (Species == 3 ? 0.07 :
(Species == 2 ? 0.07 : (Male == 0 ? 0.317 : 0.199) ))));
VGut = VGutC * BW *
(Species == 3 ? 0.049 : (Species == 2 ? 0.032 : (Male == 0 ? 0.022 : 0.020) ));
VLiv = VLivC * BW *
(Species == 3 ? 0.055 : (Species == 2 ? 0.034 : (Male == 0 ? 0.023 : 0.025) ));
VRap = VRapC * BW *
(Species == 3 ? 0.100 : (Species == 2 ? 0.088 : (Male == 0 ? 0.093 : 0.088) ));
VRespLum = VRespLumC * BW *
(Species == 3 ? (0.00014/0.03) : (Species == 2 ? (0.0014/0.3) : (0.167/70) ));
# Lumenal volumes from Styrene model (Sarangapani et al. 2002)
VRespEfftmp = VRespEffC * BW *
(Species == 3 ? 0.0007 : (Species == 2 ? 0.0005 : 0.00018 ));
# Respiratory tract volume is TB region
# will be multiplied by partition coef. below
VKid = VKidC * BW *
(Species == 3 ? 0.017 : (Species == 2 ? 0.007 : (Male == 0 ? 0.0046 : 0.0043) ));
VBld = VBldC * BW *
(Species == 3 ? 0.049 : (Species == 2 ? 0.074 : (Male == 0 ? 0.068 : 0.077) ));
VSlw = (Species == 3 ? 0.8897 : (Species == 2 ? 0.8995 : (Male == 0 ? 0.85778 : 0.856)) ) * BW
- VFat - VGut - VLiv - VRap - VRespEfftmp - VKid - VBld;
# Slowly perfused:
# Baseline mouse: 0.8897-0.049-0.017-0.0007-0.1-0.055-0.049-0.07= 0.549
# Baseline rat: 0.8995 -0.074-0.007-0.0005-0.088-0.034-0.032-0.07= 0.594
# Baseline human F: 0.85778-0.068-0.0046-0.00018-0.093-0.023-0.022-0.317= 0.33
# Baseline human M: 0.856-0.077-0.0043-0.00018-0.088-0.025-0.02-0.199= 0.4425

VPlas = FracPlas * VBld;
VBod = VFat + VGut + VRap + VRespEfftmp + VKid + VSlw; # For TCA
# Partition coefficients (data in blood/air or tissue/air)
# MICE:
#  Others: Gearhart et al. 1993
#  Gut, rapidly perfused = GM of kidney and liver
#  Respiratory tract - used kidney
#  Slowly perfused - used muscle
# RATS:
#  PB, Fat, Liver, Muscle - Gargas et al. 1989, Koizumi 1989,
#  Mahle et al., 2007
#  Skin - Mattie et al. 1994
#  Kidney, brain - Mahle et al., 2007
#  Gut = GM of kidney and liver
Rapidly perfused - used brain
Respiratory tract - used kidney
Slowly perfused - used muscle

HUMANS:

PB: Gargas et al. 1989, Sato and Nakajima 1979, Koizumi 1989,
Gearhart et al. 1993, Mahle et al., 2007, Mahle et al., 2007,
Fisher et al. 1997
Others - Gearhart et al. 1993
Gut, rapidly perfused = GM of kidney and liver
Respiratory tract - used kidney
Slowly perfused - used muscle

For blood-air, use overall mean = 14.71 as central estimate.
Error in overall mean = SEM = 0.43 under assumption that all variance
is inter-individual. Error in overall mean = S*sqrt(0.237) = 1.99 under
assumption that none of inter-group variance is inter-individual.
=>Use mean of error variances = sqrt((0.43^2+1.99^2)/2) = 1.4 as
error SD in blood:air. For interindividial variability, S = 4.09,
n=88, under assumption that all variance is inter-individual
For interindividual variability, S = 3.57, n=88, under assumption
that none of inter-group variance is inter-individual
=>Use mean of variances = sqrt((4.09^2+3.57^2)/2) = 3.84 as central
estimate of S, keep n=88
Note - 95% CI is (3.34, 4.51), well encompassing 3.57-4.09
(which are at the 0.15 and 0.78 percentiles). For others, use
Gearhart et al. (1993) as the central estimate.

PB = (PBmeas > 0.0 ? PBmeas : (PBC * (Species == 3 ? 18.6 : (Species == 2 ?
15.1 : 14.7 )))); # Blood-air
PFat = PFatC/PB * # Fat/blood
(PBC * (Species == 3 ? 1510. : (Species == 2 ? 1490. : 1450. )));
P Gut = exp(lnGutC)/PB * # Gut/blood
(PBC * (Species == 3 ? 62.1 : (Species == 2 ? 40.6 : 59.9 )));
PLiv = exp(lnLivC)/PB * # Liver/blood
(PBC * (Species == 3 ? 48.8 : (Species == 2 ? 50.3 : 61.1 )));
PRap = exp(lnRapC)/PB * # Rapidly perfused/blood
(PBC * (Species == 3 ? 62.1 : (Species == 2 ? 40.4 : 59.9 )));
Presp = exp(lnRespC)/PB * # Resp/blood =
(PBC * (Species == 3 ? 79.1 : (Species == 2 ? 32.7 : 58.6 )));
VRespEff = VRespEfftmp * Presp * PB; # Effective air volume
PKid = exp(lnKidC)/PB * # Slowly perfused/blood
(PBC * (Species == 3 ? 79.1 : (Species == 2 ? 32.7 : 58.6 )));
PSlw = exp(lnSlwC)/PB * # Slowly perfused/blood
(PBC * (Species == 3 ? 79.1 : (Species == 2 ? 21.6 : 70.5 )));

