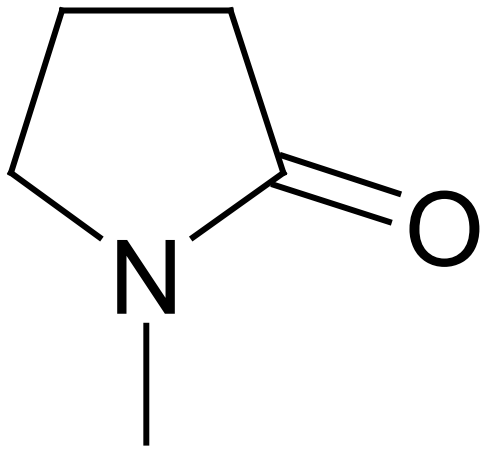
United States
Environmental Protection Agency

Office of Chemical Safety and
Pollution Prevention

Final Risk Evaluation for n-Methylpyrrolidone

Supplemental PBPK Model Code

CASRN: 872-50-4



December 2020

This supplemental document presents model code for the rat and human NMP physiologically based pharmacokinetic (PBPK) models used in the *Risk Evaluation for n-Methylpyrrolidone (NMP).* The PBPK models of Poet et al. (2010) describe the toxicokinetics of NMP in rats and humans. EPA revised the models for use in the risk evaluation, and the models underwent scientific and technical evaluations consistent with those outlined in An umbrella Quality Assurance Project Plan (QAPP) for PBPK models (EPA, 2018). These PBPK models were initially evaluated and revised by EPA in 2013 (U.S. EPA, 2013). Further modifications and calibration were conducted by Dr. Torka Poet in 2014 (personal communication). In this update, additional data were considered to further calibrate and validate the model. Model calibration consists of using data to optimize parameters when those parameters are unknown or approximated, validation is used to show the fits of the model to other datasets. EPA then evaluated the version submitted by Dr. Poet in 2014 and made additional corrections and modifications as described in Appendix J of the *Risk Evaluation for n-Methylpyrrolidone (NMP).*

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1 Rat NMP PBPK Model Code

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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
        !
        ! Updates by Paul Schlosser, U.S. EPA: Aug-Sept 2013, Dec 2014, Aug 2020

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

 CONSTANT BWINIT=0.  ! PRE-PREGNANCY BODY WEIGHT (KG)
 constant GMULT=1.      ! Multiplier for weight gain to match data. PS, U.S. EPA, July 6, 2020
 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)

        ! 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 = 906.0*BWINIT**(2.0/3.0)          ! 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
QLIVI = QLIVC * QCINIT  ! QLIV now calculate in DERIV to account for growth, PMS 3/11/20
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
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
        ! Values set in parameter .m file
  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
  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

        ! 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/1000.0 + CONCPPM*MWNMP/24451.0   ! CONVERT PPM TO MG/LITER
CONSTANT DOSEINTERVAL=24.0          ! TIME BETWEEN DAILY DOSES
constant concchppm0 = 0.0           ! Initial ppm in closed chamber
conchmg0= concchppm0*MWNMP/24451.0
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=1.0      ! 1ST ORDER RATE CONST FOR ORAL ABS from intestines, HR-1
CONSTANT KSI=1.0
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

        ! 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
CONSTANT GSTART=0.0 ! Days after start of exposure when gestation starts
schedule GAVD.at.TSTART

ALGORITHM IALG=2      ! GEAR ALGORITHM

END

DYNAMIC
DERIVATIVE
        !===============FETAL AND BW CHANGES W/PREGNANCY=======================
    DAYS = MAX((T / 24.0 + GDDAYS - GSTART), 0.0)
        ! VOLUME OF FAT (L)
    VFAT = VFATI * (1.0 + (0.0165 * DAYS * GMULT))

        ! 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 * GMULT))

        ! 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 * (8.0 * (DAYS - 6.0))) / MGKG
```

```
   ELSE
VPLA = (1.0e-8 + NUMFET * ((32.0 * EXP(-0.23 * (DAYS - 10.0)))+ (40.0 * (EXP(0.28 * (DAYS - 10.0)) -
1.0)))) / MGKG
   ENDIF

         ! VOLUME OF   UTERUS (L)
   IF (DAYS.LE.3.0) THEN
      VUTR = VUTRI
   ELSE
      VUTR = VUTRI * (1.0 + (0.077 * ((DAYS - 3.0)**1.6)) * GMULT)
   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) * GMULT))
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)
QLIV = QLIVI * (VLIV / VLIVI)

         ! TOTAL BODY FOR HNMP
QB = QRAP+QSLW+QSKN+QMAM+QUTR          !
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))) / 24.0
   ELSE IF (DAYS.LE.12.0) THEN
      QPLA = (NUMFET * (2.2 * EXP(-0.23 * (DAYS - 10.0)))) / 24.0
   ELSE
      QPLA = (NUMFET * ((2.2 * EXP(-0.23 * (DAYS - 10.0)))+ ((0.1207 * (DAYS - 12.0))**4.36))) / 24.0
```

```
    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
  RAO=KAS*AO
  RAOA = -RAO-(KSI*AO)
  AO = ODOSE+ INTEG(RAOA,0.0)          ! AMT REMAINING TO BE ABS, MG

      OABS = INTEG(RAO,0.0)
RAINTEST=KAI*AINTC    ! TRANSFER TO LIVER
RINTC=(KSI*AO)-RAINTEST         ! RATE OF CHANGE IN INTESTINES
AINTC=INTEG(RINTC,0.0)

OIBS=INTEG(RAINTEST,0.0)

          ! EQUATIONS FOR FEED DOSING
RFDOSE = DOSEF*FRACF*BW*PULSE(0.0,24.0,12.0)*2/24.0
          ! Convert to mg/h for continuous feed dosing
RABS = KSI * AF ! Rate added to amount in intestines
RAF = RFDOSE - RABS
AF = INTEG(RAF,0.0)       ! AMT intestinal lumen

          ! AL = AMOUNT NMP IN LIVER COMPARTMENT (MG)
RAL = QLIV*(CA - CVL)+ RAIP + RAO + RABS - 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          !
```

```
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*VA     ! 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 *24451.0/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'
CSKV = CSK/PSKB             ! NMP IN VENOUS BLOOD
CVSK3 = CSK*1000.0/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)
      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+CVPLA*QPLA+QUT
R*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)

        ! 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*1000.0/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
```

Payan and Wells IV 14.m

