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PROGRAM NMP.ACSL

!PBPK MODEL FOR N-METHYL PYRROLIDONE
!FINAL RAT MODEL (5/09)
!T.S. POET,P HINDERLITER. CHEMICAL DOSIMETRY GROUP, PNNL, RICHLAND, WA

!MODEL TRANSFERRED FROM SIMUSOLV TO ACSLXTREME FORMAT IN 08
!MODEL CONFIGURED FOR INHALATION (OPEN, WHOLE BODY/NOSE ONLY)
!   IV, ORAL,  DERMAL, AND IP  ROUTES OF ADMINISTRATION.

!MODEL TRACKS DISPOSITION OF NMP AND 5-HNMP.
!ASSUMPTIONS:
!    (1) FLOW-LIMITED (ALL COMPARTMENTS)
!    (2) METABOLISM OF NMP BY A SAT PATHWAY TO FORM 5HNP
!    (3) METABOLISM OF HNP BY SATURABLE PATHWAY TO ETC.
!    (5) METABOLISM OCCURS ONLY IN THE LIVER
!    (6) TISSUE:BLOOD PART. COEFF.   = HUMAN = KRISHNAN EQN
!          UPDATED IN CMD FILE TO MEASURED IN-HOUSE
!    (7) 5HNP ELIMIN FROM MIXED VENOUS - 1ST ORDER
!     THIS DIFFERS FROM 02: URINE BY *GFR CLEARANCE FROM KIDNEY
!   METAB RATE CONST. FROM REPORT - UPDATED WITH LIT VALUES IN CMD FILE
!   PREG ADDED - OTHER PARAMETERS CHANGED NOMINALLY TO HARMONIZE WITH
FETAL IPA MODEL OF
!     GENTRY ET AL. REGU TOX PHARM 36:51-68, 2002
!
! Further updates by Paul Schlosser, US EPA in August and September 2013
and December 2014

INITIAL
! MODEL UNITS
! CONCENTRATION, MG/L
! FLOW, L/HR
! BODY WT, KG

 CONSTANT  BWINIT=0.       ! PRE-PREGNANCY BODY WEIGHT (KG)
 CONSTANT  RATS=1.         !NUMBER OF ANIMALS IN EXPT
 CONSTANT  MWNMP=99.13      !MOL. WT. NMP, MG/MMOL
 CONSTANT  MWHP= 116.14     !MOL. WT. 5-HNP, MG/MMOL

!BLOOD FLOWS
!FROM BROWN ET AL TOX IND HEALTH 97
!AND/OR FROM IPA MODEL OF GENTRY ET AL.,
! BLOOD FLOWS (FRACTION OF CARDIAC OUTPUT)
  CONSTANT     QCC = 0        ! CARDIAC OUTPUT (L/HR FOR 1 KG ANIMAL)
  CONSTANT     QPC = 0       ! ALVEOLAR VENT. RATE

  CONSTANT   QFATC = 0        ! FAT (NON-PREGNANT)
  CONSTANT   QLIVC = 0        ! LIVER
  CONSTANT   QMAMC = 0        ! MAMMARY TISSUE (NON-PREGNANT)
  CONSTANT   QSKNC = 0        ! SKIN
  CONSTANT   QUTRC = 0        ! UTERUS (NON-PREGNANT)
  CONSTANT   QRAPC = 0        ! RAPID USE STATIC RAPID FOR RATS (MUST BE
CHANGED FOR HUMAN)
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! PERMEABILITY-AREA PRODUCT (L/HR)
  CONSTANT    PAFC = 0.1          ! DIFFUSION ON FETAL SIDE OF PLACENTA

! TISSUE VOLUMES (FRACTION OF BODY WEIGHT)
!FROM BROWN ET AL TOX IND HEALTH 97 FOR RATS
!OR FROM GENTRY ET AL
  CONSTANT    VLUC = 0        ! LUNG
  CONSTANT   VFATC = 0         ! FAT (NON-PREGNANT)
  CONSTANT   VLIVC = 0        ! LIVER
  CONSTANT   VMAMC = 0         ! MAMMARY TISSUE (NON-PREGNANT)
  CONSTANT   VRAPC = 0        ! RAPIDLY PERFUSED
  CONSTANT   VUTRC = 0        ! UTERUS (NON-PREGNANT)
  CONSTANT    VBLC = 0       ! TOTAL BLOOD