# TCA partitioning
TCAPlas = FracPlas + (1 - FracPlas) * 0.5 * exp(lnPRBCPlasTCAC);
# Blood/Plasma concentration ratio. Note dependence
# on fraction of blood that is plasma. Here
# exp(lnPRBCPlasTCAC) = partition coefficient
# C(blood minus plasma)/C(plasma)
# Default of 0.5, corresponding to Blood/Plasma
# concentration ratio of 0.76 in
# rats (Schultz et al 1999)
PBodTCA = TCAPlas * exp(lnPBodTCA) *
(Species == 3 ? 0.88 : (Species == 2 ? 0.88 : 0.52 ));
# Note -- these were done at 10-20 microg/ml (Abbas and Fisher 1997),
# which is 1.635-3.27 mmol/ml (1.635-3.27 x 10^-6 microM).
# At this high concentration, plasma binding should be
# saturated -- e.g., plasma albumin concentration was
# measured to be P=190-239 microM in mouse, rat, and human
# plasma by Lumpkin et al. 2003, or > 6800 molecules of
# TCA per molecule of albumin. So the measured partition
coefficients should reflect free blood-tissue partitioning.
Used muscle values, multiplied by blood:plasma ratio to get
Body:Plasma partition coefficient
Rats = mice from Abbas and Fisher 1997
Humans from Fisher et al. 1998
PLivTCA = TCAPlas * exp(lnPLivTCAC) *
   (Species == 3 ? 1.18 : (Species == 2 ? 1.18 : 0.66 ));
Multiplied by blood:plasma ratio to get Liver:Plasma
Rats = mice from Abbas and Fisher 1997
Humans from Fisher et al. 1998

# Binding Parameters for TCA
GM of Lumpkin et al. 2003; Schultz et al. 1999;
Template et al. 1993, 1995; Yu et al. 2000
Protein/TCA dissociation constant (umole/L)
kDissoc = exp(lnkDissocC) *
   (Species == 3 ? 107. : (Species == 2 ? 275. : 182. ));
BMix = NSites * Protein concentration. Sampled parameter is
BMix/kD (determines binding at low concentrations)
BMix = kDissoc * exp(lnBMixkDC) *
   (Species == 3 ? 0.88 : (Species == 2 ? 1.22 : 4.62 ));

# Absorption Rate Constants (/hr)
All priors are diffuse (log)uniform distributions
stomach absorption centered on 1.4/hr, range up or down 1000-fold
kAS = exp(lnkAS);
kASAq = exp(lnkASAq);
# transfer from stomach centered on 1.4/hr, range up or down 100-fold,
# based on human stomach half-time of 0.5 hr.
kTSD = exp(lnkTSD);
kTSDAq = exp(lnkTSDAq);
# intestinal absorption centered on 0.75/hr, range up or down
# 1000-fold, based on human transit time of small intestine
# of 4 hr (95% throughput in 4 hr)
kAD = exp(lnkAD);
kADAq = exp(lnkADAq);
kASTCA = exp(lnkASTCA);
FracAbsTCA = exp(lnFracAbsTCAC)/(1+exp(lnFracAbsTCAC));

# Metabolism parameters
Diffuse = log-uniform prior
Large uncertainty = GSD=30
Medium uncertainty = GSD=10
Modest uncertainty = GSD=5
Small uncertainty = GSD=3

# PERC Oxidative Metabolism Constants - Liver
Use Vmax/Km and Km as liver parameters.
# Medium uncertainty for liver Km (only data in rats)
# Modest uncertainty for liver Cl=Vmax/Km
KM = (Species == 3 ? 88.6*exp(lnKMC) : (Species == 2 ? 69.7*exp(lnKMC) : 55.8*exp(lnKMC)));
VMax = VLiv*exp(lnClC)*KM*
   (Species == 3 ? 1.57 : (Species == 2 ? 0.360 : 0.202));
KM2 = KM*exp(lnKM2C);#(v2.1.0)
VMax2 = (VMax/KM)*exp(lnCl2OxC)*KM2;#(v2.1.0)

# Oxidative metabolism splits
Fractional split of PERC to TCA
# exp(lnFracOtherC) = ratio of non-TCA to TCA
# Diffuse prior distribution in logit(fraction) from
# fraction=0.01 to 0.5
FracOther = exp(lnFracOtherC)/(1+exp(lnFracOtherC));

# Fractional split of PERC to TCA

# PERC Metabolism Constants for oxidation in kidney
# KM is relative to liver, modest uncertainty
# CI is relative to liver, adjusted for tissue weight, medium uncertainty
# (only data in rats)
KMKid = KM*exp(lnKMKidLivC)*
    (Species == 3 ? 0.616 : (Species == 2 ? 1.53 : 1.04 ));
VMaxKid = (VMax/KM/VLiv)*VKid*exp(lnVMaxKidLivC)*KMKid* 
    (Species == 3 ? 0.0211 : (Species == 2 ? 0.0085 : 0.0125 ));
FracKidTCA = exp(lnFracKidTCAC)/(1 + exp(lnFracKidTCAC));