```
%PROCED WELLS - IV
%WELLS AND DIGENIS 1988
prepare @clear T CV
ratparam
TCHNG=0.0167; CINT=0.01; BWINIT=0.35; IVDOSE=45; TSTOP=12; GDDAYS=0;
start @nocallback
t1=_t; c1=_cv; IVDOSE=0.1; GDDAYS=1; start @nocallback
MASBAL

% DATA WELLS (T,CV,Poet 2013 CV)
DWELLS          =          [0.08     92
0.17     69
0.25     62
0.33     59
0.5      58
0.75     58
1        55
1.5      52
2        50
4        40
6        35];

% DATA PAYAN (T,CV,)
DPAYAN = [0.080.16
0.17     0.15
0.35  0.13
0.67     0.13
1        0.12
1.5      0.11
2        0.11
3        0.1
4        0.07
6  0.014];

plot(t1, c1, DWELLS(:,1), DWELLS(:,2), ...
        _t, _cv, DPAYAN(:,1), DPAYAN(:,2), 'ivplasma.aps')
```

Oral Midgely and Ghant 14.m

```
use ratparam
prepare @clear @all

GO50M=[0.017 2.212;
0.05     4.653;
0.08     15.267;
0.5      11.097;
1        29.789;
2        15.840;
4        13.644;
8        5.875;
12       2.441];

%(T,CV,AUHP)
GO50F =[0.25   20.600  NaN;
0.50     28.793  NaN;
1.00     38.044  NaN;
1.50     21.393  NaN;
2.00     31.028  NaN;
4.00     20.942  NaN;
6.00     12.005  NaN;
8.00     5.178   NaN;
12.00    NaN     4.46;
24.00    NaN     6.54;
36.00    NaN     6.71;
48.00    NaN     6.83;
72.00    NaN     6.92;
96.00    NaN     6.97;
120.00   NaN     7.00];

%(T,CV)
MIDG =[0.25 45.2 NaN;
0.5      56.25   NaN;
2        65.00   NaN;
3.5      58.00   NaN;
6        46      1.66;
8        33.00   NaN;
12 6.1  NaN;
24       NaN     8.40;
72       NaN     8.70;
120      NaN     8.82];

% MIDGLEY ET AL, 1992
```

```
  BWINIT=0.216; DOSE=112; TSTOP=124; DOSEINTERVAL=148; CINT=0.1;
  start @nocallback
  ares=[_auhp]; cres=[_cv];

% Ghantous -males
        BWINIT=0.262; DOSE=50; start @nocallback
 cres=[cres _cv]; t1=_t;

% Ghantous - females
preg_rat_params
GDDAYS=0; CINT=0.1; TSTOP=124; BWINIT=0.221; DOSE=50*0.955; start @nocallback
ares=[ares _auhp];
% Note, dose is as reported, minus "feed residue", which was 4.5% of dose for
% the females. Also, while methods to measure dosing solution NMP are
% described, no value is given so the target is assumed and this is based on mass

plot(t1,ares, MIDG(:,1),MIDG(:,3),GO50F(:,1), GO50F(:,3),'figGHANTorAUHP.aps')
plot(t1,cres(:,1), MIDG(:,1),MIDG(:,2),t1,cres(:,2),
GO50M(:,1),GO50M(:,2),_t,_cv,GO50F(:,1),GO50F(:,2),'figGHANTorCV.aps')
```

```
Payan 2002 IV 5HNMP 14.m

prepare @clear T AUHP CVHP
ratparam
TCHNG=0.01; TSTOP=78; BWINIT=0.275; CINT=0.1; holdcvhp=[]; holdauhp=[];

for IVDOSE=[0.1 1 10 100 500]
        start @nocallback
 holdcvhp=[holdcvhp _cvhp]; holdauhp=[holdauhp _auhp];
end

%Data, 5HNMP peak mg/kg                (T, CVHP, dose in order 0.1,1,10,100,500)
%note 500 above curve
%(T,CVHP)
P5H =[5 0.035;
4       0.38;
4       3.3;
8       23.7];

%Data, 5HNMP total in urine over 3 days                (T, CVHP, dose in order 0.1,1,10,100,500)
P5HU=[72 0.01 0.11 1 13 68];

plot(_t,holdcvhp, P5H(:,1),P5H(:,2) , 'IV plasma 5HNMP.aps')
```

```
plot(_t,holdauhp(:,1:3), P5HU(:,1),P5HU(:,2),P5HU(:,1),P5HU(:,3),P5HU(:,1),P5HU(:,4), 'Payan 2002 IV urine 5HNMP.aps')
plot(_t,holdauhp(:,3:5), P5HU(:,1),P5HU(:,4),P5HU(:,1),P5HU(:,5),P5HU(:,1),P5HU(:,6), 'Payan 2002 IV urine 5HNMP high.aps')
```

Payan 2003 Dermal plasma 14.m

```
prepare @clear T CV
ratparam
%payan dermal exposures: Payan et al. DMD 03
BWINIT=0.220; TCHNG=72; TSTOP=48; SA=10; VLIQ=200e-6; CONCL=1060000; CINT=0.5;
 start @nocallback

% DATA PAYAN (T,Payan 2003     CVHP)
PAYAN = [0.25   166.86
0.75      276.04
1         354.32
1.5       418.18
2         475.86
3         535.60
3.5       556.20
4         593.28
5         570.62
6         578.86
8         564.44
10        529.42
24        107.53
26        111.65
30        59.95];

plot(_t, _cv, PAYAN (:,1), PAYAN (:,2), 'Fig 7 Payan 2003 Dermal plasma.aps')
```

Poet2013_Fig1_gestation growth.m

```
prepare @clear @all
ratparam
preg_rat_params          % Added by Paul Schlosser (PS), U.S. EPA, 05-01-2013
BWINIT=0.232; DOSEINTERVAL=24; TSTOP=528;
TCHNG=6, GDDAYS=0, MAXT=1;
BWINIT=0.262; % Matches GD6 BW of controls in Saillenfait et al. 2002; PS 5-2-13
VFETD18 = 1051.254; % Default from .csl file; PS 5-2-13
start @nocallback
```

```
  plot(_t/24, _bw, _t/24, _vfat, _t/24, _vmam, _t/24, _vpla, _t/24, _vfet, 'pregphyschanges.aps')

simres=[_t/24, _bw, _vfat, _vmam, _vpla, _vfet];

save simres @file='pregSims.csv' @format=ascii @separator=comma
```

```
Ghantous_1995 inhalation 14.m
use ratparam
prepare @clear @ALL
   VCHC=1.0e+9; TSTOP=144; TCHNG=6; DOSEINTERVAL=144;

