```
# 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 KMClara 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)
       ADuod,        # oral gavage absorption (oil) -- mice and rats only
       AStomAq,      # Amount of PERC in stomach (aqueous)
       ADuodAq,      # 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
       AExhResp,     # 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
       ANTCVC,       # 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)
```

```
#      AUCCKid,      #(vrisk)
#      AUCCRap,      #(vrisk)
#      AUCPlasTCAFree,     #(vrisk)
#      AUCPlasTCA,   #(vrisk)
#      AUCLivTCA     #(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
       PODoseTCA,    # 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
#      TotTCASysIn, #(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) oxiation 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
#      ADCAKid, #(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
#      TotOxMetabBW34, #(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
#      ADCABW34, #(vrisk)# Amount of urinary DCA formed/BW^3/4
#      ANATBW34, #(vrisk)# Amount of urinary NAcTCVC 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 CAlvPPM
CAlvPPM,      # 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,     # mouse, rat, 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)
#  kASTCA, # (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)(v2.1.0) #VMax2 for hepatic PERC oxidation (mg/hr)
#  KM2, # (vrisk)(v2.1.0) #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"
#              # (vrisk) #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)
#  VMaxClara, # (vrisk) #VMax for Tracheo-bronchial PERC oxidation (mg/hr)
#  KMClara, # (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#
#  FracDCAUrn, #(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,
  CPlasTCAMole,
  CPlasTCAFreeMole
};

#*****************************************************************************
#***                  Global Constants                                     ***
#*****************************************************************************

# Molecular Weights
        MWPERC = 165.83;        # PERC
       MWTCVC = 250.53;        # TCVC
        MWTCA = 163.39;        # TCA
       MWDCA = 128.94;           # DCA
     MWNATCVC = 292.57;        # N Acetyl TCVC

# Stoichiometry
   StochTCAPERC = MWTCA / MWPERC;
  StochTCVCPERC = MWTCVC / MWPERC;
        StochN = MWNATCVC / 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)
kAD    = 0.75;       # PERC Duodenum absorption coefficient (oil) (/hr)
kASAq  = 1.4; # PERC Stomach absorption coefficient (aqueous) (/hr)
kTSDAq = 1.4; # PERC Stomach-duodenum transfer coefficient (aqueous) (/hr)
kADAq  = 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)
KMTCVG = 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)
VMaxKidTCVG   = 1;   # VMax for renal PERC GSH conjugation (mg/hr)
KMKidTCVG     = 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

#*************************************************************************
#***                   Potentially measured covariates (constants)           ***
#*************************************************************************
BWmeas = 0.0; # Body weight
VFatCmeas     = 0.0; # Fractional volume fat
PBmeas = 0.0; # Measured blood-air partition coefficient
Hematocritmeas = 0.0; # Measured hematocrit -- used for FracPlas = 1 - HCt

#*************************************************************************
#***                   Global Sampling Parameters                            ***
#*************************************************************************
# 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
VGutC  = 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