# PERC Metabolism Constants for oxidation in Lung
# No data on lung, but can use TCE data on ratio of liver/lung.
# Scaled to liver VMax using TCE data from Green et al. (1997)
# in microsomal preparations (nmol/min/mg protein) at ~1 mM.
# For humans, used half of detection limit of 0.03=0.015
# Additional scaling by lung/liver weight ratio
# from Brown et al. Table 21 (mouse and rat) or
# ICRP Pub 89 Table 2.8 (Human female and male)
# Modest uncertainty for KM
# Small uncertainty for VMax
VMaxClara = exp(lnVMaxLungLivC) * VMax *
    (Species == 3 ? (0.55*0.7/5.5):(Species == 2 ? (0.098*0.5/3.4):(0.046*(Male == 0 ? (0.42/1.4) : (0.5/1.8))));
KMClara = KM * PLiv * exp(lnKMRespLivC) / (PB * PResp);

# PERC GSH Metabolism Constants - Liver
# Large uncertainty for both Vmax and Cl
VMaxTCVG = VLiv*exp(lnVMaxTCVGC)*
    (Species == 3 ? (35.3) : (Species == 2 ? (93.9) : (0.665)));#(v2.0.0)
KMTCVG = VMaxTCVG / (exp(lnClTCVGC)* 
    (Species == 3 ? (0.656) : (Species == 2 ? (2.22) : (0.0196))));#(v2.0.0)

# PERC GSH Metabolism Constants - Kidney
# Ratios to liver - Medium uncertainty
VMaxKidTCVG = (VMaxTCVG/VLiv)*VKid*exp(lnVMaxKidLivTCVGC)*{Species == 3 ? 0.15 :
    (Species == 2 ? 0.15 : 0.15)};
KMKidTCVG = VMaxKidTCVG /
    ((VMaxTCVG/KMTCVG/VLiv)*VKid*exp(lnVMaxKidLivTCVGC)*{Species == 3 ? 0.24 :
    (Species == 2 ? 0.098 : 0.14 )});

# TCA kinetic parameters
# Central estimate based on GFR clearance per unit body weight
# 10.0, 8.7, 1.8 ml/min/kg for mouse, rat, human
# (= 0.6, 0.522, 0.108 l/hr/kg) from Lin 1995.
# = CL_GFR / BW (BW=0.02 for mouse, 0.265 for rat, 70 for human)
# kUrn = CL_GFR / VPlas
kUrnTCA = exp(lnkTotTCAC)*exp(lnkUrnTCAC) * BW / VPlas *
    (Species == 3 ? 0.6 : (Species == 2 ? 0.522 : 0.108));
# /hr/kg^0.25
kMetTCA = exp(lnkTotTCAC)*exp(lnkMetTCAC) / BW25; #(v2.0.0)

# TCVC Kinetics in Kidney (/hr)
## Fraction of GSH conjugation resulting in DCA or NAcTCVC in urine
FracNATUrn = exp(lnFracNATUrnC)/(1+exp(lnFracNATUrnC));#
FracDCAUrn = (1-FracNATUrn)*exp(lnFracDCAUrnC)/(1+exp(lnFracDCAUrnC));

scaling parameter is logit of fraction remaining after NAT

## Delay rate constants for urinary excretion of DCA and NAcTCVC

kdCA = \exp(lnkdCAC) / BW25; 

knAT = \exp(lnknNATC) / BW25;

# CC data initialization

Rodents = NRodents; # Closed chamber simulation

VCh = VChC - (Rodents * BW);

# Calculate net chamber volume

kLoss = \exp(lnkLossC);

#******************************************************************************

#***                  State Variable Initialization and Scaling             ***
#******************************************************************************

# NOTE: All State Variables are automatically set to 0 initially,
# unless re-initialized here

ACh = (CC * VCh * MWPERC) / 24450.0; # Initial amount in chamber

};

******************************************************************************

End of Initialization ******************************************************************************

Dynamics{

#******************************************************************************

#***                       Dynamic physiological parameter scaling          ***
#******************************************************************************

# State Variables with dynamics:

# none

# Input Variables:

# QPmeas

# Other State Variables and Global Parameters:

# QC

# VPR

# DResptmp

# QPsamp

# QFatCtmp

# QGutCtmp

# QLivCtmp

# QSlwCtmp

# QKidCtmp

# FracPlas

# Temporary variables used:

# none

# Temporary variables assigned:

# QP

# DResp

# QCnow

# QFat

# QGut

# QLiv

# QSlw

# QKid

# QGutLiv

# QRap

# QCPlas

# QBodPlas

# QGutLivPlas

# Notes:

#******************************************************************************

# QP uses QPmeas if value is > 0, otherwise uses sampled value
QP = (QPmeas > 0 ? QPmeas : QPsamp);
DResp = DResptmp * QP;

# QCnow uses QPmeas/VPR if QPmeas > 0, otherwise uses sampled value
QCnow = (QPmeas > 0 ? QPmeas/VPR : QC);

# These done here in dynamics in case QCnow changes
# Blood Flows to Tissues (L/hr)
QFat = (QFatCtmp) * QCnow; #
QGut = (QGutCtmp) * QCnow; #
QLiv = (QLivCtmp) * QCnow; #
QSlw = (QSlwCtmp) * QCnow; #

    QKid = (QKidCtmp) * QCnow; #
    QGutLiv = QGut + QLiv; #
    QRap = QCnow - QFat - QGut - QLiv - QSlw - QKid;
    QRapCtmp = QRap/QCnow; #{vrisk}
    QBod = QCnow - QGutLiv; #