%female rat
CONCPPM=104.3, BWINIT=0.235; start @nocallback
 holdauhp=[_auhp]; holdcv=[_cv];

% male rat
CONCPPM=104.3, BWINIT=0.216; start @nocallback
 holdcv=[holdcv _cv]; holdauhp=[holdauhp _auhp];

%DATA GHANTIN10F (T,AUHP)
GHANTIN10F=[18          0.83;
30        1.18;
42        1.25;
54        1.29;
78        1.32;
126       1.35];

%DATA GHANTIN10M (T,AUHP)
GHANTIN10M=[18          0.86;
30        1.09;
42        1.16;
54        1.19;
78        1.24;
126       1.27];

%DATA GIN100M (T,CV,AUHP)
GIN100M=[0.251.13       NaN;
0.5       3.83      NaN;
1         8.61      NaN;
2         10.67     NaN;
4         20.47     NaN;
6         10.18     NaN;
7         17.87     NaN;
```

```
8       2.44    NaN;
10      3.36    NaN;
18.00   NaN     5.21;
30.00   NaN     6.31;
42.00   NaN     6.72;
54.00   NaN     6.88;
78.00   NaN     7.12;
102.00  NaN     7.29;
126.00  NaN     7.41];

%DATA GIN100F (T,CV,AUHP)
GIN100F=[0.25  4.22     NaN;
0.50    8.16    NaN;
1.00    17.26   NaN;
2.00    20.04   NaN;
4.00    52.42   NaN;
6.00    49.28   NaN;
7.00    30.06   NaN;
8.00    49.30   NaN;
10.00   21.79   NaN;
12.00   4.56    NaN;
18      NaN     5.78;
30      NaN     6.99;
42      NaN     7.22;
54      NaN     7.29;
78      NaN     7.48;
102     NaN     7.62;
126     NaN     7.68];

plot(_t,holdcv, GIN100F(:,1),GIN100F(:,2),GIN100M(:,1),GIN100M(:,2),'figGHANTINCV.aps')
```

Becci_1982_dermal.m

```
% Internal dose calculations for Becci et al. (1982) inhalation study
% Exposure levels (CONCMGS) are those used by Saillenfait plus an external dose BMCL
% Paul Schlosser, U.S.EPA, Aug. 28, 2013
% NOAEL= 237mg/kg/day based on a developmental study of dermal exposure of rats
% to NMP for 8-hrs, GD 6 to 15 (Becci et al, 1982).
use ratparam
use preg_rat_params
GDDAYS=6.01; TSTOP=14*24; CINT=0.01; BWINIT=0.2375; TWASH=8; DOSEINTERVAL=24; SA=25;
GDSTOP=19; res = [0,0,0,0]; prepare @clear @all
```

```
for DSK=[75 237 750]
        start @nocallback
        apk = max(_aucbb(_t>24)-_aucbb(_t<(TSTOP-24)));
        res=[res; [DSK,apk,(AUCBB*24/TSTOP),max(_cv)]]
end
plot(_days,_cv)
```

DAILY_SAILLENFAIT_METRICS.m

```
% Simulations of Saillenfait et al. (2002) oral gavage bioassay
%t poet changes indicated.
use ratparam
use preg_rat_params
prepare @clear @all  % T DAYS AUCBB CV
BWINIT=0.259;  % T Poet - GD6 average (257-262)
GDDAYS=6.01; TSTART=0.2; TSTOP=TSTART+24; CINT=0.01; GDSTOP=20;
DOSEINTERVAL=24; AUCAVG=[]; AUCTOT=[]; DAY=[]; CMAX=[]; dose=[];

for DOSE2=128.5 %[125 250 500 750]
        for id=2:15
                TSTOP=TSTART+id*24; dose=[dose; DOSE2];
                start @nocallback
                AUCAVG=[AUCAVG; AUCBB*24/TSTOP];
                        %NOTE, THIS WILL BE OFF BY THE 0.2 HR OFFSET FOR DOSING
                AUCTOT=[AUCTOT; AUCBB];
                DAY=[DAY; (TSTOP-TSTART)/24];
                CMAX=[CMAX; max(_cv)];
        end
end
[dose, DAY, AUCAVG, CMAX]
```

DAILY_SAILLENFAIT_INHALATION_METRICS.m

```
% Simulations of Saillenfait et al. (2002) oral gavage bioassay
%t poet changes indicated.
use ratparam
use preg_rat_params
prepare @clear @all  % T DAYS AUCBB CV
BWINIT=0.270  % T Poet - GD6 average (268-273)
GDDAYS=6.01; CINT=0.01; TCHNG=6; DOSEINTERVAL=24;
AUCAVG=[]; AUCTOT=[]; DAY=[]; CMAX=[]; conc=[];
```

```
%CONCMGS=[122 243 302 487]
for CONCPPM = [30 60 121]
        for d=15
                TSTOP=TSTART+d*24; conc=[conc; CONCPPM];
                start @nocallback
                AUCAVG=[AUCAVG; AUCBB*24/TSTOP];
          %NOTE, THIS WILL BE OFF BY THE 0.2 HR OFFSET FOR DOSING
                AUCTOT=[AUCTOT; AUCBB];
                DAY=[DAY; (TSTOP-TSTART)/24];
                CMAX=[CMAX; max(_cv)];
        end
end
plot(_t,_cv)
plot(_days,_aucbb)
[conc, DAY, AUCTOT, AUCAVG, CMAX]
```

DAILY_BECCI_METRICS.m

```
% Internal dose calculations for Becci et al. (1982) inhalation study
% Exposure levels (CONCMGS) are those used by Saillenfait plus an external dose BMCL
% Paul Schlosser, U.S.EPA, Aug. 28, 2013
% NOAEL= 237mg/kg/day based on a developmental study of dermal exposure of rats
% to NMP for 8-hrs, GD 6 to 15 (Becci et al, 1982).
use ratparam
use preg_rat_params
GDDAYS=6.01; TSTOP=1*24; CINT=0.005; BWINIT=0.263; TWASH=8; DOSEINTERVAL=24;
SA=25; VLIQ=1e55;
prepare @clear @all
DOSEINTERVAL=24; AUCAVG=[]; AUCTOT=[]; DAY=[]; CMAX=[]; dose=[];

