```
!
! Magnolia CSL model file created on 2019-04-18T10:21:02.815
! PBPK Gas Uptake Model for 2,2-DCPe converted from original acslx model by EMK
! Units of this model are liters (L), hours (h), milligrams (mg), BW in kilograms (kg)

model DCP22

initial  ! The INITIAL section contains statements evaluated 1x @ begin simulation

!***********! Physiological Parameters*********************}
CONSTANT    QPC = 13.2        ! Alveolar Ventilation Rate(l/hr-kg), Clewell et al., 2014, Table 6.1, p. 264
CONSTANT    QCC = 13.2        ! Cardiac Output(l/hr-kg), Clewell et al., 2014, Table 6.1, p. 264
CONSTANT    QLC = 0.242       ! Fract. Blood Flow to Liver, Table 25, p. 439, Brown et al., 1997
CONSTANT    QFC = 0.082       ! Fract. Blood Flow to Fat, Table 25, p. 439, Brown et al., 1997
CONSTANT    QSC = 0.257       ! Fract. Blood Flow to Poorly Perfused T., , Table 25, p. 439, Brown et al., 1997 (muscle +
skin)
        QRC = 1.0 - QLC - QFC - QSC      ! Fract. Blood Flow to Richly Perfused T

CONSTANT    BW = 0.222        ! Body Weight(kg), experiment-specific, mean & SD all rats 0.222+/-0.0184
CONSTANT   VLC = 0.036        ! Volume Fraction Liver, Brown et al., 1997, Table 8, p. 418
CONSTANT   VFC = 0.076        ! Volume Fraction Fat, Brown et al., 1997, equation, p. 422 using avg BW
CONSTANT   VSC = 0.7          ! Volume Fraction Poorly Perfused T., muscle + skin, Table 5, p. 416, Brown et al., 1997
       VRC = 1.0 - VLC - VFC - VSC    ! Volume Fraction Richly Perfused T.

  !************! Chemical Specific Parameters for DCPs***********************}
  ! Partition Coeffs Estimated Based on method of Beliveau et al., (2003)}
CONSTANT      PL =  1.81      ! Liver/Blood
CONSTANT      PF  = 22.03     ! Fat/Blood
CONSTANT      PS  = 0.84      ! Poorly/Blood (muscle is representative tissue)
CONSTANT      PR  = 1.81      ! Richly/Blood (liver is representative tissue)
CONSTANT      PB  = 3.75      ! Blood/Air
CONSTANT      MW  = 112.99    ! Molecular Wt (g/mol)
```

```
!VmaxC & Km starting values - final values are estimated from set of vapor uptake curves
!CONSTANT     VmaxC = 4.46   ! mg/hr-kg
!CONSTANT        Km = 3.77   ! mg/L
CONSTANT     KFC = 1.18            ! L/hr-kg, use if assuming first order metabolism

 ! Chamber/Rat/Exposure Parameters}
CONSTANT      CONC = 500.                                    ! Init. Inhaled Conc (ppm), experiment-specific
CONSTANT      RATS = 1                                              ! Number of rats in chamber, always 1
CONSTANT      VCHC = 3.8                                            ! Closed chamber vol (l)
CONSTANT      KLOS = 0.04                                           ! Closed chamber loss, hr-1, experiment-specific
    NETVOL = VCHC - (RATS * BW)                          ! Net Chamber Vol (l), i.e. volume of chamber not taken up by rats
      AIO = (CONC * NETVOL * MW)/24450             ! Initial Conc of chemical in Chamber (mg/l)
CONSTANT   TSTOP = 6.00                    ! Length of experiment (hrs)
CONSTANT  points = 100.                    ! No. of points in plot

!*******Scaled Parameters********}

       QC = QCC * (BW**0.75)      ! Cardiac Output (l/hr)
       QP = QPC * (BW**0.75)      ! Alveolar Ventilation Rate (l/hr)
       QL = QLC * QC            ! Flow Liver Compartment (l/hr)
       QF = QFC * QC                  ! Flow Fat Compartment (l/hr)
       QS = QSC * QC            ! Flow Slowly Perf. Tis. Cmpt. (l/hr)
       QR = QRC * QC                  ! Flow Richly Perf. Tis. Cmpt. (l/hr)
       VL = VLC * BW                  ! Volume Liver Compartment, Total
       VF = VFC * BW                  ! Volume Fat Compartment
       VS = VSC * BW                  ! Volume Slowly Perfused Tis. Cmpt.