lnPGutC      = 0.0; # Scaled to species-specific central estimates and by Blood:air
lnPLivC      = 0.0; # Scaled to species-specific central estimates and by Blood:air
lnPRapC      = 0.0; # Scaled to species-specific central estimates and by Blood:air
lnPRespC     = 0.0; # Scaled to species-specific central estimates and by Blood:air
lnPKidC      = 0.0; # Scaled to species-specific central estimates and by Blood:air
lnPSlwC      = 0.0; # Scaled to species-specific central estimates and by Blood:air

# Partition Coefficients for TCA
lnPRBCPlasTCAC      = 0.0; # Scaled to species-specific central estimates
lnPBodTCAC    = 0.0; # Scaled to species-specific central estimates
lnPLivTCAC    = 0.0; # Scaled to species-specific central estimates

# Plasma Binding for TCA
lnkDissocC    = 0.0; # Scaled to species-specific central estimates
lnBMaxkDC     = 0.0; # Scaled to species-specific central estimates

# Oral Absorption rates
lnkAS  = 0.336;
lnkTSD = 0.336;
lnkAD  = -0.288;
lnkASAq      = 0.336;
lnkTSDAq     = 0.336;
lnkADAq      = -0.288;
lnkASTCA     = -0.288;
lnFracAbsTCAC= 2.94;

# PERC Metabolism
lnVMaxC      = 0.0; # Scaled by liver weight and species-specific central estimates
lnKMC  = 0.0; # Scaled to species-specific central estimates
lnClC  = 0.0; # Scaled to species-specific central estimates
lnKM2C = 0.0; # Scaled to KM of first pathway#(v2.1.0)
lnCl2OxC     = 0.0; # Scaled to clearance of first pathway#(v2.0.0)
lnFracOtherC  = -2.197;     # Ratio of oxidation of non-TCA to TCA
lnVMaxTCVGC   = 0.0; # Scaled by liver weight and species-specific central estimates
lnKMTCVGC     = 0.0; # Scaled to species-specific central estimates
lnClTCVGC     = 0.0; # Scaled to species-specific central estimates
lnVMaxKidLivC= 0.0; # Ratio of kidney VMax to Liver VMax, Scaled by kidney weight and
species-specific central estimates
lnKMKidLivC   = 0.0; # Ratio of kidney KM to liver Km, Scaled to species-specific
central estimates
lnClKidLivC   = 0.0; # Ratio of kidney Cl to liver Cl, Scaled to species-specific
central estimates
lnFracKidTCAC= 0.0; # Ratio of "directly" to urine to systemic TCA
lnVMaxKidLivTCVGC   = 0.0; # Ratio of kidney Vmax to liver Vmax, Scaled by kidney
weight and species-specific central estimates
lnKMKidTCVGC  = 0.0; # Scaled to species-specific central estimates
lnClKidLivTCVGC     = 0.0; # Ratio of kidney Cl to liver Cl, Scaled to species-
specific central estimates
lnVMaxLungLivC      = 0.0; # Ratio of lung Vmax to liver Vmax, scaled to species-
specific central estimates
lnKMRespLivC  = 0.0; # Ratio of lung to liver KM


# TCA Metabolism/clearance
lnkUrnTCAC    = 0.0; # Scaled by (plasma volume)^-1 and species-specific central
estimates
lnkMetTCAC    = 0.0; # Scaled by BW^-0.25
lnkTotTCAC    = 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 uniformative, 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_lnKMKidLivC     = 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_lnDRespC    = 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_PBC  = 1.0;
M_PFatC       = 1.0;
M_lnPGutC     = 1.0;
M_lnPLivC     = 1.0;
M_lnPRapC     = 1.0;
M_lnPRespC    = 1.0;
M_lnPKidC     = 1.0;
M_lnPSlwC     = 1.0;


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


M_lnkDissocC  = 1.0;
M_lnBMaxkDC   = 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_lnKMC       = 1.0;
M_lnClC       = 1.0;
M_lnKM2C      = 1.0;#(v2.1.0)
M_lnCl2OxC    = 1.0;#(v2.0.0)
M_lnFracOtherC      = 1.0;
M_lnVMaxTCVGC= 1.0;
M_lnKMTCVGC   = 1.0;
M_lnClTCVGC   = 1.0;
M_lnVMaxKidLivC     = 1.0;
M_lnKMKidLivC= 1.0;
M_lnClKidLivC= 1.0;
M_lnFracKidTCAC     = 1.0;
M_lnVMaxKidLivTCVGC = 1.0;
M_lnKMKidTCVGC      = 1.0;
M_lnClKidLivTCVGC   = 1.0;
M_lnVMaxLungLivC    = 1.0;