%for DSK=[75 237 750]
DSK=166.5
for id=[2 10] %2:10
        TSTOP=TSTART+id*24;
        start @nocallback
        AUCAVG=[AUCAVG; AUCBB*24/TSTOP];
  %NOTE, THIS WILL BE OFF BY THE 0.2 HR OFFSET FOR DOSING
        AUCTOT=[AUCTOT; AUCBB]; DAY=[DAY; (TSTOP-TSTART)/24];
        CMAX=[CMAX; max(_cv)]; dose=[dose; DSK];
end
[dose, DAY, AUCAVG, CMAX]
```

DAILY_SOLOMON_INALATION_METRICS.m

```
% Simulations of Solomon et al. 1995/Staples - INHALATION
use ratparam
use preg_rat_params
prepare @clear @all  % T DAYS AUCBB CV
BWINIT=0.310  % T Poet - GD6 average (268-273)
GDDAYS=0.01; CINT=0.01; TCHNG=6; DOSEINTERVAL=24; TSTOP=TSTART+24
AUCAVG=[]; AUCTOT=[]; DAY=[]; CMAX=[]; conc=[];

for CONCPPM=[10, 51, 116]
        for d=20 %2:20
                TSTOP=TSTART+d*24; start @nocallback
                AUCAVG=[AUCAVG; AUCBB*24/TSTOP];
          %NOTE, THIS WILL BE OFF BY THE 0.2 HR OFFSET FOR DOSING
                AUCTOT=[AUCTOT; AUCBB]; CMAX=[CMAX; max(_cv)];
                DAY=[DAY; (TSTOP-TSTART)/24]; conc=[conc; CONCPPM]
        end
end
plot(_t,_cv)
plot(_days,_aucbb)
[conc, DAY, AUCAVG, CMAX]
```

DAILY_THORNTON_FEED_METRICS.m

```
% Simulations of THORNTON FEED STUY
%ESTIMATED ASSUMING A 12 HR "INFUSION" RATE FOR AN ORAL DOSE.
use ratparam
use preg_rat_params
prepare @clear @all  % T DAYS AUCBB CV
BWINIT=0.264  % T Poet - GD6 average (257-262)

GDDAYS=0.01; TSTART=0.2; TSTOP=TSTART+24; CINT=0.1;
KAS=0.083, KAI=0, DOSEF=554 %57%171%554
AUCAVG=[]; AUCTOT=[]; DAY=[]; CMAX=[]; dose=[];

for id=1:20
        TSTOP=TSTART+id*24; start @nocallback
        AUCAVG=[AUCAVG; AUCBB*24/TSTOP]; dose=[dose; DOSEF];
                %NOTE, THIS WILL BE OFF BY TEH 0.2 HR OFFSET FOR DOSING
        AUCTOT=[AUCTOT; AUCBB]; DAY=[DAY; (TSTOP-TSTART)/24];
        CMAX=[CMAX; max(_cv)];
end
```

```
plot(_t,_cv)
plot(_days,_aucbb)
[dose, DAY, AUCAVG, CMAX]
```

Daily_Becci_metrics_revised.m

```
% Internal dose calculations for Becci et al. (1982) inhalation study
% Exposure levels (CONCMGS) are those used by Saillenfait plus an external dose BMCL
% Paul Schlosser, U.S.EPA, Aug. 28, 2013
% NOAEL= 237mg/kg/day based on a developmental study with dermal exposure of rats
% to NMP for 8-hrs, GD 6 to 15 (Becci et al, 1982).
% Simplified code with for-loops Chris Brinkerhoff Aug 6, 2014

use ratparam
use preg_rat_params
GDDAYS=6.01; CINT=0.01; TSTART=0; TSTOP=24; GDSTOP=19;
BWINIT=0.263; TWASH=8; DOSEINTERVAL=24; SA=25; VLIQ=1e55;
prepare @clear @all

DSKS=[75 237 750];
%DSKS=402;
%DSKS=237;
lastday=14; res = []; DAILYAUC=[]; AUCTOT=[];

for j = 1:length(DSKS)
        DSK = DSKS(j)
        for i = 1:lastday
                TSTOP=TSTART+i*24
                start @nocallback
                AUCTOT((j-1)*lastday+i) = AUCBB;
                if i == 1
                        DAILYAUC((j-1)*lastday+i) = AUCBB;
                else
                        DAILYAUC((j-1)*lastday+i) = AUCBB - AUCTOT((j-1)*lastday+i-1);
                end
                res(:,(j-1)*lastday+i) = [DSK; i; max(_cv); DAILYAUC((j-1)*lastday+i)];
        end
end
res(:,[1 14 15 28 29 42])
%save res @file='Becci_1982_dermal_results_2nd_time.csv' @format=ascii @separator=comma
```

Exxon91.m

```
use ratparam
use preg_rat_params
prepare @clear @all  % T DAYS AUCBB CV
CINT=1; TSTART=0; % Used for bolus dosing, not needed here
GSTART=7; % Day after start of exposure when gestation begins
        % GSTART should be high enough to reach periodicity or steady state

TSTOP=(GSTART+21)*24; TCHNG=TSTOP+1; % Allows 21 days of gestation
BWINIT=mean([324.3 305.4 281.5])/1000; NUMFET=14;
gdosestart = (GSTART+6)*24; % Time (h) to start calculating pregnancy average concentration
gesthr=TSTOP-gdosestart; % Total hours over which pregnancy dose is calculated

DOSEF=95.4; start @nocallback
[BWINIT, DOSEF, NUMFET, _bw(TSTOP-24), (_aucbb(find(_t==TSTOP))-
_aucbb(find(_t==gdosestart)))*24/gesthr]
return

TSTOP=GSTART*24; % Don't simulate pregnancy for juvenile animal/growth period
TCHNG=TSTOP+1; % TCHNG turns off dosing if < TSTOP, for analyzing stop-dose studies
doses = [50 160 500]; % mg/kg/d 27.93 %
tres = [0, doses];          % First row of results table

%for BWINIT=[50 100 150 200 300 400]/1000;
for BWINIT=[50 250 350 450]/1000;
        rres = BWINIT;   % Start row of results table
        for DOSEF=doses
                start @nocallback
                sscheck = _cv(GSTART*24)/_cv((GSTART-1)*24) - 1;        % check for periodicity/SS,
should be ~ 0
                rres = [rres, (_aucbb(TSTOP) - _aucbb(TSTOP-24))/24]; % AUC for last day of exposure
                %rres = [rres, mean(_cv(((GSTART-1)*24):(GSTART*24)))]; % AUC for last day of
exposure
        end
        %plot(_t/24,_cv)
        tres = [tres; rres];          % Append results row
end
tres, doses(1)*202/rres(2)

