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PROGRAM BDCM_inh2
  ! This version does in vitro scaling of metabolism directly in the model and is used
       ! for evaluation of impact of variability in scaling factors for microsomal protein (MPPGL)
       ! and liver mass (FVL), Basis for Manuscript in Journal of Applied Toxicology, 2016

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
  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

  !Legacy dosing code follows, leave for reference
  !  inh_dose = ddose * 0.067          ! Tan et al, J Exp Sci Envl Epi 2007 (Henry's Law) ppm
  !  drml_dose = ddose - inh_dose       ! ppm
  !  inh_dose = inh_dose * 1000         ! ug/L


  ! CONSTANT   idose = 10              ! inhaled dose (ppm)
  !  inh_only_dose = (idose * MW)/24.45    ! inhaled dose (ug/L)
  ! CONSTANT   kergr_factr = 1.8         ! (ug/m3)air/(ug/L)water, Kerger (2000) Risk Analysis
  !  drml_dose = ddose*1000             ! BDCM conc in water(ug/L)
  !  drml_inh = drml_dose * kergr_factr    ! inhaled dose (ug/m3) fr shower
  !  drml_inh_dose = drml_inh / 1000.     ! convert ug/m3 to ug/L
  !  inh_dose = drml_inh_dose + inh_only_dose

  CONSTANT   d_exposr_length = 0.0167    ! Length of dermal exposure(h)
  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)
  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
  CONSTANT   Fqpp = 0.25        ! Fraction bld flow to poorly perfused
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  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)

  ! Compartment Vols 4/13/09 Note:  body currently divided up 80/20 for poorly/richly perfused.
  ! May need to eventually change to add lumen and unperfused rest of body (nails, hair, urine)
  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
  CONSTANT   Lsk = 2.0          ! skin thickness (mm), Changed 9/16/09

! partition coeffs (unitless)
  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 = 17.13    ! in vitro vmax (ug/hr-mg MSP)
  CONSTANT    MMPGL = 39.79     ! mg microsomal protein (MSP) per g Liver
  CONSTANT   VfcBDCM = 0.0036   ! Scaled Vmax2 for BDCM (1/h/kgbw)
  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 =  4.0       ! Length of simulation (h)
  CONSTANT   points = 40        ! Number of comm intervals

  SA = 0.0239*(Height**0.417)*(BW**0.517)      ! Total skin surface area (m2)
  SAsk = FSAsk*SA                      ! Exposed skin area(m2)

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

  !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

  LuBDCMi = Bioavail*Odose*BW/Vlum           !Initial BDCM in lumen (ug/L)
   !V1cBDCM is scaled Vmax in units of ug/hr-kg
   V1cBDCM = ivvmax1 * MMPGL * Vlgram
    V1BDCM = V1cBDCM*BW**0.75              ! pathway 1 vmax (ug/h)
    V2BDCM = VfcBDCM*BW**0.75              ! pathway 2 vmax (ug/h)

  !Initial Tissue amts of BDCM (ug)
  AvBDCMi = CvBDCMi*Vven                 ! Venous blood (Vven)
  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
  ALGORITHM IALG = 2
END  !End of Initial


DYNAMIC
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DISCRETE inh_on
  INTERVAL Inhaledose = 48.0
  inhale_sw = inh_switch
  SCHEDULE inh_off .AT. t + i_exposr_length       ! when to shut off inhaln exposure
END

DISCRETE drml_on
  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

  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)

  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)
  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)
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  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
  AlBDCM = INTEG(RlBDCM, AlBDCMi)
  ClBDCM = AlBDCM/Vl                    ! liver (ug/L)

  RmBDCM = R1BDCM+R2BDCM                ! BDCM metabolism rate (ug/h)
  R1BDCM = (V1BDCM*ClBDCM)/(Km1BDCM+ClBDCM)
  M1BDCM = INTEG(R1BDCM, 0.0)
  R2BDCM = (V2BDCM*ClBDCM*Vl)
  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
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 ! mass balance check;  balbdcm should be an itty-bitty number, less than 10-7
 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)

END                                   ! of dynamic block
END                                   ! of program PROGRAM BDCM_inh2
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