M_lnKMRespLivC      = 1.0;




M_lnkUrnTCAC  = 1.0;
M_lnkMetTCAC  = 1.0;
M_lnkTotTCAC  = 1.0;#(v2.0.0)


M_lnFracNATUrnC     = 1.0;
M_lnFracDCAUrnC     = 1.0;
M_lnkNATC     = 1.0;
M_lnkDCAC     = 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_QGutC       = 1.0;
V_QLivC       = 1.0;
V_QSlwC       = 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_lnPRBCPlasTCAC    = 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_CSpl       = 1;
Ve_CBrn       = 1;
Ve_zAExh      = 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)
#      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
#                    (i.e., via first pass)
#      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 NAcTCVC in urine#
#      FracDCAUrn    Fraction of GSH conjugation to DCA urine#
#      kNAT          Delay rate constant for NAcTCVC 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
#      lnkASAq
#      lnkTSDAq
#      lnkADAq
#      lnkASTCA
#      lnFracAbsTCAC
#      lnVMaxC
#      lnKMC
#      lnClC
#      lnKM2C#(v2.1.0)
#      lnCl2OxC#(v2.0.0)
#      lnFracOtherC
#      lnVMaxTCVGC
#      lnClTCVGC
#      lnKMTCVGC
#      lnVMaxKidLivC
#      lnClKidLivC
#      lnKMKidLivC
#      lnFracKidTCAC
#      lnVMaxKidLivTCVGC
#      lnClKidTCVGC
#      lnKMKidLivTCVGC
#      lnVMaxLungLivC
#      lnKMRespLivC
#      lnkUrnTCAC
#      lnkMetTCAC
#      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(lnVPRC)*
              (Species == 3 ? 2.5 : (Species == 2 ? 1.9 : 0.96 ));
       # Mouse: QP/BW=116.5 ml/min/100 g (Brown et al. 1997, Tab. 31), VPR=2.5
       #      Assume uncertainty CV of 0.2 similar to QC, truncated at 4xCV
       #      Consistent with range of QP in Tab. 31
       # Rat: QP/BW=52.9 ml/min/100 g (Brown et al. 1997, Tab. 31), VPR=1.9
       #      Assume uncertainty CV of 0.3 similar to QC, truncated at 4xCV
       #      Used larger CV because Tab. 31 shows a very large range of QP
       # Human: Average of Male VE=9 l/min, resp. rate=12 /min,
       #      dead space=0.15 l (QP=7.2 l/min), and Female
       #      VE=6.5 l/min, resp. rate=14 /min, dead space=0.12 l
       #      (QP=4.8 l/min), VPR = 0.96
       #      Assume uncertainty CV of 0.2 similar to QC, truncated at 4xCV
       #      Consistent with range of QP in Tab. 31
       QPsamp = QC*VPR;

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

# 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*
       (Species == 3 ? 0.07 : (Species == 2 ? 0.07 : (Male == 0 ? 0.085 : 0.05) ));
       QGutCtmp = QGutC*
       (Species == 3 ? 0.141 : (Species == 2 ? 0.153 : (Male == 0 ? 0.21 : 0.19) ));
       QLivCtmp = QLivC*
       (Species == 3 ? 0.02 : (Species == 2 ? 0.021 : 0.065 ));
       QSlwCtmp = QSlwC*
       (Species == 3 ? 0.217 : (Species == 2 ? 0.336 : (Male == 0 ? 0.17 : 0.22) ));
       QKidCtmp = QKidC*
              (Species == 3 ? 0.091 : (Species == 2 ? 0.141 : (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 = (Hematocritmeas > 0.0 ? (1-Hematocritmeas) : (FracPlasC *
       (Species == 3 ? 0.52 : (Species == 2 ? 0.53 : (Male == 0 ? 0.615 : 0.567)))));

# 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 = Tracheobroncial region (trachea+broncial basal+
#             broncial 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:
#   PB - Gargas et al. 1989, Reitz et al. 1996, Gearhart et al. 1993
#   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 interindividual 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
              (Species == 3 ? 1510. : (Species == 2 ? 1490. : 1450. ));
       PGut = exp(lnPGutC)/PB *          # Gut/blood
              (Species == 3 ? 62.1 : (Species == 2 ? 40.6 : 59.9 ));
       PLiv = exp(lnPLivC)/PB *  # Liver/blood
              (Species == 3 ? 48.8 : (Species == 2 ? 50.3 : 61.1 ));