TSTOP=(GSTART+21)*24; TCHNG=TSTOP+1; % Allows 21 days of gestation

"Simulations for gestational exposure P2/F2A"
BWs=[324.3 305.4 281.5]/1000; % Initial BWs for each exposure group, from Table 53
```

```
% Below calculates mean intake (dose rate) for each group, from values for GD 6-20 in Table 67.
doses=[mean([55.1 52.5 51.4 50.9]), mean([170.9 167.8 162.9 165.4]), mean([514.3 524.6 479.7
457.8])];
nfet=[17 19 14]; % # of fetuses for each dose group, chose to approximately match GD 20 BW
% *** nfet does *NOT* match the observed number born, reported by Exxon (1991).
% nfet is the # for which the combined maternal/fetal BW at GD 20 most closely matches
% the maternal BW in Table 53 (Exxon, 1991) at GD 20.
p2f2a=[]; % empty results array
for n=1:3;
        BWINIT=BWs(n); DOSEF=doses(n); NUMFET=nfet(n); % Assign group input values
        start @nocallback
        sscheck = _cv(GSTART*24)/_cv((GSTART-1)*24) - 1;        % check for periodicity/SS @ GSTART,
should be ~ 0
        % Below appends inputs and results to array
        p2f2a = [p2f2a; [BWINIT, DOSEF, NUMFET, _bw(TSTOP-24), (_aucbb(find(_t==TSTOP))-
_aucbb(find(_t==gdosestart)))*24/gesthr]];  % AUC/time = avg conc
        %p2f2a = [p2f2a; [BWINIT, DOSEF, NUMFET, _bw(TSTOP-24), (AUCBB-
_aucbb(find(_t==gdosestart)))*24/gesthr]];  % AUC/time = avg conc
        %p2f2a = [p2f2a; [BWINIT, DOSEF, NUMFET, _bw(TSTOP-24), (AUCBB-
_aucbb(find(_t==gdosestart)))/15]];  % AUC/DAYS = avg auc
        plot(_t/24,_cv)
        end
p2f2a

"Simulations for gestational exposure P2/F2B"
BWs=[370.6 353.6 318.7]/1000; % Initial BWs for each exposure group, from Table 56
% Below calculates mean intake (dose rate) for each group, from values for GD 6-20 in Table 69.
doses=[mean([53.7 51.2 47.9 44.6]), mean([165.6 164.8 152.9 143.5]), mean([508.5 491.1 460.4
406.5])];
nfet=[18 19 12]; % # of fetuses for each dose group, chose to approximately match GD 20 BW
% *** nfet does *NOT* match the observed number born, reported by Exxon (1991).
% nfet is the # for which the combined maternal/fetal BW at GD 20 most closely matches
% the maternal BW in Table 56 (Exxon, 1991) at GD 20.
p2f2b=[]; % empty results array
for n=1:3;
        BWINIT=BWs(n); DOSEF=doses(n); NUMFET=nfet(n);  % Assign group input values
        start @nocallback
        sscheck = _cv(GSTART*24)/_cv((GSTART-1)*24) - 1        % check for periodicity/SS @ GSTART,
should be ~ 0
% Below appends inputs and results to array
        p2f2b = [p2f2b; [BWINIT, DOSEF, NUMFET, _bw(TSTOP-24), (_aucbb(find(_t==TSTOP))-
_aucbb(find(_t==gdosestart)))/gesthr]];  % AUC/time = avg conc
        %plot(_t/24,_cv)
        end
```

p2f2b

NMP_99_SD.m

```
% Simulations of THORNTON FEED STUDY
%ESTIMATED ASSUMING A 12 HR "INFUSION" RATE FOR AN ORAL DOSE.
use ratparam
use preg_rat_params
prepare @clear @all  % T DAYS AUCBB CV

load @file='NMP_99_SD.csv' @format=ascii @separator=comma
dat=NMP_99_SD; GDDAYS=0.01; TSTART=0.01; CINT=0.1; res=[]; GSTART=7;

BWINIT=mean(dat(g,1))/1000; TSTOP=(20+GSTART)*24;
DOSEF=164; start @nocallback
rng=find((_t/24)>=GSTART);
[BWINIT, DOSEF, (AUCBB-_aucbb(rng(1)))/20, max(_cv(rng))]

for g = 1:length(dat)
        BWINIT=dat(g,1)/1000; TSTOP=(7+GSTART)*24; DOSEF=dat(g,2); start @nocallback
        DOSEF=dat(g,3); TSTOP=(14+GSTART)*24; continue @nocallback
        DOSEF=dat(g,4); TSTOP=(20+GSTART)*24; continue @nocallback
        rng=find((_t/24)>=GSTART);
        res = [res; [g, dat(g,1), (AUCBB-_aucbb(rng(1)))/20, max(_cv(rng))]]
end

plot((_t/24) - GSTART,_cv,'SD_preg_99.aps')
dat=[dat,res]

save dat @file='NMP_99_SD_res.csv' @format=ascii @separator=comma
```

NMP_99_Wistar.m

```
% Simulations of THORNTON FEED STUY
%ESTIMATED ASSUMING A 12 HR "INFUSION" RATE FOR AN ORAL DOSE.
use ratparam
use preg_rat_params
prepare @clear @all  % T DAYS AUCBB CV

load @file='NMP_99_Wistar.csv' @format=ascii @separator=comma
dat=NMP_99_Wistar; GDDAYS=0.01; TSTART=0.01; CINT=0.1; res=[]; GSTART=7;
```