       VR = VRC * BW                  ! Volume Richly Perfused Tis. Cmpt.

!Comment in/out eq below if running w/ michaelis-menten vs. first order}
  !VMAX = VMAXC * BW**0.75    ! VMAX scaled
 KF = KFC * BW**0.75       !
end ! initial

dynamic   !  The DYNAMIC section statements evaluated at each output time point
```

```
derivative

    RAI = (RATS * QP * (CX - CI)) - (KLOS*AI)      ! mg/hr
     AI = INTEG(RAI, AIO)                          ! mg
     CI = AI / NETVOL                                                  ! mg/l
     CP = (CI* 24450/MW)                                               ! chamber conc, ppm, data is in ppm

! chamber loss
   RLOSS = (KLOS * AI)                             ! mg/hr
    LOSS = INTEG(RLOSS, 0.0)

  CA = ((QC * CV) + (QP * CI)) / (QC + (QP / PB))  ! arterial (mg/L)

 !exhaled breath
    RAX = QP * CX                                  ! mg/hr
     AX = INTEG(RAX, 0.0)                          ! mg
     CX = CA/PB                                              ! Conc. DCPe in exhaled air(mg/l)
   CXPPM = ((0.7 * CX) + (0.3 * CI)) * (24.45/MW)             ! Conc. DCPE in ppm  exhaled breath
     AXKG = AX/BW                                                      ! mg exhaled/kg body weight

!slowly perfused tissue group
  RAS = QS * (CA - CVS)              ! mg/hr
   AS = INTEG(RAS,0.0)               ! mg
  CVS = AS / (VS * PS)                                  ! Conc partition to slow per. tis.(mgl)
  CS  = AS / VS                              ! Conc in volume slow per. tis.(mg/l)

!rapidly perfused tissue group
  RAR = QR * (CA - CVR)              ! mg/hr
   AR = INTEG(RAR, 0.0)              ! mg
  CVR = AR / (VR * PR)                                  ! Conc partition to rap per. tis.(mg/l)
   CR = AR / VR                         ! Conc in volume rap per. tis.(mg/l)

!fat
```

```
   RAF = QF * (CA - CVF)            ! mg/hr
    AF = INTEG(RAF, 0.0)            ! mg
   CVF = AF / (VF * PF)                        ! Conc partition to fat(mg/l)
   CF  = AF / VF                               ! Conc in fat volume(mg/l)

!liver
   RAL = QL * (CA - CVL) - RAM        ! mg/hr
    AL = INTEG(RAL, 0.0)            ! mg
   CVL = AL / (VL * PL)                                  ! Conc partition to liver(mg/l)
    CL = AL / VL                               ! Conc in liver volume(mg/l)

!Note: RAM rate of metabolism can be switched between being expressed as
!Michaelis-Menten terms (mg/hr) and Clearance terms (L/hr) by commenting
!in or out between the two equations below.  Note that parameters need to
!be changed within the inital section also (2 places) VMAX vs. KF & VMAXC vs KFC}

!    RAM   = (VMAX * CVL) / (KM + CVL)
   RAM = KF * CVL
    AM = INTEG(RAM, 0.0)

   CV = (QF*CVF + QL*CVL + QS*CVS + QR*CVR) / QC       ! venous blood conc (mg/l)

   DOSE = AIO - AI                                                  ! amt dcp in rat (mg)

   DMASS = (AF + AL + AS + AR + AM)*RATS

!Criterion - mass balance (MB)  should be near zero, i.e. <= ~e10-8.}

   MB = DOSE - DMASS - LOSS          ! mass balance (mg)

   TERMT(T >= TSTOP)                ! Condition for terminating simulation

end ! derivative
```

```
end ! dynamic

end ! program
```

```
! Parameter estimation script for 2,2-DCP PBPK model
! Closed-chambed rat data, 2,2-dichloropropane

load 'DCP22.csl'

! Any or all but one individial line can be commented out to simulate a single expt.