       PRap = exp(lnPRapC)/PB *          # Rapidly perfused/blood
              (Species == 3 ? 62.1 : (Species == 2 ? 40.4 : 59.9 ));
       PResp = exp(lnPRespC)/PB *              # Resp/blood =
              (Species == 3 ? 79.1 : (Species == 2 ? 32.7 : 58.6 ));
       VRespEff = VRespEfftmp * PResp * PB; # Effective air volume
       PKid = exp(lnPKidC)/PB *          # Slowly perfused/blood
              (Species == 3 ? 79.1 : (Species == 2 ? 32.7 : 58.6 ));
       PSlw = exp(lnPSlwC)/PB *          # Slowly perfused/blood
              (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(lnPRBCPlasTCA) = 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(lnPBodTCAC) *
              (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;
       #      Templin et al. 1993, 1995; Yu et al. 2000
       # Protein/TCA dissociation constant (umole/L)
       kDissoc = exp(lnkDissocC) *
              (Species == 3 ? 107. : (Species == 2 ? 275. : 182. ));
       # BMax = NSites * Protein concentration.  Sampled parameter is
       #      BMax/kD (determines binding at low concentrations)
       BMax = kDissoc * exp(lnBMaxkDC) *
              (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
# Cl 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(lnClKidLivC)*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(lnClKidLivTCVGC)*(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 * #(v2.0.0)
             (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(lnkNATC) / 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
#      PODoseTCA
#      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
#      VSlw
#      PSlw
#      VFat
#      PFat
#      VGut
#      PGut
#      VLiv
#      PLiv
#      VRespLum
#      VRespEff
#      VKid
#      PKid
#      VBld
#      VMaxClara
#      KMClara
#      PB
#      Rodents
#      VCh
#      kLoss
#      VMax
#      KM
#      VMaxTCVG
#      KMTCVG
#      VMaxKidTCVG
#      KMKidTCVG
#      VMaxKid
#      KMKid
# Temporary variables used:
#      QM
#      QFat
#      QGutLiv
#      QSlw
#      QRap
#      QKid
#      kIV
#      QCnow
#      CInh
#      QP
#      RAO
# Temporary variables assigned:
#      QM
#      CRap
#      CSlw
#      CFat
#      CGut
#      CLiv
#      CInhResp
#      CResp
#      CExhResp
#      ExhFactor
#      CMixExh
#      CKid
```

```
#      CVRap
#      CVSlw
#      CVFat
#      CVGut
#      CVLiv
#      CVTB
#      CVKid
#      CVen
#      RAMetLng
#      CArt_tmp
#      CArt
#      CAlv
#      RAMetLiv1
#      RAMetLiv2
#      RAMetKid1
#      RAMetKid2
# Notes:
#*******************************************************************************
#

#****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
    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;
    dt(AInhResp) = (QM*CInh + DResp*(CResp-CInhResp) - QM*CInhResp);
    RAMetLng = (VMaxClara * CResp)/(KMClara + CResp);
    dt(AResp) = (DResp*(CInhResp + CExhResp - 2*CResp) - RAMetLng);
    CArt_tmp = (QCnow*CVen + QP*CInhResp)/(QCnow + (QP/PB));
    dt(AExhResp) = (QM*(CInhResp-CExhResp) + QP*(CArt_tmp/PB-CInhResp) +
             DResp*(CResp-CExhResp));
    CMixExh = (CExhResp > 0 ? CExhResp : 1e-15); # mixed exhaled breath

# 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
#      CPlasTCAFree
#      APlasTCAFree
#      CPlasTCABnd
#      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)
       CPlasTCABnd = (CPlasTCA<CPlasTCAFree ? 0 : CPlasTCA-CPlasTCAFree);
# 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);     # free in equilibrium
       CVBodTCA = CPlasTCABnd + CVBodTCAFree;
       CVLivTCAFree = (CLivTCA / PLivTCA);
       CVLivTCA = CPlasTCABnd + CVLivTCAFree;  # free in equilibrium