# Plasma Flows to Tissues (L/hr)
QCPlas = FracPlas * QCnow; #
QBodPlas = FracPlas * QBod; #
QGutLivPlas = FracPlas * QGutLiv; #

*** Exposure and Absorption calculations ***

# State Variables with dynamics:
# AStom
# ADuod
# AStomAq
# ADuodAq
# AStomTCA
# Input Variables:
# IVDose
# PDose
# PDoseAq
# Drink
# Conc
# IVDoseTCA
# PDoseTCA
# DrinkTCA
# Other State Variables and Global Parameters:
# ACh
# CC
# VCh
# MWPERC
# BW
# TChng
# kAS
# kTSD
# kAD
# kASAq
# kTSDAq
# kADAq
# kASTCA
# FracAbsTCA
# Temporary variables used:
# none
# Temporary variables assigned:
# kIV - rate into CVen
# kIA - rate into CArt
# kPV - rate into portal vein
# kStom - rate into stomach
# kDrink - incorporated into RAO
# RAO - rate into gut (oral absorption - both gavage and drinking water)
# CInh - inhalation exposure concentration
# kIVTCA - rate into blood
# kStomTCA - rate into stomach
# kPOTCA - rate into liver (oral absorption)
# kDrinkTCA - rate for drinking water
# Notes:
# For oral dosing, using "Spikes" for instantaneous inputs
# Inhalation Concentration (mg/L)
# CInh uses Conc when open chamber (CC=0) and
# ACh/VCh when closed chamber CC>0.
#******************************************************************************
### PERC DOSING
## IV route
kIV = (IVDose * BW) / TChng;  # IV infusion rate (mg/hr)
    # (IVDose constant for duration TChng)
kIA = (IADose * BW) / TChng;  # IA infusion rate (mg/hr)
kPV = (PVDose * BW) / TChng;  # PV infusion rate (mg/hr)
kStom = (PDose * BW) / TChng;  # PO dose rate (into stomach) (mg/hr)
    # oil
kStomAq = (PDoseAq * BW) / TChng;  # PO dose rate (into stomach) (mg/hr)
    # aqueous

## Oral route - oil
# Amount of PERC in stomach -- for oral dosing only (mg)
dt(AStom) = kStom - AStom * (kAS + kTSD);
# Amount of PERC in duodenum -- for oral dosing only (mg)
dt(ADuod) = (kTSD * AStom) - kAD * ADuod;

## Oral route - aqueous
# Amount of PERC in stomach -- for oral dosing only (mg)
dt(AStomAq) = kStomAq - AStomAq * (kASAq + kTSDAq);
# Amount of PERC in duodenum -- for oral dosing only (mg)
dt(ADuodAq) = (kTSDAq * AStomAq) - kADAq * ADuodAq;

# Rate of absorption from drinking water
kDrink = (Drink * BW) / 24.0;  # Ingestion rate via drinking water (mg/hr)
# Total rate of absorption including gavage (oil and aqueous) and drinking water
RAO = kDrink + (kAS * AStom) + (kAD * ADuod) +
    (kASAq * AStomAq) + (kADAq * ADuodAq);
## Inhalation route
CInh = ACh/VCh + Conc*MWPERC/24450.0;  # in mg/l

#### TCA Dosing
kIVTCA = (IVDoseTCA * BW) / TChng;  # TCA IV infusion rate (mg/hr)
kStomTCA = (PODoseTCA * BW) / TChng;  # TCA PO dose rate into stomach
dt(AStomTCA) = kStomTCA - AStomTCA * kASTCA;
kPOTCA = AStomTCA * kASTCA;  # TCA oral absorption rate (mg/hr)
kDrinkTCA = FracAbsTCA * (DrinkTCA * BW) / 24.0;
    # Ingestion rate of TCA
    # via drinking water (mg/hr)

******************************************************************************
#***                       PERC Model                                       ***
******************************************************************************
# State Variables with dynamics:
# ARap,  # Amount in rapidly perfused tissues
# ASlw,  # Amount in slowly perfused tissues
# AFat,  # Amount in fat
# AGut,  # Amount in gut
# ALiv,  # Amount in liver
# AInhResp,  
# AResp,  
# AExhResp,  
# AKid,    # Amount in Kidney -- currently in Rap tissue  
# ABld,    # Amount in Blood -- currently in Rap tissue  
# ACh,     # Amount of PERC in closed chamber  
# Input Variables:  
# none  
# Other State Variables and Global Parameters:  
# VRap  
# PRap  
# VS1w  
# PS1w  
# VFat  
# PFat  
# VGut  
# PGut  
# VFat  
# PLiv  
# VLiv  
# VRapLum  
# VRespEff  
# VKid  
# PKid  
# VBld  
# VMaxClara  
# KMClara  
# PB  
# Rodents  
# VCh  
# kLoss  
# VMax  
# KM  
# VMaxTCVG  
# KMTCVG  
# VMaxKidTCVG  
# KMKidTCVG  
# VMaxKid  
# KMKid  
# Temporary variables used:  
# QM  
# QFat  
# QGutLiv  
# QS1w  
# QRap  
# QKid  
# kIV  
# QCnow  
# CInh  
# QP  
# RAO  
# Temporary variables assigned:  
# QM  
# CRap  
# CS1w  
# CFat  
# CGut  
# CLiv  
# CInhResp  
# CResp  
# CExhResp  
# ExhFactor  
# CMixExh  
# CKid
**Blood (venous)**

