```
PROGRAM BDCM_inh
  ! This is file C:\bdcm_inh\bdcm_inh.csl   Added inhalation route. July 2009
  ! Evolved fr Leavens model (whole body instead of 1 arm). C Eklund

  ! Added algorithm tying inhaled dose to dermal dose while showering.
  ! See Kerger 2000, Risk Analysis.  C Eklund  August 2010

  ! Created by Teresa Leavens 7/26/2000 to describe disposition of BDCM
  ! substituted for Jack Valentine's Model

  ! Modified 2/15/2007
  ! EMK modified metabolism 2/23/09, Xref RNB 1620 p. 62

  ! 2/15/2007 Removed coding for multiday dosing; changed to constant water conc in
  ! tank; added conversion to ng/L (ppt) for reporting blood concentration
  ! Updated Kbdcm (Skin perm.) to Xu (2002)TAP 184 19-26 in vitro value
  ! Updated 4/14/09 to change skin and arm description by TLL

  ! EMK changed skin thickness parameter to LSK=2.0 mm (dermis + epidermis)
  ! Notebook crossreference is NHEERL 1620, p. 84-88
  ! Version CE 1/20/11 runs all routes separately + dermal & inhal simultaneously

INITIAL

   CONSTANT   idose = 0.01              ! 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

   !  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


  ! 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
  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 correct 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 - rat tissue (Lilly et al.'97) / human bld:air avg
  CONSTANT   PbBDCM = 15.97      ! Blood:Air; from R. Pegram avg M & F
  CONSTANT   PrpBDCM = 1.93      ! Rapidly perfused tissue:blood
```

```
CONSTANT   PppBDCM = 0.78     ! Poorly perfused tissue:blood
CONSTANT   PskBDCM = 2.91     ! Skin:blood
CONSTANT   PwsBDCM = 5.6      ! Skin:Water
CONSTANT   PlBDCM = 1.93      ! liver:blood
CONSTANT   PgBDCM = 1.93      ! BDCM gut:blood
CONSTANT   PfBDCM = 33.2      ! fat:blood
CONSTANT   PkBDCM = 1.05      ! kidney:blood
CONSTANT   KBDCM = 0.18       ! BDCM thru skin (cm/h) coeff Xu(2002)
CONSTANT   V1cBDCM = 250000    ! Scaled Vmax CYP pathway  BDCM (ug/h/kgbw)
CONSTANT   Mvol = 4.093e-5     ! Molar volume of gases at 25C
                    ! and 1.0013atm (mol/ml)

!CONSTANT   ivvmax1 = 1239840  ! in-vitro vmax (ug/hr-mg MSP)
!CONSTANT   mmpgl = 39.79      ! mg microsomal protein (MSP)/g liver
CONSTANT   VfcBDCM = 0.0036    ! Scaled GST Clearanc BDCM (1/h/kgbw)
CONSTANT   Km1BDCM = 1675      ! BDCM Michelis Menten const (ug/L)
CONSTANT   KaBDCM = 4.0        ! BDCM Oral absorption const (h-1)
CONSTANT   Bioavail = 1.0      ! Bioavailability in stomach

CONSTANT   tstop =  4.0        ! Length of simulation (h)
CONSTANT   points = 2400       ! 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)

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 = Vl*1000                         ! Liver Volume in grams
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)
   V1BDCM = V1cBDCM*BW**0.75             ! pathway 1 CYP vmax (ug/h))
   V2BDCM = VfcBDCM*BW**0.75             ! pathway 2 GST clearance (l/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

 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)


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

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

  RmBDCM = R1BDCM+R2BDCM                ! BDCM tot liver metabolism rate (ug/h)
  R1BDCM = (V1BDCM*ClBDCM)/(Km1BDCM+ClBDCM)   ! BDCM rate metabol CYP (ug/h)
  M1BDCM = INTEG(R1BDCM, 0.0)           ! BDCM amt metab CYP (ug)
  R2BDCM = (V2BDCM*ClBDCM)              ! BDCM rate metab GST (ug/h)
  M2BDCM = INTEG(R2BDCM, 0.0)           ! BDCM amt metab GST (ug/h)
  MBDCM = M1BDCM+M2BDCM                 !Tot Amt BDCM met in liver
  TRAML = INTEG(RmBDCM, 0)                                                    !Tot
Amt BDCM met in liver, alt x-chk
  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 conc(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 an itty-bitty number.
 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
```