! FOR PARENT MODEL, SKIN COMPARTMENT IS ONLY DEFINED AS DOSED SKIN
  CONSTANT    VSKC = 0.19           ! SKIN
  CONSTANT      SA = 0.01         !SURFACE AREA EXPOSED, SQ.CM
           TSA = 906.*BWINIT**(2./3.)   !TOTAL BODY SURFACE AREA, SQ.CM.
                                            !MCDOUGAL ET AL. T.A.P.
85(1996)286
   IF (CONCL.GT.0.0) THEN
           VSKCC = VSKC*SA/TSA
      QSKCC = QSKNC*SA/TSA
   ELSE
           VSKCC = VSKC*SA/TSA
      QSKCC = QSKNC*SA/TSA
   ENDIF

! SLOWLY PERFUSED (DEFINED AS BALANCE OF TISSUES AND FLOWS)
 VSC = 0.91 - (VLUC + VFATC + VLIVC + VMAMC + VRAPC + VUTRC + VBLC +
VSKCC)
       ! NOTE: 0.91 IS APPROX WHOLE BODY LESS BONE
 QSC = 1. - (QFATC + QLIVC + QMAMC + QRAPC + QUTRC + QSKCC)

! SCALED BLOOD FLOWS (L/HR)
    QCINIT = QCC * (BWINIT**0.75)
     QFATI = QFATC * QCINIT
      QLIV = QLIVC * QCINIT
     QMAMI = QMAMC * QCINIT
      QRAP = QRAPC * QCINIT
      QSKN = QSKCC * QCINIT
      QSLW = QSC * QCINIT
     QUTRI = QUTRC * QCINIT

! SCALED TISSUE VOLUMES (L)
       VLU = VLUC * BWINIT
     VFATI = VFATC * BWINIT
      VLIVI = VLIVC * BWINIT
      VRAP = VRAPC * BWINIT
      VSLW = VSC * BWINIT
     VMAMI = VMAMC * BWINIT
     VUTRI = VUTRC * BWINIT
       VSK = VSKCC * BWINIT
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       VBL = VBLC * BWINIT     ! TOTAL BLOOD
                 VA = 0.25*VBL          !ARTERIAL BLOOD
            VV = 0.75*VBL          !VENOUS BLOOD

! PREGNANCY PARAMETERS
  CONSTANT  NUMFET = 7.0          ! NUMBER OF FETUSES
  CONSTANT   PUPBW = 4500.        ! BIRTH WEIGHT (MG)
  CONSTANT VFETD18 = 1051.254     ! VOLUME OF  FETUS AT DAY 18 ( ) OF
PREGNANCY

! CONVERSION FACTORS
  CONSTANT    MGKG = 1.0E6        ! CONVERSION FACTOR FROM MG TO KG

!PARTITION COEFFICIENTS
!EXPERIMENTALLY MEASURED VALUES
   CONSTANT PB=0.     !NMP BLOOD:AIR
   CONSTANT PF=0            !NMP FAT:BLOOD - MEASURED
   CONSTANT PL=0            !MEASURED
   CONSTANT PR=0            !MEASURED LIVER
   CONSTANT PS=0            !NOT MEASURED MUSCLE - CORRECTED FOR FILTER
ERROR USING SKIN PROPORTIONALITY
   CONSTANT PSKL=0          !MEASURED
   CONSTANT PLU=0     !NMP LUNG:BLOOD
   CONSTANT PSKA= 0   !NMP SKIN:AIR
            CONSTANT PSKB=0   !NMP SKIN:BLOOD
   CONSTANT PM=0            !MAMMARY, ESTIMATED FORM LIVER
   CONSTANT PPLA=0
   CONSTANT PUTR=0


!EXPERIMENTALLY MEASURED VALUES
   CONSTANT PLHNP=0            !LIVER MEASURED
   CONSTANT PBHNP=0         !ESTIMATED AVG OF "OTHER" TISSUES
   CONSTANT PFHNP=0            !MEASURED
   CONSTANT PPLHNP=0