# Tissue Concentrations (mg/L)
CRap = ARap/VRap;
CSlw = ASlw/VSlw;
CFat = AFat/VFat;
CGut = AGut/VGut;
CLiv = ALiv/VLiv;
CKid = AKid/VKid;

# Venous Concentrations (mg/L)
CVRap = CRap / PRap;
CVSlw = CSlw / PSlw;
CVFat = CFat / PFat;
CVGut = CGut / PGut;
CVLiv = CLiv / PLiv;
CVKid = CKid / PKid;

# Concentration of PERC in mixed venous blood (mg/L)
CVen = ABld/VBld;

# Dynamics for blood
\[ \frac{d}{dt}(ABld) = (QFat*CVFat + QGutLiv*CVLiv + QSlw*CVSlw + QRap*CVRap + QKid*CVKid + kIV) - CVen * QCnow; \]

**Gas exchange and Respiratory Metabolism**

# QM = QP/0.7; # Minute-volume
CInhResp = AInhResp/VRespLum;
CResp = AResp/VRespEff;
CExhResp = AExhResp/VRespLum;
\[ \frac{d}{dt}(AInhResp) = (QM*CInh + DResp*(CResp-CInhResp) - QM*CInhResp); \]
\[ \text{RAmetLng} = (VMaxClara * CResp)/(KMClara + CResp); \]
\[ \frac{d}{dt}(AResp) = (DResp*(CInhResp + CExhResp - 2*CResp) - RAmetLng); \]
\[ \text{CArt_tmp} = (QCnow*CVen + QP*CInhResp)/(QCnow + (QP/PB)); \]
\[ \frac{d}{dt}(AExhResp) = (QM*(CInhResp*CExhResp) + QP*(CArt_tmp/PB-CInhResp) + \]
\[ DResp*(CResp-CExhResp)); \]
\[ \text{CMixExh} = (CExhResp > 0 \ ? \ CExhResp : 1e-15); \]

# Concentration in alveolar air (mg/L)
# Correction factor for exhaled air to account for
# absorption/desorption/metabolism in respiratory tissue
# = 1 if DResp = 0
ExhFactor_den = (QP * CArt_tmp / PB + (QM-QP)*CInhResp);
ExhFactor = (ExhFactor_den > 0) ? (QM * CMixExh / ExhFactor_den) : 1;
# End-exhaled breath (corrected for absorption/
# desorption/metabolism in respiratory tissue
CAlv = CArt_tmp / PB * ExhFactor;

# Concentration in arterial blood entering circulation (mg/L)
CArt = CArt_tmp + kIA/QCnow;  # add inter-arterial dose

#**** Other dynamics for inhalation/exhalation ********************************
# Dynamics for amount of PERC in closed chamber
dt(ACh) = (CC>0) ? ((Conc == 0) ? ((Rodents * (QM * CMixExh - QM * ACh/VCh)) - (kLoss * ACh)) : 0.0) : 0.0;

#**** Non-metabolizing tissues ********************************************************
# Amount of PERC in rapidly perfused tissues (mg)
dt(ARap) = QRap * (CArt - CVRap);
# Amount of PERC in slowly perfused tissues
dt(ASlw) = QSlw * (CArt - CVSlw);
# Amount of PERC in fat tissue (mg)
dt(AFat) = QFat*(CArt - CVFat);
# Amount of PERC in gut compartment (mg)
dt(AGut) = (QGut * (CArt - CVGut)) + RAO;

#**** Liver ---------------------------------------------------------------------
# Rate of PERC oxidation by P450 to TCA and other in liver (mg/hr)
RAMetLiv1 = (VMax * CVLiv) / (KM + CVLiv) +
            (VMax2 * CVLiv) / (KM2 + CVLiv);#(v2.1.0)
# Rate of PERC metabolized to TCVG in liver (mg)
RAMetLiv2 = (VMaxTCVG * CVLiv) / (KMTCVG + CVLiv);
# Dynamics for amount of PERC in liver (mg)
dt(ALiv) = (QLiv * (CArt - CVLiv)) + (QGut * (CVGut - CVLiv)) -
          RAMetLiv1 - RAMetLiv2 + kPV;  # added PV dose

#**** Kidney -------------------------------------------------------------------
# Rate of PERC oxidized in kidney (mg) #
RAMetKid1 = (VMaxKid * CVKid) / (KMKid + CVKid);
# Rate of PERC metabolized to TCVG in kidney (mg) #
RAMetKid2 = (VMaxKidTCVG * CVKid) / (KMKidTCVG + CVKid);
# Amount of PERC in kidney compartment (mg)
dt(AKid) = (QKid * (CArt - CVKid)) - RAMetKid1 - RAMetKid2;