```
BWINIT=mean(dat(g,1))/1000; TSTOP=(20+GSTART)*24;
DOSEF=74; start @nocallback
rng=find((_t/24)>=GSTART);
[BWINIT, DOSEF, (AUCBB-_aucbb(rng(1)))/20, max(_cv(rng))]

for g = 1:length(dat)
        BWINIT=dat(g,1)/1000; TSTOP=(7+GSTART)*24; DOSEF=dat(g,2); start @nocallback
        DOSEF=dat(g,3); TSTOP=(14+GSTART)*24; continue @nocallback
        DOSEF=dat(g,4); TSTOP=(20+GSTART)*24; continue @nocallback
        rng=find((_t/24)>=GSTART);
        res = [res; [g, dat(g,1), (AUCBB-_aucbb(rng(1)))/20, max(_cv(rng))]]
end
        plot(_t/24 - GSTART,_cv,'Wistar_preg_99.aps')
dat=[dat,res]

save dat @file='NMP_99_Wistar_res.csv' @format=ascii @separator=comma

% results for P0 males, using observed BW at week 17 and TWA achieved doses
bws=[400.6      399.2    403.7]/1000; doses=[48.7 155.8 487.0];
TSTOP=GSTART*24; r2=[];
for g=1:3
        BWINIT=bws(g); DOSEF=doses(g); start @nocallback
        r2 = [r2; [BW DOSEF (AUCBB-_aucbb(find(_t==(TSTOP-24))))]];
        plot(_t/24 - GSTART,_cv)
end
r2

r3=[];
for DOSEF=[50, 160, 450]
rr=DOSEF;
for BWINIT=(2:6)/10
                start @nocallback
                rr=[rr, (AUCBB-_aucbb(find(_t==(TSTOP-24))))];
        end
r3 = [r3;rr]
end
plot(_t,_cv)
```

2 Human NMP PBPK Model Code

```
PROGRAM NMPhumPG.csl

! PBPK MODEL FOR N-METHYL PYRROLIDONE in pregnant women

! T.S. POET, P HINDERLITER. CHEMICAL DOSIMETRY GROUP, PNNL, RICHLAND, WA
! First Created 8.8.08
! FINAL REPORT FROM INITIAL rat MODEL DEVELOPMENT SUBMITTED 9.02
! 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. RAT = 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
!   Other parameters changed nominally to harmonize with fetal IPA model of
!     Gentry et al. Regu Tox Pharm 36:51-68, 2002
! Gentry model notes:
! -Coding for pregnancy is from MeHgFat.CSL with some minor changes
! -Physiological parameters are from MeHgFat.CSL (ajusted as needed)
! -Non-pregnant mammary tissue and uterine volume is from ICRP
! -Non-pregnant mammary tissue and uterine blood flows are based on the
! - ratios of mammary and uterine tissue volumes to rapidly perfused
! - tissue volume and blood flow to rapidly perfused tissue where rapidly
! - perfused tissue includes liver, lung, etc.
! - ((VMamC/VRapC)*QRapC) and ((VUtrC/VRapC)*QRapC)
! -Data used to fit curve for growing rapidly perfused tissue in
! - MeHgFat.CSL was refit separately to fit curves for growing uterus
! - and mammary tissue in this model
! -Body weight and cardiac output are calculated as the initial values
! - plus the change in the growing compartments
! -Increase in blood flow to fat, mammary tissue, and uterus are modeled
! - as being proportional to the increase in volume in those compartments
! - based on the data in Thoresen and Wesche, 1988 (uterus and mammary
! - tissue)
!
```

```
! Further updates by Paul Schlosser, US EPA in Aug 2013, Sept 2014, Apr-Dec 2020


INITIAL
table reslvl, 1, 2881 / 2881*0.0, 2881*0.0 /
table pvlf, 1, 3 / 0.0, 0.5, 1.0, 4.78e-4, 4.78e-4, 2.05e-3 /
        ! PVLF returns the estimated permeability from NMP solutions estimated for 50% NMP (4.78e-4)
        ! when the argument (weight fraction, WF) is between 0 and 0.5, and linear interpolation to
        ! the value measured for neat NMP (2.05e-3) for WF between 0.5 and 1.0
! Human Total Pulmonary Ventilation Rate (L/hr for 1 kg animal)
 CONSTANT    QPC = 27.75

! Human Blood Flows (fraction of cardiac output)
 CONSTANT    QCC = 12.9         ! Cardiac output (L/hr for 1 kg animal)
 CONSTANT   QFatC = 0.052       ! Fat (non-pregnant female)
 CONSTANT   QLivC = 0.227       ! Liver
 CONSTANT   QMamC = 0.027   ! Mammary tissue (non-pregnant female)
 CONSTANT   QRapC = 0.325       ! Rapidly perfused
 CONSTANT   QSkC = 0.058        ! Skin
 CONSTANT   QUtrC = 0.0062     ! Uterus (non-pregnant female)

! Permeability-Area Product (L/hr)
 CONSTANT    PAFC = 0.01        ! Diffusion on fetal side of placenta from Gentry

! Human Tissue Volumes (fraction of body weight)
 CONSTANT      BWInit = 67.8    ! Pre-pregnancy body weight (kg)
 CONSTANT      VAlvC = 0.0079  ! Alveolar blood
 CONSTANT      VBLC=0.06
 CONSTANT      VFatC = 0.273    ! Fat (non-pregnant female)
 CONSTANT      VLivC = 0.026    ! Liver
 CONSTANT      VMamC = 0.0062          ! Mammary tissue (non-pregnant female)
 CONSTANT      VRapC = 0.1044 ! Rapidly perfused
 ! CONSTANT    VSlwC              ! Slowly perfused is calculated below
 CONSTANT      VUtrC = 0.0014  ! Uterus (non-pregnant female)
 CONSTANT      VSKC=0.19        ! Skin

! Human Dermal Exposure Parameters
 CONSTANT PV = 31.0    ! PERMEABILITYT CONSTANT (CM/HR) FOR VAPOR
        ! CONSTANT PVL = 0.0    ! PERMEABILITYT CONSTANT (CM/HR) FOR liquid
 CONSTANT FAD = 0.0    ! FRACTION ABSORBED - FROM BADER ET AL, CALCULATE FROM AMNT
REMAINING ON GAUZE

 ! FOR PARENT MODEL, SKIN COMPARTMENT IS ONLY DEFINED AS DOSED SKIN
  CONSTANT     SAL = 0.01         ! SURFACE AREA EXPOSED to liquid, SQ.CM
```

```
  CONSTANT     SAvc = 0.25       ! fraction SURFACE AREA EXPOSED to gas/vapor, SQ.CM
  Constant     amask = 0.03      ! Fraction surface area covered by a face mask
  CONSTANT     HT=170.0          ! height (or length) of reference man
    TSA = 71.81*(BWinit**0.425)*(HT**0.725)     !for humans, DuBois and DuBois, 1916, as reported in
Reference Man
          SAv = SAVC*TSA          ! SURFACE AREA EXPOSED to gas/vapor, SQ.CM
          VSKlC = VSKC*SAl/TSA
          QSKlC = QSKC*SAl/TSA
          VSKvC = VSKC*SAv/TSA
          QSKvC = QSKC*SAv/TSA