!METABOLIC RATE CONSTANTS
     CONSTANT  KM=0               !MICHAELIS CONSTANT, MG/L
     CONSTANT  VMAXC=0  !MAX. ENZ. ACT., MG/HR/L
     VMAX1 = VMAXC*BWINIT**0.75

  !5HNP TO OTHER METABS
     CONSTANT  KM2=0         !MICHAELIS CONSTANT, MG/L
     CONSTANT  VMAX2C=0           !MAX. ENZ. ACT., MG/HR/L
     VMAX2 = VMAX2C*BWINIT**0.75

!URINARY ELIMINATION OF 5-HNMP - CLEARED FROM BLOOD
  CONSTANT KLC=0
  KL=KLC/(BWINIT**0.25)
 CONSTANT KLNC=0            !URINARY LOSS OF NMP, L/HR
      KLN=KLNC/(BWINIT**0.25)


!FRACTIONAL ABSORPTION
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    CONSTANT  FRACIN = 1     !FRACTIONAL UPTAKE OF NMP BY INHAL,START AT
65%
                                  !OF ALVEOLAR - AS IN AKESSON ET AL
1997
    CONSTANT  FRACOR = 1.0      !FRACTION ABSORBED ORALLY, INITALLY 100%
    CONSTANT FRACF=1


! INITIAL CONDITIONS FOR CLOSED CHAMBER INHALATION
  CONSTANT    VCHC = 9E9   ! VOLUME OF CLOSED CHAMBER (L),START LARGE FOR
OPEN
  CONSTANT   KLOSS = 0.0   ! CHAMBER LOSS RATE /HR


!TIMING COMMANDS

      CONSTANT  TCHNG=6.0    !END OF INHAL EXPOSURE, HR
    CONSTANT  TSTOP=24.0    !END OF EXPERIMENT/SIMULATION, HR
      CONSTANT MAXT=0.01          !MAXIMUM STEP SIZE, HR
      CONSTANT MINT=1E-7
      CONSTANT CINT = 0.2    !DATA LOGGING RATE /HR
    CONSTANT  GDDAYS=0.0   ! OFFSET FOR GESTATIONAL DAY SIMULATION
    CONSTANT  GDMONTHS=0.0  !OFFSET FOR HUMAN GD SIMULATION

!INITIAL EXPOSURE CONDITIONS
  ! EXPOSURE CONDITIONS BASED ON USER DEFINED INITIAL AMOUNTS OF CHEMICAL
(MG)
    CONSTANT  CONCPPM = 0.0                  !AIR CONCENTRATION IN PPM!
           constant concmgs = 0.0
      ! Used to set air conc'n as mg/m3
          VCH = VCHC-(RATS*BWINIT)         !VOLUME OF OCCUPIED CHAMBER
          CONCMG = CONCMGS/1000 + CONCPPM*MWNMP/24451.    !CONVERT PPM TO
MG/LITER
          CONSTANT   DOSEINTERVAL=24                            !TIME
BETWEEN DAILY DOSES
                 constant concchppm0 = 0
           ! Initial ppm in closed chamber
                 conchmg0= concchppm0*MWNMP/24451.
          ACHO = conchmg0 * VCH              !INIT. AMT IN CHAMBER, MG!
   !ORAL
      CONSTANT  KAS=1.0          !1ST ORDER RATE CONST FOR ORAL ABS from
stomach,HR-1
                 CONSTANT KAI=1                                     !1ST
ORDER RATE CONST FOR ORAL ABS from intestines,HR-1
      CONSTANT KSI=1
      CONSTANT  DOSE=0.0         !ORAL DOSE IN MG/KG BW
      ODOSE = FRACOR*DOSE*BWINIT        !CONVERT MG/KG BW TO MG
TOTAL(ORAL)
                       ! ODOSE multiplied by FRACOR to reduce oral
bioavailability
                       constant   dose2=0.0                  ! ORAL
Dose in mg/kg BW, but total dose increases w/ BW
                 gavds=dose2*FRACOR*BWINIT   ! Initial value for this
dose
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   !FEED
      CONSTANT  KASF=1.0          !1ST ORDER RATE CONST FOR ORAL ABS,HR-1
      CONSTANT  DOSEF=0.0         !ORAL DOSE IN MG/KG BW in feed
     !IV
      CONSTANT IVDOSE=0.0        !IV DOSE, MG/KG NMP
   !DERMAL
      CONSTANT CONCL = 0.0       !CONC OF NMP IN LIQUID, MG/L
      CONSTANT KPL = 0.0         !PERM COEFF FOR LIQUID, CM/HR
      CONSTANT VLIQ = 1.0E-99      !INITIAL VOLUME APPLIED, L
      CONSTANT DENSITY=     1.03
                 constant DSK=0.0 ! Initial amount (mg/kg BW) rubbed into
skin
                       ASKO=DSK*BWINIT
                 constant GDSTOP=15     ! Last GD of dermal dosing
                 constant twash=8.0     ! Wash time in Becci et al.
(1982) exposures
       CONSTANT FAD=0.78  !FRAC no absorbed in Payan et al
          !IN VITRO HUMAN VAN DYK ET AL. AIHA J 56: 651-660
        !START WITH SMALL SA SO VSKE IS NON-ZERO (USED IN DENOMINATOR OF
CSK CALCULATION)

