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PROGRAM BDCM_pedsscaling.csl
  ! This version does in vitro scaling directly in the model and is used for evaluation of impact of variability
    ! in scaling factors (FVL, MPPGL, CYP2E1) on pharmacokinetic outcomes in adults and pediatric populations
  ! Modified by EMK & contractor (ICF) Sept-Dec. 2016 (see comments in code)

INITIAL
  ! Dosing independently turned on/off for each route in this version of model
   CONSTANT   idose = 10              ! inhaled dose (ppm)
    inh_dose = (idose * mw)/24.45       ! inhaled dose, ug/L --Raga: 24.45 is vol in L of a mole (gram mol wt) of a gas at 1 atm & 25 C
   CONSTANT   ddose = 0.036            ! tank conc for dermal dose (ppm)
    drml_dose = ddose * 1000           ! ug/L
   CONSTANT   odose = 0.0174           ! Oral dose (ug/kg BW)
            cw = (odose * BW)/0.25   ! Water ppb conc equiv. to odose w/ drink 1/4 L


   CONSTANT   d_exposr_length = 0.0167    ! Length of dermal exposure(h) --Raga: equals to 1 min
   CONSTANT   i_exposr_length = 0.0167    ! Length of inhalation exposure (h)
   CONSTANT   drml_switch = 1.0           ! dermal exposure switch
   CONSTANT   inh_switch = 1.0            ! inhalation exposure switch

   CONSTANT   Height = 180              ! Height of individual (cm)
   CONSTANT   BW = 70                 ! Body Weight (kg)
   CONSTANT   CvBDCMi = 0.0             ! Baseline BDCM(ug/L)
   CONSTANT   MW = 164                ! Molecular weight of BDCM
   CONSTANT   Vtank = 8.5             ! tank vol water (L)--Raga: used where?
   CONSTANT   PBDCM = 1.98              ! Density of BDCM
   CONSTANT   Mvol = 4.093e-5           ! Molar volume of gases at 25C
                        ! and 1.0013atm (mol/ml)

   ! Flow rates
   CONSTANT   Qpc = 212.4        ! Scaled minute ventiln (L/h/m2 sa)
   CONSTANT   Deadspace = 0.238   ! Deadspace fraction
   CONSTANT   Rqpco = 0.8        ! alv vent to cardiac output ratio
   CONSTANT   Fqrp = 0.75        ! Fraction bld flow to richly perfused
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  CONSTANT   Fqpp = 0.25        ! Fraction bld flow to poorly perfused
  CONSTANT   Fqg = 0.16         ! Fraction blood flow to gut
  CONSTANT   Fql = 0.09         ! Fraction blood flow to liver
  CONSTANT   Fqf = 0.05         ! Fraction blood flow to fat
  CONSTANT   Fqk = 0.15         ! Fraction blood flow to kidney
  CONSTANT   Qsksa = 0.58       ! Blood flow to skin normalized to
                        ! surface area (L/min/m2)--Raga will it change with change in surface area

  ! Compartment Vols 4/13/09 Note:  body currently divided up 80/20 for poorly/richly perfused.
  CONSTANT   FVbd = 0.079       ! Fraction of BW as blood (L/kg)
  CONSTANT   FVart = 0.25       ! Fraction blood as arterial
  CONSTANT   FVven = 0.75       ! Fraction blood as venous
  CONSTANT   FVrp = 0.20        ! Fraction BW as richly perfusd tissue
  CONSTANT   FVpp = 0.80        ! Fraction BW as poorly perfusd tissue
  CONSTANT   FVl = 0.034        ! Fraction BW as liver
  CONSTANT   FVgi = 0.0165      ! Fraction BW as gi tract
  CONSTANT   FVf = 0.10         ! Fraction BW as fat
  CONSTANT   FVk = 0.004        ! Fraction BW as kidney
  CONSTANT   Vlum = 2.1         ! Volume of lumen (L)
  CONSTANT   FSAsk = 0.055      ! Fraction total body sfc exposed during bathing or showering
  CONSTANT   Lsk = 2.0          ! skin thickness (mm), Changed 9/16/09