! Each line below calls data file and species parameters that change with each experiment
data @file='dcp2_60a.csv' ds1  t='t' cp='cp' tstop=4.17 bw=0.217 klos=0.0305 conc=49
data @file='dcp2_60b.csv' ds2  t='t' cp='cp' tstop=4.17 bw=0.222 klos=0.0332 conc=50
data @file='dcp2_60c.csv' ds3  t='t' cp='cp' tstop=5.00 bw=0.214 klos=0.0208 conc=57
data @file='dcp2_60d.csv' ds4  t='t' cp='cp' tstop=5.00 bw=0.209 klos=0.0312 conc=60
data @file='dcp2_200a.csv' ds5  t='t' cp='cp' tstop=4.33 bw=0.213 klos=0.045 conc=190
data @file='dcp2_200b.csv' ds6  t='t' cp='cp' tstop=4.33 bw=0.226 klos=0.025 conc=183
data @file='dcp2_230a.csv' ds7  t='t' cp='cp' tstop=4.17 bw=0.211 klos=0.043 conc=221
data @file='dcp2_500a.csv' ds8  t='t' cp='cp' tstop=6.0 bw=0.231 klos=0.032 conc=454
data @file='dcp2_500b.csv' ds9  t='t' cp='cp' tstop=6.1 bw=0.267 klos=0.036 conc=496
data @file='dcp2_600a.csv' ds10  t='t' cp='cp' tstop=5.67 bw=0.219 klos=0.059 conc=586
data @file='dcp2_600b.csv' ds11  t='t' cp='cp' tstop=6.17 bw=0.210 klos=0.065 conc=617
data @file='dcp2_1150a.csv' ds12 t='t' cp='cp' tstop=5.92 bw=0.189 klos=0.0468 conc=1105
data @file='dcp2_1150b.csv' ds13 t='t' cp='cp' tstop=6.1 bw=0.266 klos=0.063 conc=1141
data @file='dcp2_1150c.csv' ds14 t='t' cp='cp' tstop=6.33 bw=0.248 klos=0.0035 conc=1242
data @file='dcp2_1300a.csv' ds15 t='t' cp='cp' tstop=5.92 bw=0.197 klos=0.0518 conc=1288

! A procedure to plot all data sets
! Used to plot the fits before and after parameter estimation
procedure plotall

   set tstop=4.17 bw=0.217 klos=0.0305 conc=49
   start
   plot cp 'ds1:cp' @title='2,2-DCP 60a'

   set tstop=4.17 bw=0.222 klos=0.0332 conc=50
   start
   plot cp 'ds2:cp' @title='2,2-DCP 60b'
```

```
set tstop=5.00 bw=0.214 klos=0.0208 conc=57
start
plot cp 'ds3:cp' @title='2,2-DCP 60c'

 set tstop=5.00 bw=0.209 klos=0.0312 conc=60
 start
 plot cp 'ds4:cp' @title='2,2-DCP 60d'

 set tstop=4.33 bw=0.213 klos=0.045 conc=190
 start
 plot cp 'ds5:cp' @title='2,2-DCP 200a'

 set tstop=4.33 bw=0.226 klos=0.025 conc=183
 start
 plot cp 'ds6:cp' @title='2,2-DCP 200b'

 set tstop=4.17 bw=0.211 klos=0.043 conc=221
 start
 plot cp 'ds7:cp' @title='2,2-DCP 230a'

 set tstop=6.0 bw=0.231 klos=0.032 conc=454
 start
 plot cp 'ds8:cp' @title='2,2-DCP 500a'

 set tstop=6.1 bw=0.267 klos=0.036 conc=496
 start
 plot cp 'ds9:cp' @title='2,2-DCP 500b'

 set tstop=5.67 bw=0.219 klos=0.059 conc=586
 start
 plot cp 'ds10:cp' @title='2,2-DCP 600a'

 set tstop=6.17 bw=0.210 klos=0.065 conc=617
```

```
   start
   plot cp 'ds11:cp' @title='2,2-DCP 600b'

   set tstop=5.92 bw=0.189 klos=0.0468 conc=1105
   start
   plot cp 'ds12:cp' @title='2,2-DCP 1150a'

   set tstop=6.1 bw=0.266 klos=0.063 conc=1141
   start
   plot cp 'ds13:cp' @title='2,2-DCP 1150b'

   set tstop=6.33 bw=0.248 klos=0.0035 conc=1242
   start
   plot cp 'ds14:cp' @title='2,2-DCP 1150c'

   set tstop=5.92 bw=0.197 klos=0.0518 conc=1288
   start
   plot cp 'ds15:cp' @title='2,2-DCP 1300a'

end


prepare @clear T CP

set kfc = 1.08 @min=0.1 @max=2.16

plotall

fit @method=ml @errormodel=mixed kfc

plotall
```

```
!