    !IP
      CONSTANT IPDOSE = 0.0      !IP DOSE, MG/KG NMP
      CONSTANT KIP=1.0           !1ST ORDER RATE OF ABS, HR-1
      PDOSE = IPDOSE*BWINIT       !TOTAL IP DOSE, MG

!DOSING SCHEDULE
           if (DSK.GT.0.0) then
                 schedule SKWASH.AT.TWASH
           ENDIF
     SCHEDULE OFFD.AT.TCHNG     !TURN OFF EXPOSURE AT TCHNG
     CIZONE = 1.0               !START WITH INHALATION ON
     IVZONE = 1.0               !START WITH IV ON
IF (CONCL.GT.0.0) THEN
     DZONE = 1.0             !START WITH DERMAL ON
ELSE
           DZONE = 0.0
ENDIF
constant tstart=0.2    ! offset start-time for gavage dosing
                 schedule GAVD.at.TSTART
     ALGORITHM IALG=2          !GEAR ALGORITHM

END

DYNAMIC

DERIVATIVE
!===============FETAL AND BW CHANGES W/PREGNANCY=======================
    GDMONTH=GDMONTHS/0.64    !TO WAG GROWTH
                                              HOURS = T
   MINUTES = T * 60.0
      DAYS = T / 24.0 + GDDAYS +GDMONTH

! VOLUME OF FAT (L)
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      VFAT = VFATI * (1.0 + (0.0165 * DAYS))

! VOLUME OF FETUS (KG)
     IF (DAYS.LT.10.0) THEN
         VFET = (1.0e-8 + NUMFET * ((0.1206 * DAYS)**4.53)) / MGKG
     ELSE IF (DAYS.LT.17.0) THEN
         VFET = (1.0e-8 + NUMFET * ((1.5 * (DAYS - 9))**2.8)) / MGKG
     ELSE
         VFET = (1.0e-8 + NUMFET * (VFETD18 + (((PUPBW - VFETD18) / 4.0)
* (DAYS - 17)))) / MGKG
     ENDIF

! VOLUME OF   MAMMARY TISSUE (L)
      VMAM = VMAMI * (1.0 + (0.27 * DAYS))

! VOLUME OF   PLACENTA (L)
     IF (DAYS.LT.6.0) THEN
         VPLA = 1.0e-8
     ELSE IF (DAYS.LT.10.0) THEN
         VPLA = (1.0e-8 + NUMFET * (8. * (DAYS - 6.))) / MGKG
     ELSE
         VPLA = (1.0e-8 + NUMFET * ((32 * EXP(-0.23 * (DAYS - 10)))+ (40
* (EXP(0.28 * (DAYS - 10)) - 1)))) / MGKG
     ENDIF

! VOLUME OF   UTERUS (L)
     IF (DAYS.LE.3.0) THEN
         VUTR = VUTRI
     ELSE
         VUTR = VUTRI * (1.0 + (0.077 * ((DAYS - 3.)**1.6)))
     ENDIF

!VOLUME OF LIVER INCREASE   !Corley et al CRC 03,BUELKE-SAM ET AL '82 AND
OTHERS
IF (DAYS.LT.5.0) THEN
VLIV=VLIVI
ELSE
VLIV= VLIVI * (1.0 + (0.0455 * ((DAYS - 5.0))))
ENDIF