! partition coeffs
  CONSTANT    PbBDCM = 26.6     ! Blood:Air
  CONSTANT   PrpBDCM = 1.15     ! Rapidly perfused tissue:blood
  CONSTANT   PppBDCM = 0.47     ! Poorly perfused tissue:blood
  CONSTANT   PskBDCM = 5.3      ! Skin:bld
  CONSTANT   PwsBDCM = 5.6      ! Skin:Water
  CONSTANT    PlBDCM = 1.15     ! liver:blood
  CONSTANT    PgBDCM = 1.15     ! BDCM gut:blood
  CONSTANT    PfBDCM = 19.77    ! fat:blood
  CONSTANT    PkBDCM = 1.24     ! kidney:blood
  CONSTANT    KBDCM = 0.18      ! BDCM thru skin (cm/h) coeff Xu(2002)
  CONSTANT   ivvmax1 = 0.201    ! in vitro vmax (ug/hr-pmolCYP2E1)
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  CONSTANT     MPPGL = 39.79     ! mg microsomal protein (MSP) per g Liver--Raga: input
  CONSTANT                CYP2E1 = 43.26              !pmolCYP2E1/mg MSP
  CONSTANT   VfcBDCM = 0.0036    ! Scaled Vmax2 for BDCM (1/h/kgbw)--Raga: pathway 2 GST pathway
  CONSTANT   Km1BDCM = 221       ! BDCM Michelis Menten const (ug/L)
  CONSTANT    KaBDCM = 8.3       ! BDCM Oral absorption const (h-1)
  CONSTANT   Bioavail = 1.0      ! Bioavailability in stomach

  CONSTANT   tstop =  2.0        ! Length of simulation (h)
  CONSTANT   points = 40         ! Number of comm intervals--Raga: comm interval in the interval at which the simulation
                                   ! communicates externally to the hardware and updates it, it is not the integration step-length

!Logical Constrints for Mass Balance - flows & volumes
  Fqrpi = Fqrp/Qcci         ! 0.75 - Fraction bld flow to richly perfused
  Fqppi = Fqpp/Qcci         ! 0.25 - Fraction bld flow to poorly perfused
  Fqgi =  Fqg/Qcci          ! 0.16 - Fraction blood flow to gut
  Fqli =  Fql/Qcci          ! 0.09 - Fraction blood flow to liver
  Fqfi =  Fqf/Qcci          ! 0.05 - Fraction blood flow to fat
  Fqki =  Fqk/Qcci          ! 0.15 - Fraction blood flow to kidney
  Qsksai =  Qsksa/Qcci      ! 0.58 - Blood flow to skin normalized to surface area (L/min/m2)

  FVbdi = FVbd/Vti       ! 0.079 - Fraction of BW as blood (L/kg)
  FVrpi = FVrp/Vti       ! 0.20 - Fraction BW as richly perfusd tissue
  FVppi = FVpp/Vti       ! 0.80 - Fraction BW as poorly perfusd tissue
  FVli =  FVl/Vti        ! 0.034 - Fraction BW as liver
  FVgii = FVgi/Vti       ! 0.0165 - Fraction BW as gi tract
  FVfi =  FVf/Vti        ! 0.10 - Fraction BW as fat
  FVki =  FVk/Vti        ! 0.004 - Fraction BW as kidney

!Logical constraint tissue blood perfusion rates re-parameterized for global SA
  Qcci = fqrp +fqpp +fqgi + fql + fqf + fqk + qsksa

! Logical constraint tissue  masses re-parameterized for global SA
  Vti = FVbd + FVrp + FVpp + FVl + FVgi + FVf + FVk
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!For adult vs. pediatric, comment in/out for SA age specific population calculation
 SA = 0.0239*(Height^0.417)*(BW^0.517)        ! Total skin surface area (m2)--for adult
 !SA=(Height^0.725)*(BW^0.425)*0.007184              ! Total skin surface child (m2)71.84 cm^2 is equal to 0.007184 m^2
        SAsk = FSAsk*SA                    ! Exposed skin area(m2)--Raga: needs to change for children

  Qp = Qpc*SA*(1-Deadspace)              ! Alveolar ventilation (L/h)
  Qc = Qp/Rqpco                    ! Cardiac output (L/h)

  Vbd = FVbd*BW                          ! Blood volume
  Vart = FVart*Vbd                       ! Arterial blood volume
  Vven = FVven*Vbd                       ! Venous blood volume
  Vk = FVk*BW                            ! Kidney volume
  Vl = FVl*BW                            ! Liver volume
  Vlgram = FVl*1000                      ! Liver Volume in grams liver/kg BW
  Vgi = FVgi*BW                          ! GI Tract volume
  Vf = FVf*BW                            ! Fat volume
  Vsk = Lsk*SAsk                         ! Exposed skin volume
  Vrp = FVrp*BW-Vl-Vgi-Vbd-Vk             ! Richly perfused volume
  Vpp = FVpp*BW-Vf-Vsk                   ! Poorly perfused volume
  Volbalance = BW-Vbd-Vk-Vl-Vgi-Vf-Vsk-Vrp-Vpp        ! test for Volume Balance, should be less than 10e-12
  VTOT=VBD+VK+VL+VGI+VF+VSK+VRP+VPP              !EMK add 2/13/17, additional cross check for QA