#******************************************************************************
#***                       TCA Sub-model                                    ***
#******************************************************************************
# State Variables with dynamics:
# APlasTCA
# ABodTCA
# ALivTCA
# AUrnTCA
# AUrnTCA_sat
# AUrnTCA_collect
# Input Variables:
# TCAUrnSat
# UrnMissing
# Other State Variables and Global Parameters:
# VPlas
# MWTCA
# kDissoc
# BMax
# kMetTCA -- hepatic metabolism of TCA (e.g., to DCA)
# VBod
# PBodTCA
# PLivTCA
# kUrnTCA
# StochTCAPERC
# Temporary variables used:
# kIVTCA
# kPOTCA
# kDrinkTCA
# QBodPlas
# QGutLivPlas
# QCPlas
# RAMetLiv1
# RAMetKid1
# RAMetLng
# Temporary variables assigned:
# CPlasTCA
# CPlasTCAMole
# a, b, c
# CPlasTCAFreeMole
# APlasTCAFree
# CPlasTCAFree
# CBodTCAFree
# CLivTCAFree
# CBodTCA
# CLivTCA
# CVBodTCA
# CVLivTCA
# RUrnTCAplas
# RUrnTCA
# RAMetTCA
# Notes:
#******************************************************************************
#**** Plasma ******************************************************************
# Concentration of TCA in plasma (umoles/L)
CPlasTCA = (APlasTCA<1.0e-15 ? 1.0e-15 : APlasTCA/VPlas);
# Concentration of free TCA in plasma in (umoles/L)
CPlasTCAMole = (CPlasTCA / MWTCA) * 1000.0;
a = kDissoc+BMax-CPlasTCAMole;
b = 4.0*kDissoc*CPlasTCAMole;
c = (b < 0.01*a*a ? b/2.0/a : sqrt(a*a+b)-a);
CPlasTCAFreeMole = 0.5*c;
# Concentration of free TCA in plasma (mg/L)
CPlasTCAFree = (CPlasTCAFreeMole * MWTCA) / 1000.0;
APlasTCAFree = CPlasTCAFree * VPlas;
# Concentration of bound TCA in plasma (mg/L)
CPlasTCAFree = (CPlasTCAFreeMole * MWTCA) / 1000.0;
APlasTCAFree = CPlasTCAFree * VPlas;
# Concentration of free TCA in plasma (mg/L)
CPlasTCAFree = (CPlasTCAFreeMole * MWTCA) / 1000.0;
# Concentration of bound TCA in plasma (mg/L)
CPlasTCAFree = (CPlasTCAFreeMole * MWTCA) / 1000.0;
# Concentration in body and liver
CBodTCA = (ABodTCA<0 ? 0 : ABodTCA/VBod);
CLivTCA = (ALivTCA<1.0e-15 ? 1.0e-15 : ALivTCA/VLiv);
# Total concentration in venous plasma (free+bound)
CVBodTCAFree = (CBodTCA / PBodTCA);
CVLivTCAFree = (CLivTCA / PLivTCA);
# Rate of urinary excretion of TCA
RUrnTCAPlas = kRUrnTCA * APlasTCAFree;
# Dynamics for amount of total (free+bound) TCA in plasma (mg)
dt(APlasTCA) = kIVTCA + (QBodPlas*CVBodTCAFree) +
(QGutLivPlas*CVLivTCA) - (QCPlas * CPlasTCA) - RUrnTCAplas;

#**** Body *****************************************************
# Dynamics for amount of total TCA in the body (mg)
dt(ABodTCA) = QBodPlas * (CPlasTCAFree - CVBodTCAFree) +
StochTCAPEC*(1 - FracOther)*RAMetLng +
StochTCAPEC*(1 - FracOther)*(1 - FracKidTCA)*RAMetKid1;

#**** Liver *****************************************************
# Rate of metabolism of TCA
RAMetTCA = kMetTCA * ALivTCA;

# Dynamics for amount of TCA in the liver (mg)
dt(ALivTCA) = kPOTCA + QGutLivPlas*(CPlasTCAFree - CVLivTCAFree) + kDrinkTCA - RAMetTCA + ((1 - FracOther) * StochTCApERc * RAMetLiv1);

#**** Urine *****************************************************
# Dynamics for amount of TCA in urine (mg)
RUrnTCA = RUrnTCAplas + StochTCApERc*(1 - FracOther)*FracKidTCA*RAMetKid1;
# includes direct from kidney
dt(AUrnTCA) = RUrnTCA;
dt(AUrnTCA_sat) = TCAUrnSat*(1-UrnMissing)* RUrnTCA;
# Saturated, but not missing collection times
dt(AUrnTCA_collect) = (1-TCAUrnSat)*(1-UrnMissing)*RUrnTCA;
# Not saturated and not missing collection times

#******************************************************************************
#***                       TCVC Sub-model                                   ***
#******************************************************************************
# State Variables with dynamics:
# ANTCVC #
# ADCA #
# AUrnNTCVC #
# AUrnDCA #
# Input Variables:
# none
# Other State Variables and Global Parameters:
# VKid
# MWTCVC
# StochTCVCpERc
# FracNATUrn ##
# FracDCAUrn ##
# StochN
# StochDCA TCVC
# Temporary variables used:
# RAMetLiv2
# RAMetKid2
# Temporary variables assigned:
# RAUrnTCVC
# RAUrnDCA
# Notes:
# Cannot detect TCVC in blood, so assume all is locally generated
# and excreted or bioactivated in kidney.
# Removed TCVC compartment, replaced by "delay" compartments for
# urinary excretion
#******************************************************************************

# Dynamics for amount of N Acetyl TCVC excreted (mg)
RUrnNTCVC = ANTCVC * kNAT; ##
dt(ANTCVC) = (RAMetLiv2 + RAMetKid2) * FracNATUrn * ##
StochTCVCpERc * StochN - RUrnNTCVC; ##
dt(AUrnNTCVC) = RUrnNTCVC; ##

# Dynamics for amount of DCA excreted as a result of Beta Lyase (mg)
RUrnDCA = ADCA * kDCA; ##
dt(ADCA) = (RAMetLiv2 + RAMetKid2) * FracDCAUrn * ##
StochTCVCpERc * StochDCA TCVC - RUrnDCA; ##
dt(AUrnDCA) = RUrnDCA; ##