  ! Slowly perfused (defined as balance of tissues and flows)
  VSlwC = 0.91 - (VFatC + VLivC + VMamC + VRapC + VUtrC + VSKvC + VSKlC)
           ! NOTE: 0.91 IS APPROX WHOLE BODY LESS BONE
  VSLwC5=0.91 - (VFatC + VLivC + VRapC)
   QSlwC = 1.0 - (QFatC + QLivC + QMamC + QRapC + QUtrC + QSKvC + QSKlC)
  QSlwC5 = 1.0 - (QFatC + QLivC + QRapC)

! Molecular Weights
 CONSTANT      MW=99.13        ! MOL. WT. NMP, MG/MMOL
CONSTANT       MW1= 116.14     ! MOL. WT. 5-HNP, MG/MMOL

    Stoch = MW1/MW     ! Stoichiometric multiplier

! Human NMP/Blood Partition Coefficients
! EXPERIMENTALLY MEASURED RATVALUES
 CONSTANT    PB = 450.0         ! Blood/air
 CONSTANT    PFat = 0.61        ! Fat
 CONSTANT    PLiv = 1.00        ! Liver
 CONSTANT    PMam = 1.0         ! Mammary tissue, estimated from liver
 CONSTANT    PPla = 0.31        ! Placenta
 CONSTANT    PRap = 1.0         ! Rapidly perfused tissue, liver
 CONSTANT    PSlw = 0.30        ! Slowly perfused tissue, muscle
 CONSTANT    PUtr = 0.34        ! Uterus
 CONSTANT    PSKA = 44.5        ! use (blood/air)*(rat skin:liquid)/(human blood:liquid)
 CONSTANT    PSKL = 0.42        ! MEASURED SKIN;LIQUID (rat)
 CONSTANT    pskb = 0.099       ! (rat skin:liquid)/(human blood:liquid)
 CONSTANT    PLU= 0.1           ! LUNG:BLOOD

! METABOLIC RATE CONSTANTS
! **THESE ARE FROM PAYAN ET AL
 ! NMP TO 5HNP
                CONSTANT Af1 = 0.0112          ! AFFINITY CONSTANT, l/MG
                CONSTANT VK1C = 0.4663         ! Vmaxc/Km, 1/(hr * BW^0.75 )
```

```
! Human 5HNMP volume of distribution
        CONSTANT VOD5Hc = 0.3          ! VOLUME-OF-DISTRIBUTION
                VOD5H = VOD5Hc*BWinit
 ! No fetal compartment for metabolite, NMP is considered the active moiety

! 5HNP TO OTHER METABS
   ! CONSTANT   KM2=22.8         ! MICHAELIS CONSTANT, MG/L
   ! CONSTANT   VMAX2C=1.0      ! MAX. ENZ. ACT., MG/HR/L
   CONSTANT VK2C=0.0326         ! VMAX2C/KM2, since clearance ~ liner 1/(hr*kg^0.75)
! Human Uptake and Clearance Parameters
 ! URINARY ELIMINATION OF 5-HNMP - CLEARED FROM BLOOD
 ! note first order rate commented out, saturable fits better
    CONSTANT KAS=5.0
    CONSTANT KME=3.83           ! First-order constant for 5HNMP in urine (L/hr)
   CONSTANT KUMNE=0.182         ! First-order CONSTANT FOR NMP IN URINE (L/hr)

! Initialize Human Concentrations in Tissues (mg/L)
 CONSTANT   ICArt = 0.0          ! Blood
 CONSTANT   ICFat = 0.0          ! Fat
 CONSTANT   ICLiv = 0.0          ! Liver
 CONSTANT   ICRap = 0.0          ! Rapidly perfused
 CONSTANT   ICSkn = 0.0          ! Skin
 CONSTANT   ICSlw = 0.0          ! Slowly perfused
        ICMam = ICSlw  ! Mammary tissue
        ICUtr = ICRap    ! Uterus

! Dosing Parameters
 CONSTANT    Concppm = 0.0    ! Inhaled concentration (ppm)
 CONSTANT   CONCMGM = 0.0  ! Inhaled concentration (mg/m3)
 CONSTANT   IVDose = 0.0         ! IV dose (mg/kg)
 CONSTANT   PDose = 0.0          ! Oral dose (mg/kg)
 CONSTANT   PDrink = 0.0         ! Drinking water dose (mg/kg/day)
 CONSTANT   TChng = 24.0         ! Length inh. exposure or IV inj.(hrs)
 CONSTANT   DaysWk = 5.0         ! Number of exposure days per week
 CONSTANT    TMax = 24.0         ! Maximum time for exposures
CONSTANT s2=0.0
        ! INHALATION ON
CONSTANT p2=3.0
        ! INHALATION EXPOSURE
CONSTANT S3=3.16       ! INHALATION RESUME (HANOVER STUDY and other scenarios)
CONSTANT P3=3.0        ! SECOND DAILY EXPOSURE PERIOD
logical on3, on4, on5     ! Set to zero to turn off 2nd daily pulse;
```

```
CONSTANT s4=7.0         ! Third daily exposure start, period assumed = P3
constant s5=11.0        ! Fourth daily exposure start, period assumed = p3
constant on3=0 ! Set to one to turn on 2nd daily pulse;
constant on4=0 ! Set to one to turn on 3rd daily pulse;
constant on5=0 ! Set to one to turn on 3rd daily pulse;
constant fullweek =168.0        ! hours in a full week
hrsweek = 24.0*DaysWk           ! h/week in workplace

! STARTDS IS ADDED TO TCHNG TO ALLOW FOR DOSING THAT DOES NOT START AT T=0
! INITIAL EXPOSURE CONDITIONS
 ! DERMAL
    CONSTANT CONCL = 0.0        ! CONC OF NMP IN LIQUID, MG/L
    constant srate = 0.0        ! mg/hr delivered to skin by spray application
    CONSTANT VLIQ0 = 1.0e-99    ! INITIAL VOLUME APPLIED, L
    CONSTANT DENSITY=1.02e6 ! Density (mg/L) @ 40C, ~ skin temperature
    CONSTANT RESID=0.0          ! AMOUNT STICKING TO EXPOSURE SYSTEM, MG
    constant BRUSH = 0.0        ! Set to 1.0 for brush/liquid exposure
    DDN = (CONCL - 1.0)*VLIQ0*FAD       ! Subtract 1 mg/L, ~ 1 ppm, from initial conc. to avoid VLIQ --> 0
WF0 = (CONCL - 1.0)*FAD/DENSITY         ! Initial weigh fraction in liquid
          AH20 = (DENSITY+1.0-CONCL)*VLIQ0      ! ... and add 1 ppm to H20.
! Note, for application of 100% NMP, it is not possible for CSURF to drop below 100%.
! 100% NMP is not diluted in anything, so the "solution" can't become less dilute.
! The volume (VLIQ) would actually decrease until it's all absorbed.
! Unless the experiment runs long enough for 100% absorption, treat VLIQ as
! extremely large, ~ 10^9, for 100% NMP.
! But check that you don't predict more absorption than was actually applied!