  !Blood Flows to tissues (L/h)
  Ql = Fql*Qc                    ! Liver-hepatic artery
  Qg = Fqg*Qc                    ! Gi tract (portal to liver)
  Qk = Fqk*Qc                    ! Kidney
  Qrp = (Fqrp*Qc)-Ql-Qk-Qg       ! Richly perfused tissue
  Qf = Fqf*Qc                    ! Adipose tissue
  Qsk = Qsksa*SAsk*60            ! Skin-Exposed flow
  Qpp = Fqpp*Qc-Qf-Qsk           ! Poorly perfused tissue
  Flowbalance = Qc-Ql-Qg-Qk-Qrp-Qf-Qsk-Qpp                    ! test for flow balance, should be less than 10e-12
  QTOT=QL+QG+QK+QRP+QF+QSK+QPP                                 !EMK add 2/13/17, additional QA check

  LuBDCMi = Bioavail*Odose*BW/Vlum          !Initial BDCM in lumen (ug/L)
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   OdBDCM = Bioavail*Odose*BW                    !Dose to lumen in ug BDCM
   V1cBDCM = ivvmax1 * MPPGL *CYP2E1* Vlgram     !--Raga: scaling invitro vmax by mult by mppgl, cyp2e1 and liver volume in grams for use
                                                 !in CYP pathway
    V1BDCM = V1cBDCM*BW**0.75          ! pathway 1 vmax (ug/h)!--Raga: CYP pathway used in liver and metabolism part of code
    V2BDCM = VfcBDCM*BW**0.75          ! pathway 2 vmax (ug/h)!--Raga: GST pathway

  ! Initial Tissue amts of BDCM (ug), used when model evaluation data give background blood levels for BDCM
  AvBDCMi = CvBDCMi*Vven               ! Venous blood (Vven)--Raga: CvBDCMi is baseline BDCM
  ArpBDCMi = CvBDCMi*PrpBDCM*Vrp       ! Rich perfused tissue
  AppBDCMi = CvBDCMi*PppBDCM*Vpp       ! Poorly perfused tissue
  AfBDCMi = CvBDCMi*PfBDCM*Vf          ! Fat
  AkBDCMi = CvBDCMi*PkBDCM*Vk          ! Kidney
  AgBDCMi = CvBDCMi*PgBDCM*Vgi         ! Gut
  AlBDCMi = CvBDCMi*PlBDCM*Vl          ! Liver
  AskBDCMi = CvBDCMi*PskBDCM*Vsk       ! Skin
! init total amt
  Abodyi = AvBDCMi+ArpBDCMi+AppBDCMi+AfBDCMi+AkBDCMi+AgBDCMi+AlBDCMi+AskBDCMi

  Cint=tstop/points      !--Raga: comm interval is the interval at which the simulation communicates externally to the hardware and
                         !updates it, it is not the integration step-length

  ALGORITHM IALG = 2
END  !End of Initial


DYNAMIC
!--Raga: Discrete section contains statements executed at discrete points in time
 DISCRETE inh_on
   INTERVAL Inhaledose = 48.0          !--Raga: interval triggers the discrete
   inhale_sw = inh_switch              !--Raga: switch used to multiply the inhalation rate in teh derivative section to turn it off
   SCHEDULE inh_off .AT. t + i_exposr_length    ! when to shut off inhaln exposure
 END

 DISCRETE drml_on
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  INTERVAL Dermaldose = 48.0
  drml_sw = drml_switch
  SCHEDULE drml_off .AT. t + d_exposr_length
 END

 DISCRETE drml_off
  drml_dose = 0.0
 !  inh_dose = 0.0
  drml_sw = 0
 !  inhale_sw = 0
 END

 DISCRETE inh_off
  inh_dose = 0.0
  inhale_sw = 0
 END

 DERIVATIVE
!--Raga INTEG (rate, initial condition) is the general way of integrating continuously to solve
   rai = qp * inh_dose * inhale_sw                    ! rate ug/hr
   ai = INTEG(rai, 0.)                              ! amt inhaled, ug

   CartBDCM = (Qc*CvBDCM + qp*inh_dose)/(Qp/PbBDCM+Qc)  ! Arterial Blood Conc (ug/L)
   RexBDCM = Qp*CartBDCM/PbBDCM                       ! Amt exhaled (ug)
   exBDCM = INTEG(RexBDCM, 0.0)

   CBDCMtidal = CalvBDCM*(1-Deadspace)
   CalvBDCM = CartBDCM/PbBDCM                           ! exhaled breath (ug/L)
                CalvBDCM1 = CalvBDCM*1000               ! exhaled breath (ug/m^3)
   AUCalvBDCM = INTEG(CalvBDCM1,0.0)                    ! AUC for exhaled breath