! Magnolia CMD script created on 2020-02-24T16:12:57.165
! Sensitivity Analysis 22-DCP Global Morris Method

load 'DCP22.csl'

set    QPC = 13.2  @min=10 @max=16   ! Alveolar Ventilation Rate(l/hr-kg), Clewell et al., 2014, Table 6.1, p. 264
set    QCC = 13.2  @min=10 @max=16    ! Cardiac Output(l/hr-kg), Clewell et al., 2014, Table 6.1, p. 264
set    QLC = 0.242 @min=0.2 @max=0.28          !Fract. Blood Flow to Liver, Table 25, p. 439, Brown et al., 1997
set    QFC = 0.082 @min=0.05 @max=0.11 ! Fract. Blood Flow to Fat, Table 25, p. 439, Brown et al., 1997
set    QSC = 0.257 @min=0.23 @max=0.28        ! Fract. Blood Flow to Poorly Perfused T., , Table 25, p. 439, Brown et al., 1997 (muscle + skin)

set   BW = 0.222    @min=0.19 @max=0.25          ! Body Weight(kg), experiment-specific, mean & SD all rats 0.222+/-0.0184
set   VLC = 0.036   @min=0.028 @max=0.044 ! Volume Fraction Liver, Brown et al., 1997, Table 8, p. 418
set   VFC = 0.076           @min=0.05 @max=0.09             ! Volume Fraction Fat, Brown et al., 1997, equation, p. 422 using avg BW
set   VSC = 0.7              @min=0.65 @max=0.75   ! Volume Fraction Poorly Perfused T., muscle + skin, Table 5, p. 416, Brown et al., 1997

  !************! Chemical Specific Parameters for DCPs***********************}
  ! Partition Coeffs Estimated Based on method of Beliveau et al., (2003)}
set       PL =  1.81    @min=1.0 @max=2.6   ! Liver/Blood
set       PF  = 22.03   @min=18 @max=26   ! Fat/Blood
set       PS  = 0.84    @min=0.6 @max=1.2   ! Poorly/Blood (muscle is representative tissue)
set       PR  = 1.81    @min=1.0 @max=2.6   ! Richly/Blood (liver is representative tissue)
set       PB  = 3.75    @min=2.8 @max=4.7   ! Blood/Air
set       MW  = 112.99     ! Molecular Wt (g/mol)

!VmaxC & Km starting values - final values are estimated from set of vapor uptake curves
set     KFC = 1.18            @min=0.1 @max=2.2   ! L/hr-kg, hepatic clearance

! Chamber/Rat/Exposure Parameters}
set      CONC = 50.      ! Init. Inhaled Conc (ppm), experiment-specific, use 50, 200, 500 and 1150 ppm
set      RATS = 1                ! Number of rats in chamber, always 1
set      VCHC = 3.8             ! Closed chamber vol (l)
set      KLOS = 0.04        @min=0.02 @max=0.06            ! Closed chamber loss, hr-1, experiment-specific
```

```
set	TSTOP = 6.00	! Length of exposure

prepare t, cp, mb

output @clear t cp mb

start @nocallback
plot @title = 'Gas Uptake GSA Setup', @xlabel = 'Time (hrs)', @ylabel = 'CP (ppm)', cp

! Global sensitivity analysis, Morris method, response is cp
gsa @method=morris @nlevels=10 @nsamps=50 @response=cp @coeffile='cp_gsa.csv' QPC QCC QLC QFC QSC BW VLC VFC VSC...
PL PF PS PR PB KFC KLOS
line @xvar=t @file='cp_gsa.csv' QPC QCC QLC QFC QSC BW VLC VFC VSC...
PL PF PS PR PB KFC KLOS
```