! INCREASE IN   BODY WEIGHT (KG)
               BW = BWINIT + (VFAT - VFATI) + VFET + (VMAM - VMAMI) +
VPLA + (VUTR - VUTRI)+(VLIV - VLIVI)

! SCALED   ALVEOLAR VENTILATION (L/HR)
        QP = QPC * ((BW-VFET-VPLA)**0.75)

! INCREASE IN   BLOOD FLOWS (L/HR)
      QFAT = QFATI * (VFAT / VFATI)
      QMAM = QMAMI * (VMAM / VMAMI)
      QUTR = QUTRI * (VUTR / VUTRI)

! TOTAL BODY FOR HNMP
           QB = QRAP+QSLW+QSKN+QMAM+QUTR !
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      VB = VRAP+VSLW+VLU+VSK+VMAM+VUTR !

!   BLOOD FLOW TO PLACENTA (L/HR)
     IF (DAYS.LT.6.0) THEN
         QPLA = 0.0
     ELSE IF (DAYS.LT.10.0) THEN
         QPLA = (NUMFET * (0.55 * (DAYS - 6.0))) / 24
     ELSE IF (DAYS.LE.12.0) THEN
         QPLA = (NUMFET * (2.2 * EXP(-0.23 * (DAYS - 10)))) / 24
     ELSE
         QPLA = (NUMFET * ((2.2 * EXP(-0.23 * (DAYS - 10)))+ ((0.1207 *
(DAYS - 12.0))**4.36))) / 24
     ENDIF

! INCREASED   CARDIAC OUTPUT (L/HR)
                QC = QFAT+QLIV+QSLW+QRAP+QSKN+QMAM+QPLA+QUTR
! SCALED PERMEABILITY-AREA PRODUCT
       PAF = PAFC * (VFET**0.75)

!==================FIRST MODEL FOR TRACKING NMP=========================

!EQUATIONS FOR ORAL GAVAGE DOSING
!note this is an oral model that expects some direct absorption to liver
and some transfered to intestine for absorption to liver
!this structure explains early peak and slow elimination observed in
Midgely oral exposure data. Validated by Ghantous data
    RAOA = -(KAS * AO)-(KSI*AO)
     AO = ODOSE+ INTEG(RAOA,0.0)  !AMT REMAINING TO BE ABS, MG
   RAO=KAS*AO
        OABS = INTEG(RAO,0.0)
RINTC=(KSI*AO)-(KAI*AINTC)  !RATE OF CHANGE IN INTESTINES
AINTC=INTEG(RINTC,0.0)
RAINTEST=KAI*AINTC  !TRANSFER TO LIVER
OIBS=INTEG(RAINTEST,0.0)


!EQUATIONS FOR FEED DOSING
      FDOSE = DOSEF*FRACF*BW        !CONVERT MG/KG BW TO MG TOTAL(ORAL)
                      RAF = KASF * AF    !*FRACF
     AF = FDOSE - INTEG(RAF,0.0)  !AMT REMAINING TO BE ABS, MG!
   FABS = INTEG(RAF,0.0)

!AL = AMOUNT NMP IN LIVER COMPARTMENT (MG)
      RAL = QLIV*(CA - CVL)+ RAIP + RAO + RAF - RAML+RAINTEST
       AL = INTEG(RAL, 0.0)
      CVL = AL/(VLIV*PL)

     RAML = (VMAX1*CVL)/(KM+CVL)    !SATURABLE METABOLISM, MG/HR
      AML = INTEG(RAML,0.0)       !AMT NMP METAB BY SATURABLE PATH, MG
    AML1B = RATS*AML*MWHP/MWNMP  !TOT AMT HNP PRODUCED IN LIVER, MG

!EQUATIONS FOR IP DOSING
    RAIP = KIP * AIP
     AIP = INTEG(-RAIP,PDOSE)  !AMT REMAINING TO BE ABS, MG!
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        IPABS = INTEG(RAIP,0.0)

!EQUATIONS FOR IV INFUSION
    IVR = IVZONE*IVDOSE*BW/Tchng  !RATE OF INFUSION, MG/HR using Tchng
    TIV = INTEG(IVR,0.0)         !TOTAL AMOUNT INJECTED, MG