   RvBDCM=Qrp*CvrpBDCM+Qpp*CvppBDCM+(Ql+Qg)*CvlBDCM+Qf*CvfBDCM+Qk*CvkBDCM+Qsk*CvskBDCM-Qc*CvBDCM
   AvBDCM = INTEG(RvBDCM, AvBDCMi)
   CvBDCM = AvBDCM/Vven                             ! Venous Blood Conc (ug/L)
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AUCvenBDCM = INTEG(CvBDCM, 0)                    ! AUC for CV (ug-hr/L)

RrpBDCM = Qrp*(CartBDCM-CvrpBDCM)
CvrpBDCM = CrpBDCM/PrpBDCM
ArpBDCM = INTEG(RrpBDCM, ArpBDCMi)
CrpBDCM = ArpBDCM/Vrp                            ! richly perfused (ug/L)

RppBDCM = Qpp*(CartBDCM-CvppBDCM)
CvppBDCM = CppBDCM/PppBDCM
AppBDCM = INTEG(RppBDCM, AppBDCMi)
CppBDCM = AppBDCM/Vpp                            ! poorly pefused (ug/L)

RfBDCM = Qf*(CartBDCM-CvfBDCM)
CvfBDCM = CfBDCM/PfBDCM
AfBDCM = INTEG(RfBDCM, AfBDCMi)
CfBDCM = AfBDCM/Vf                               ! fat (ug/L)

RkBDCM = Qk*(CartBDCM-CvkBDCM)
CvkBDCM = CkBDCM/PkBDCM
AkBDCM = INTEG(RkBDCM, AkBDCMi)
CkBDCM = AkBDCM/Vk                               ! kidney (ug/L)

RgBDCM = Qg*(CartBDCM-CvgBDCM)+RoBDCM
CvgBDCM = CgBDCM/PgBDCM
AgBDCM = INTEG(RgBDCM, AgBDCMi)                  ! gut (ug/L)
CgBDCM = AgBDCM/Vgi

RluBDCM = -KaBDCM*LuBDCM                         ! gut absorption rate (ug/L/h)
RoBDCM = -RluBDCM*Vlum
OBDCM =INTEG(RoBDCM, 0.0)                  ! amt BDCM absorbed (ug)
LuBDCM = INTEG(RluBDCM, luBDCMi)

RlBDCM = Ql*CartBDCM+Qg*CvgBDCM-(Ql+Qg)*CvlBDCM-RmBDCM
CvlBDCM = ClBDCM/PlBDCM
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  AlBDCM = INTEG(RlBDCM, AlBDCMi)
  ClBDCM = AlBDCM/Vl                                    ! liver (ug/L)

  RmBDCM = R1BDCM+R2BDCM                                ! BDCM metabolism rate (ug/h)
  R1BDCM = (V1BDCM*ClBDCM)/(Km1BDCM+ClBDCM)             !--Raga: CYP pathway
  M1BDCM = INTEG(R1BDCM, 0.0)
  R2BDCM = (V2BDCM*ClBDCM*Vl)                           !--Raga: GST pathway
  M2BDCM = INTEG(R2BDCM, 0.0)
  MBDCM = M1BDCM+M2BDCM                                 !Tot Amt BDCM met in liver
  TRAML = INTEG(RmBDCM, 0)                              !Tot Amt BDCM met in liver
  TRAMKG = TRAML/BW                                     !Tot Amt met per kg BW

  RskBDCM = Qsk*(CartBDCM-CvskBDCM)+RdBDCM
  CvskBDCM = CskBDCM/PskBDCM
  AskBDCM = INTEG(RskBDCM, AskBDCMi)
  CskBDCM = AskBDCM/Vsk                                 ! Exposed Skin (ug/L)

  RdBDCM = drml_sw*KBDCM*SAsk*10*(drml_dose-CskBDCM/PwsBDCM)  ! skin absorption rate (ug/h)
  DBDCM = INTEG(RdBDCM, 0.0)
END ! of derivative block

! mass balance check;  balbdcm should be a very small number,. Less than 10e-10.
BalBDCM = Abodyi + OBDCM + DBDCM + ai - &
      ExBDCM - AvBDCM - ArpBDCM - AppBDCM - AfBDCM - &
      AkBDCM - AgBDCM - AlBDCM - AskBDCM - MBDCM

CalvBDCMppb = CartBDCM/(PbBDCM * mw * Mvol)             ! Alveolar conc (ppbv)
CvBDCMppt = CvBDCM*1000                                 ! Central venous blood conc (ppt)

TERMT (T .GT. TSTOP)!--Raga: setting the STOP flag, stop when T reached TSTOP

END                             ! of dynamic block
END                             ! of program
```