# Rate of urinary excretion of TCA
       RUrnTCAplas = kUrnTCA * APlasTCAFree;
# Dynamics for amount of total (free+bound) TCA in plasma (mg)
    dt(APlasTCA) = kIVTCA + (QBodPlas*CVBodTCA) + (QGutLivPlas*CVLivTCA)
                     - (QCPlas * CPlasTCA) - RUrnTCAplas;

#**** Body ********************************************************************
# Dynamics for amount of TCA in the body (mg)
    dt(ABodTCA) = QBodPlas * (CPlasTCAFree - CVBodTCAFree) +
                      StochTCAPERC*(1 - FracOther)*RAMetLng +
                     StochTCAPERC*(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 ##
#      kNAT ##
#      kDCA ##
#      StochN
#      StochDCATCVC
# 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 * StochDCATCVC - 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)*StochTCAPERC*AMetLiv1 + #(vrisk)
#             StochTCAPERC*(1 - FracOther)*(AMetKid1 + AMetLng); #(vrisk)
#      TotTCASysIn = AOTCA + ((1 - FracOther)*StochTCAPERC*(AMetLiv1 + #(vrisk)
#             AMetLng)) + #(vrisk)
#             StochTCAPERC*(1 - FracOther)*(1 - FracKidTCA)*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) * FracNATUrn * ##(vrisk)
#             StochTCVCPERC * StochN; ##(vrisk)
# Mass balance of NAcTCVC
#      MassBalNTCVC = ANTCVCIn - ANTCVC - AUrnNTCVC;#(vrisk)
# Total production of urinary DCA
#      dt(ADCAIn) = (RAMetLiv2 + RAMetKid2) * FracDCAUrn * ##(vrisk)
#             StochTCVCPERC * StochDCATCVC; ##(vrisk)
# Mass balance of DCA
#      MassBalDCA = ADCAIn - ADCA - AUrnDCA; #(vrisk)

#*****************************************************************************
#***                        Dynamic Outputs                                  ***
```

```
#*****************************************************************************
# Amount exhaled during exposure (mg)
    dt(AExhExp) = (Conc > 0 ? RAExh : 0);

#*****************************************************************************
#***                          Dose Metrics                                  ***
#*****************************************************************************
#**** AUCs in mg-hr/L unless otherwise noted ***********************************
#AUC of PERC in arterial blood
#    dt(AUCCBld) = CArt; #(vrisk)
#AUC of PERC in liver
#    dt(AUCCLiv) = 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 ######################################


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);
       zRAExh = (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);
       CSpl = CRap;
       CBrn = CRap;
       zAExh = (AExh < 1.0e-15 ? 1.0e-15 : AExh);
       zAExhpost = ((AExh - AExhExp) < 1.0e-15 ? 1.0e-15 : AExh - AExhExp);
       FracRetExh = zAExhpost/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;
       zAUrnTCA = (AUrnTCA < 1.0e-15 ? 1.0e-15 : AUrnTCA);
       zAUrnTCA_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 ? 1.01e-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
#     TotTCASysInBW = TotTCASysIn/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 = (AMetLng+AMetLiv1+AMetKid1)/BW75;#(vrisk)
#     AMetLngBW34 = AMetLng/BW75; #(vrisk)
#     AMetLivOtherBW34 = AMetLivOther/BW75; #(vrisk)
#     ADCABW34 = ADCAIn/BW75;#(vrisk)#
#     ANATBW34 = ANTCVCIn/BW75;#(vrisk)#
#     AGSHOtherBW34 = AGSHOther/BW75;#(vrisk)#

# Scaled by tissue volume
#     AMetLiv1Liv = AMetLiv1/VLiv; #(vrisk)
#     AMetLivOtherLiv = AMetLivOther/VLiv; #(vrisk)
#     AMetLngResp = AMetLng/VRespEfftmp; #(vrisk)
#     AMetGSHKid = AMetGSH/VKid;#(vrisk)#
#     ADCAKid = ADCAIn/VKid;#(vrisk)#
#     ANATKid = ANTCVCIn/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)
#     VBldCtmp = VBld/BW; #(vrisk)
#     VSlwCtmp = VSlw/BW; #(vrisk)
#     VPlasCtmp = VPlas/BW; #(vrisk)
#     VBodCtmp = VBod/BW; #(vrisk)


};
```