! ARTERIAL BLOOD
     RAAB = (QC * (CVLU - CA))-RAUNP
      AAB = INTEG(RAAB, 0.0) !AMOUNT, MG
       CA = AAB / VA        !CONCENTRATION, MG/L
    AAUCB = INTEG(CA, 0.0)   !AUC, HR*MG/L
      RAUNP = KLN*CA*VV           !FIRST ORDER RATE OF LOSS (URINE
            AUNP = INTEG(RAUNP,0.0)

! CHAMBER CONCENTRATION (MG/L)
     RACH = (RATS * QP * CLEX) - (FRACIN * RATS * QP * CI) - (KLOSS *
ACH)
      ACH = INTEG(RACH, ACHO)


! THE FOLLOWING CALCULATION YIELDS AN AIR CONCENTRATION EQUAL TO
! THE CLOSED CHAMBER VALUE IF A CLOSED CHAMBER RUN IS IN PLACE AND
! A SPECIFIED CONSTANT AIR CONCENTRATION IF AN OPEN CHAMBER RUN IS IN
PLACE

      CCH = (ACH / VCH)! * CIZONE) + (CONCMG * (1.0 - CLON))

    CCPPM = CCH *24451/MWNMP
    CLOSS = INTEG(KLOSS * ACH,0.0)
CI = CCH*PULSE(0., DOSEINTERVAL,TCHNG) + CIZONE*CONCMG   ! MG/L

! LUNGS
        RALU = (QP * ((FRACIN * CI) - CLEX)) + RVV - (QC * CVLU)
        ALU = INTEG(RALU, 0.0)
      CLU = ALU / VLU             !CONCENTRATION, MG/L
     CVLU = CLU / PLU           !EXITING CONCENTRATION, MG/L

!  AMOUNT INHALED
     RINH = FRACIN * QP * CCH *CIZONE
     AINH = INTEG(RINH, 0.0)   ! MG PER
    AINHC = AINH * RATS        ! MG FOR A GROUP OF RATS

!  AMOUNT EXHALED
     CLEX = CV / PB           ! CONCENTRATION, MG/L
     RAEX = QP * CLEX
      AEX = INTEG(RAEX, 0.0)   ! AMOUNT, MG PER
     AEXC = AEX * RATS          ! AMOUNT, MG, FOR A GROUP OF RATS

!ASK = AMOUNT NMP IN SKIN TISSUES (MG) AND DERMAL DOSING
      RASK = QSKN*(CA - CSKV) + RADL
       ASK = INTEG(RASK,ASKO)     ! Initial value, ASKO, added for Becci
et al. (1982) exposures
       CSK = ASK/VSK              !'NMP IN SKIN, MG/L'
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                 CSKV = CSK/PSKB                          ! NMP IN VENOUS
BLOOD
     CVSK3 = CSK*1000/MWNMP     !'NMP IN CVSK, MICROMOL/L'


CONCL2=CONCL*FAD
CSURF=(CONCL2-(ADL/VLIQ))*DZONE
RADL=(KPL*SA/1000.0)*((CSURF-(CSK/PSKL))*DZONE - (1.0-DZONE)*(CSK/PSKA))
!
! 2ND term, (1.0-DZONE)*(CSK/PSKA), allows for evaporative loss when
DZONE=0
ADL=INTEG(RADL,0.0)

       ! NOTE - NO LOSS TERM. TRY WITHOUT OR ADD LOSS UP-FRONT BY
SUBTRACTING
       ! AMOUNT RECOVERED FOR EACH STUDY WITH AMOUNT (CONC) ORIGINALLY
APPLIED
       ! "LOSS" OR STICKING PROBABLY ESSENTIALLY IMMEDIATE AND NOT
KINETIC
       ! REPORTS OF ~11-24% STICKING TO DRESSING

! AMOUNT IN FAT (MG)
     RAFAT = QFAT * (CA - CVFAT)
      AFAT = INTEG(RAFAT, 0.0)
      CFAT = AFAT / VFAT
     CVFAT = CFAT / PF

! AMOUNT IN FETUSES (MG)
     RAFET = PAF * (CPLA - CFET)
      AFET = INTEG(RAFET, 0.0)
                 CFET = AFET / VFET
   AUCCFET = INTEG(CFET, 0.0)