# Dynamics for untracked GSH conjugation in perc equivalents ##
# dt(AGSHOther) = (RAMetLiv2 + RAMetKid2) * #(vrisk)##
# (1-FracNATUrn-FracDCAUrn); #(vrisk)##
#*****************************************************************************
#***                       Total Mass Balance                               ***
#*****************************************************************************

#**** Mass Balance for PERC **********************************************

# Total intake from inhalation (mg)
RInhDose = QM * Cinh;
dt(InhDose) = RInhDose;

# Amount of PERC absorbed by non-inhalation routes (mg)
#   dt(AO) = RAO + kIV + kIA + kPV; #(vrisk)

# Total dose
#   TotDose = InhDose + AO; #(vrisk)

# Total in tissues
#   TotTissue = #*(vrisk)
#     ARap + ASlw + AFat + AGut + ALiv + AKid + ABld + #*(vrisk)
#     AInhResp + AResp + AExhResp; #(vrisk)

# Total metabolized
#   dt(AMetLng) = RAMetLng; #
#   dt(AMetLiv1) = RAMetLiv1; #
#   dt(AMetLiv2) = RAMetLiv2; #
#   dt(AMetKid1) = RAMetKid1; #
#   dt(AMetKid2) = RAMetKid2; #
#   ATotMetLiv = AMetLiv1 + AMetLiv2; #
#   ATotMetKid = AMetKid1 + AMetKid2; #
#   TotMetab = AMetLng + ATotMetLiv + ATotMetKid; #
#   AMetLivOther = AMetLiv1 * FracOther; #
#   AMetGSH = AMetLiv2 + AMetKid2; #

# Amount exhaled (mg)
#   RAExh = QM * CMixExh;
#   dt(AExh) = RAExh;

# Mass balance
#   PERCDiff = TotDose - TotTissue - TotMetab; #(vrisk)
#   MassBalPERC = PERCDiff - AExh; #(vrisk)

#**** Mass Balance for TCA **********************************************

# Total production/intake of TCA
#   dt(AOTCA) = kPOTCA + kIVTCA + kDrinkTCA; #(vrisk)
#   TotTCAIn = AOTCA + (1 - FracOther)*StochTCA*AMetLiv1 + #*(vrisk)
#     StochTCA*AMetLiv2; #
#   TotTCASysIn = AOTCA + ((1 - FracOther)*StochTCA*AMetLiv1 + #*(vrisk)
#     AMetLiv2) + #*(vrisk)
#   StochTCA*AMetLiv1 + #*(vrisk)
#   StochTCACAPERC*(1 - FracOther)*1.5*AMetKid1; #*(vrisk)

# Total in tissues
#   TotTissueTCA = APlasTCA + ABodTCA + ALivTCA; #(vrisk)

# Total metabolism of TCA
#   dt(AMetTCA) = RAMetTCA; #(vrisk)

# Mass balance
#   TCADiff = TotTCAIn - TotTissueTCA - AMetTCA; #(vrisk)
#   MassBalTCA = TCADiff - AUrnTCA; #(vrisk)

#**** Mass Balance for Urinary NAcTCVC ********************************

# Total production of urinary NAcTCVC
#   dt(ANTCVCIn) = RAMetLiv2 + RAMetKid2) * FracNAT Urn * #*(vrisk)
#   StochTCVC*StochN; #*(vrisk)

# Mass balance of NAcTCVC
#   MassBalNTCVC = ANTCVCIn - ANTCVC - AUrnNTCVC; #(vrisk)

# Total production of urinary DCA
#   dt(ADCAIn) = RAMetLiv2 + RAMetKid2) * FracDCA*Urn * #*(vrisk)
#   StochDCATCVC*StochDCATCVC; #*(vrisk)

# Mass balance of DCA
#   MassBalDCA = ADCAIn - ADCA - AUrnDCA; #(vrisk)

#*****************************************************************************
#***                       Dynamic Outputs                                  ***
#*****************************************************************************
# Amount exhaled during exposure (mg)
\[ dt(AExhExp) = (\text{Conc} > 0 \ ? \ RAExh : 0); \]

```plaintext
#******************************************************************************
# AUC of PERC in arterial blood
#    dt(AUCCBld) = CArt; #(vrisk)
# AUC of PERC in liver
#    dt(AUCLiv) = CLiv; #(vrisk)
# AUC of PERC in kidney
#    dt(AUCCKid) = CKid; #(vrisk)
# AUC of PERC in rapidly perfused
#    dt(AUCCRap) = CRap; #(vrisk)
# AUC of free TCA in the plasma (mg/L * hr)
#    dt(AUCPlasTCAFree) = CPlasTCAFree; #(vrisk)
# AUC of total TCA in plasma (mg/L * hr)
#    dt(AUCPlasTCA) = CPlasTCA; #(vrisk)
# AUC of TCA in liver (mg/L * hr)
#    dt(AUCLivTCA) = CLivTCA; #(vrisk)
#
#******************************************************************************
```