! AMOUNT IN UTERUS (MG)
     RAUTR = QUTR * (CA - CVUTR)
      AUTR = INTEG(RAUTR, 0.0)
      CUTR = AUTR / VUTR
     CVUTR = CUTR / PUTR

! AMOUNT IN MAMMARY TISSUE (MG)
     RAMAM = QMAM * (CA - CVMAM)
      AMAM = INTEG(RAMAM, 0.0)
      CMAM = AMAM / VMAM
     CVMAM = CMAM / PM

! AMOUNT IN PLACENTA (MG)
     RAPLA = (QPLA * (CA - CVPLA)) + (PAF * (CFET - CPLA))
      APLA = INTEG(RAPLA, 0.0)
           CPLA = APLA / VPLA
     CVPLA = CPLA / PPLA

!AS = AMOUNT IN SLOWLY PERFUSED TISSUES (MG)
       RAS = QSLW*(CA - CVS)
        AS = INTEG(RAS, 0.0)
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       CVS = AS/(VSLW*PS)
        CS = AS/VSLW

!AR = AMOUNT IN RAPIDLY PERFUSED TISSUES (MG)
       RAR = QRAP*(CA - CVR)
        AR = INTEG(RAR, 0.0)
       CVR = AR/(VRAP*PR)
        CR = AR/VRAP

!MIXED VENOUS BLOOD
      RVV = QC*CV
      RV=(QFAT*CVFAT+QLIV*CVL+QSLW*CVS+QRAP*CVR+QSKN*CSKV+CVMAM*QMAM+CVPL
A*QPLA+QUTR*CVUTR+IVR)-RVV
      AV=INTEG(RV,0.0)
      CV=AV/VV
      AUCBB=INTEG(CV,0.0)    !AUC, HR*MG/L

!-----------MASS BALANCE NMP --------------
  BODY = (AFAT+AR+AS+AL+ASK+AV+ALU+AAB+APLA+AMAM+AUTR)
  TMASS = RATS*(BODY + AML + AEX+AUNP+AFET)!COMPARE TO
                                  !AINH FOR OC MASS BAL
                                  !OR OABS FOR ORAL MASS BAL
                                  !OR TIV FOR IV MASS BAL
                                  !OR ADL FOR DERMAL LIQUID
 MASBAL=TMASS/(AINH+OABS+TIV+ADL+OIBS+1E-9)

! CHECK BLOOD FLOWS
      QTOT = QFATI + QLIV + QRAP + QSKN + QSLW + QUTRI +QMAM+QPLA
    QRECOV = 100.0 * (QTOT / QC)

!===============SECOND MODEL FOR TRACKING HNP=====================

!ALHP = AMOUNT HNMP IN LIVER COMPARTMENT (MG)
  RALHP = QLIV*(CAHP-CVLHP)+ RAML1 - RAMLH
  RAML1=RAML*MWHP/MWNMP
  AML2B=INTEG(RAML1,0.0)
   ALHP = INTEG(RALHP,0.0)   !AMT IN MG HNMP, CORRECTED FOR MW
  CVLHP = ALHP/(VLIV*PLHNP)  !TOTAL HNMP

    RAMLH = (VMAX2*CVLHP)/(KM2+CVLHP)   !SATURABLE METABOLISM, MG/HR
     AMLH = INTEG(RAMLH,0.0) !AMT HNMP METAB BY SATURABLE PATH, MG
      rdose=ramlh/(BW**0.75)
      tdose=integ(rdose,0.0)

!ABHP = AMOUNT HNMP IN TISSUES (MG)
  RABHP = QB*(CAHP - CBSHP)
   ABHP = INTEG(RABHP,0.0)
  CBSHP = ABHP/(VB*PBHNP)

!AFHP = AMOUNT HNMP IN FAT (MG)
    RFSHP = QFAT*(CAHP - CVFHP)
     AFHP = INTEG(RFSHP,0.0)
  CVFHP = AFHP/(VFAT*PFHNP)
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```
!CVHP = MIXED VENOUS BLOOD CONC TOTAL HNMP (MG/L)
  CRHP = (QLIV*CVLHP + QB*CBSHP + QFAT*CVFHP + QPLA*CVPLHP)-QC*CVHP-RAUHP
  AVHP = INTEG (CRHP,0.0)
  CVHP = AVHP/VBL
  CAHP = CVHP
  CVHP2 = CVHP*1000/MWHP      !VENOUS BLOOD TOT CONC HNMP IN MICROM

  AUCVHP = INTEG(CVHP2,0.0)  !AUC HNMP VEN. BLOOD, MICROMOL*HR/L

  ! AMOUNT IN PLACENTA (MG)
     RAPLHP = (QPLA * (CAHP - CVPLHP)) + (PAF * (CFETHP - CPLHP))
      APLHP = INTEG(RAPLHP, 0.0)
                 CPLHP = APLHP / VPLA
     CVPLHP = CPLHP / PPLHNP

  ! AMOUNT IN FETUSES (MG)
      RAFETHP = PAF * (CPLHP - CFETHP)
             AFETHP = INTEG(RAFETHP, 0.0)
                             CFETHP = AFETHP / VFET
        AUCFETHP = INTEG(CFETHP, 0.0)

 !RATE OF ELIM IN THE URINE, RAUHP, FROM MIXED BLOOD
   RAUHP = KL*CAHP*VA             !FIRST ORDER RATE
      AUHP = INTEG(RAUHP,0.0)    !CUMULATIVE AMT HNMP IN URINE (MG), NOT
MGEQ

!-----------MASS BALANCE--------------
!-----------MASS BALANCE 5-HNMP SUBMODEL--------------
  BODYHP = (AFHP+ABHP+ALHP+AVHP+AFETHP+APLHP)*RATS
  TMASHP = RATS*(AUHP + BODYHP +AMLH)         !COMPARE TO AML1B

! CHECK BLOOD FLOWS 5HNMP COMPARTMENT
      QTOTH = QLIV + QFAT + QB+QPLA
    QRECOVH = 100.0 * (QTOTH / QC)

TERMT(T .GE. TSTOP)    !----STATEMENT TO STOP EXECUTION---

END     !END OF DERIVATIVE

! The following discrete block allows for repeated gavage dosing, but
with
! the total dose (gavds) only updated every 3 days, per the protocol of
! Becci et al. (1982) and Saillenfait et al. (2002); PMS 9-16-13
      discrete GAVD
            IF (ROUND(DAYS).EQ.9.0)      gavds=FRACOR*dose2*BW
            IF (ROUND(DAYS).EQ.12.0)     gavds=FRACOR*dose2*BW
            IF (ROUND(DAYS).EQ.15.0)     gavds=FRACOR*dose2*BW
            IF (ROUND(DAYS).EQ.18.0)     gavds=FRACOR*dose2*BW
            ODOSE=ODOSE+gavds
            if (DAYS.LT.GDSTOP) schedule GAVD .at. (T+DOSEINTERVAL)
      end

!EXPOSURE CONTROL
DISCRETE SKWASH
```

```
      ASK = 0.0   ! Assume skin washing in Becci et al. (1982) removes all
NMP from skin
      if (DAYS.LT.GDSTOP) SCHEDULE REAPPLY.AT.(T+DOSEINTERVAL-TWASH)
END
DISCRETE REAPPLY
      IF (ROUND(DAYS).EQ.9.0)      ASKO=DSK*BW
      IF (ROUND(DAYS).EQ.12.0)     ASKO=DSK*BW
      IF (ROUND(DAYS).EQ.15.0)     ASKO=DSK*BW
      IF (ROUND(DAYS).EQ.18.0)     ASKO=DSK*BW
      ASK = ASK + ASKO
      SCHEDULE SKWASH.AT.(T+TWASH)
END
DISCRETE OFFD
  IVZONE=0.0      !TURN IV OFF
  CIZONE=0.0      !TURN INHAL EXPOSURE OFF
  DZONE=0.0 !TURN OFF DERMAL
      SCHEDULE OND.AT.(T+DOSEINTERVAL-TCHNG)
END
DISCRETE OND
  CIZONE=1.0      !TURN INHAL EXPOSURE ON
      SCHEDULE OFFD.AT.(T+TCHNG)
END

END     !END OF DYNAMIC
END     !END OF PROGRAM
```