### End of Dynamics

```plaintext
CalcOutputs{

### Static outputs for comparison to data

# PERC
RetDose = ((InhDose - AExhExp) > 1e-15 ? (InhDose - AExhExp) : 1e-15);
FracRetMetab = ((TotMetab/RetDose) > 1e-15 ? (TotMetab/RetDose) : 1e-15);
TotMetab = (TotMetab > 1e-15 ? TotMetab : 1e-15);
RAExh = (RAExh < 1.0e-15 ? 1.0e-15 : RAExh);
CAlvPPM = (CAlv < 1.0e-15 ? 1.0e-15 : CAlv / 24450.0 / MWPERC);
CInhPPM = (ACh < 1.0e-15 ? 1.0e-15 : ACh/VCh*24450.0/MWPERC);
# CInhPPM Only used for CC inhalation
CArt = (CArt < 1.0e-15 ? 1.0e-15 : CArt);
CVen = (CVen < 1.0e-15 ? 1.0e-15 : CVen);
CBldMix = (CArt + CVen) / 2;
CFat = (CFat < 1.0e-15 ? 1.0e-15 : CFat);
CGut = (CGut < 1.0e-15 ? 1.0e-15 : CGut);
CRap = (CRap < 1.0e-15 ? 1.0e-15 : CRap);
CSlw = (CSlw < 1.0e-15 ? 1.0e-15 : CSlw);
CHrt = CRap;
CKid = (CKid < 1.0e-15 ? 1.0e-15 : CKid);
CLiv = (CLiv < 1.0e-15 ? 1.0e-15 : CLiv);
CLung = CRap;
CMus = (CSlw < 1.0e-15 ? 1.0e-15 : CSlw);
CSp = CRap;
CBnr = CRap;
AExh = (AExh < 1.0e-15 ? 1.0e-15 : AExh);
AExhpost = ((AExh - AExhExp) < 1.0e-15 ? 1.0e-15 : AExh - AExhExp);
FracRetExh = AExhpost/RetDose;

# TCA
CPlasTCA = (CPlasTCA < 1.0e-15 ? 1.0e-15 : CPlasTCA);
CBldTCA = CPlasTCA*TCAPlas;
CBodTCA = (CBodTCA < 1.0e-15 ? 1.0e-15 : CBodTCA);
CLivTCA = (CLivTCA < 1.0e-15 ? 1.0e-15 : CLivTCA);
CKidTCA = CBodTCA;
CLungTCA = CBodTCA;
AUrnTCA = (AUrnTCA < 1.0e-15 ? 1.0e-15 : AUrnTCA);
AUrnTCA_sat = (AUrnTCA_sat < 1.0e-15 ? 1.0e-15 : AUrnTCA_sat);
```
zAUrnTCA_collect = (AUrnTCA_collect < 1.0e-15 ? 1.0e-15 : AUrnTCA_collect);

# Other
zAUrnNTCVC = (AUrnNTCVC < 1.0e-15 ? 1.0e-15 : AUrnNTCVC);
zAUrnDCA = (AUrnDCA < 1.0e-15 ? 1.0e-15 : AUrnDCA);

# Misc
CVenMole = CVen / MWPERC;
CPlasTCAmole = (CPlasTCAmole < 1.0e-15 ? 1.0e-15 : CPlasTCAmole);
CPlasTCAFReeMole = (CPlasTCAFReeMole < 1.0e-15 ? 1.0e-15 : CPlasTCAFReeMole);
FracBndPlasTCA = (CPlasTCAmole - CPlasTCAFReeMole) / CPlasTCAmole;

#**** Additional Dose Metrics

# TotTCAInBW = TotTCAIn/BW; #(vrisk) includes direct to urine
# TotTCSysInBW = TotTCSysIn/BW; #(vrisk) does not include direct to urine

# Scaled by BW^3/4
# TotMetabBW34 = TotMetab/BW75; #(vrisk)
# AMetGSHBW34 = AMetGSH/BW75; #(vrisk)
# TotDoseBW34 = TotDose/BW75; #(vrisk)
# AMetLiv1BW34 = AMetLiv1/BW75; #(vrisk)
# TotOxMetabBW34 = (AMetLg1 + AMetLiv1 + AMetKid1) / BW75; #(vrisk)
# AMetLgqBW34 = AMetLg1 / BW75; #(vrisk)
# AMetLivOtherBW34 = AMetLivOther / BW75; #(vrisk)
# ADCABW34 = ADCAIn/BW75; #(vrisk)
# ANATBW34 = ANATVCIn/BW75; #(vrisk)
# AGSHOtherBW34 = AGSHOther/BW75; #(vrisk)

# Scaled by tissue volume
# AMetLiv1Liv = AMetLiv1 / VLiv; #(vrisk)
# AMetLivOtherLiv = AMetLivOther / VLiv; #(vrisk)
# AMetLgqResp = AMetLg1 / VRespEfftmp; #(vrisk)
# AMetGSHKid = AMetGSH / VKid; #(vrisk)
# ADCAKid = ADCAIn / VKid; #(vrisk)
# ANATKid = ANATVCIn / VKid; #(vrisk)
# AGSHOtherKid = AGSHOther / VKid; #(vrisk)

#**** Fractional Volumes

# VFatCtmp = VFat / BW; #(vrisk)
# VGutCtmp = VGut / BW; #(vrisk)
# VLivCtmp = VLiv / BW; #(vrisk)
# VRapCtmp = VRap / BW; #(vrisk)
# VRespLumCtmp = VRespLum / BW; #(vrisk)
# VRespEffCtmp = VRespEfftmp / BW; #(vrisk)
# VKidCtmp = VKid / BW; #(vrisk)
# VBlodCtmp = VBlod / BW; #(vrisk)
# VSlwCtmp = VSlw / BW; #(vrisk)
# VPlasCtmp = VPlas / BW; #(vrisk)
# VBodCtmp = VBod / BW; #(vrisk)