! 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)

  ! Exposure Conditions Based on User Defined Initial Amounts of Chemical (mg)
  IF (concppm.EQ.0.0) THEN
    concmg=concmgm/1000.0     ! Convert MG/M3 to mg/L
  ELSE
     CONCmg = CONCppm*MW/24451.  ! Convert ppm to mg/Liter!
  ENDIF

! Simulation Control Parameters
  CONSTANT StartDs = 0.0          ! Time first dose is given (hrs)
  CONSTANT   TStop = 6480.0       ! Run simulation for about 9 months
  CONSTANT   CIntC = 0.1
CONSTANT   GDstart = 0.0          ! Gestation day on which simulation starts

! Scaled Human Pulmonary Ventilation Rate (L/hr)
```

```
      QP = QPC * (BWInit**0.75)
     QAlv = 0.67 * QP

! Scaled Human Tissue Volumes (L)
     VAlv = VAlvC * BWInit
     VFatg0 = BWInit*0.09*exp(-12.90995862)     ! Fat weight growth term at start of pregnancy (g0)
     VFatI = BWInit*VFatC + VFatg0              ! Total fat weight at g0
     VFetI = 3.50 * (exp(-16.081)+ exp(-140.178)) ! Fetal weight function value at g0
    VMamg0 = BWInit*0.0065*exp(-7.444868477)          ! Mammary weight growth term at g0
     VMamI = BWInit*VMamC + VMamg0              ! Total mammary weight at g0
     VPlaI = 0.85*exp(-9.434)                   ! Placenta weight function value at g0
     VUtrg0 = BWInit*0.02*exp(-4.715669973)     ! Uterus weight growth term at g0
     VUtrI = BWInit*VUtrC + VUtrg0              ! Total uterus weight at g0
     VLiv = VLivC * BWInit
     VRap = VRapC * BWInit
    VSKl = VSKlC * BWinit
    VSKv = VSKvC * BWinit
      VBL= VBLC * BWINIT
      VSlw = VSlwC * BWInit

BW0 = BWInit + VFatg0 + VMamg0 + VUtrg0 + VFetI + VPLaI

! Scaled Human Blood Flows (L/hr)
   QCInit = QCC * (BW0**0.75)
   QFatI = QFatC * QCInit
   QLiv = QLivC * QCInit
   QMamI = QMamC * QCInit
   QPlaI = 58.5 * VPlaI     ! value for 'days'=0 per calculation below
   QRap = QRapC * QCInit
   QSlw = (QSlwC * QCInit) - QPlaI
   QUtrI = QUtrC * QCInit
   QSkl = QSKlC * QCInit
   QSkv = QSKvC * QCInit

! Scaled Human Metabolism Parameters
VK1 = VK1C * (BW0**0.75)
          VK2 = VK2C * (BW0**0.75)
! Initialize Human NMP Amounts in Tissues
    IAArt = ICArt * VAlv
    IAFat = ICFat * VFatI
    IALiv = ICLiv * VLiv
    IAMam = ICMam * VMamI
    IARap = ICRap * VRap
    IASkl = ICSkn * VSKl
```

```
    IASkv = ICSkn * VSKv
    IASlw = ICSlw * VSlw
    IAUtr = ICUtr * VUtrI
  InitTot = IAArt + IAFat + IALiv + IAMam + IARap + IASkl + IASkv + IASlw + IAUtr

! Initialize Starting Values
      BW = BWInit
    Drink = (PDrink * BW0) / 24.0! Drinking water dose (mg/hr)
     CINT = CIntC
       IV = 0.0
   DayExp = 1.0
     CInh = 0.0
    CONSTANT FRACIN = 0.97      ! 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%

! Convert oral dose from ug/kg to umoles
! Modify dose to account for fractional absorption
ODOSE1= PDOSE * BW0 * FRACOR          ! mg

DZONE = 1.0      ! Start with dermal and fixed conc inhalation exposure on
schedule offd.at.p2
schedule OND2.at.24.0

! With the following three schedules it is assumed the length of use is the same
! for all three, set by p3.
if (on3) schedule OND3.at.s3
if (on4) schedule ond3.at.s4
if (on5) schedule ond3.at.s5

END      ! End of Initial


DYNAMIC
ALGORITHM IALG = 2     ! Gear stiff method

DISCRETE DoseOn          ! Start dosing
INTERVAL DoseInt = 24.0           ! Interval to repeat dosing
SCHEDULE DoseOff .AT. T + TChng
IF ((T.GE.StartDs) .AND. (T.LT.TMax)) THEN
                    IF (T.LE.(StartDs+TChng)) THEN
                              IF (IVDose.GT.0.0) CINT = MIN(CIntC, (TChng/10.0))
                              IV = (IVDose*BW) / TChng    ! Rate of intravenous dosing (mg/hr)
                    ENDIF
```

```
        ENDIF
END     ! DoseOn

DISCRETE DoseOff
CInh = 0.0
CINT = CIntC
IV = 0.0
END

discrete OND2
        DZONE=1.0
        SCHEDULE OND2.AT.(T+24.0)
        SCHEDULE OFFD.AT.(T+P2)
END

discrete OND3
        DZONE=1.0
        SCHEDULE OND3.AT.(T+24.0)
        SCHEDULE OFFD.AT.(T+P3)
END

! EXPOSURE CONTROL
DISCRETE OFFD
        DZONE=0.0       ! TURN OFF DERMAL & FIXED CONC INHALATION
END

DERIVATIVE
   Hours = T
  Minutes = T * 60.0
    Days = T / 24.0 + GDstart
 Gtime = T + GDstart*24.0

! Volume of human fat (L)
    VFat = BWInit*(VFatC+(0.09*exp(-12.90995862*exp(-0.000797*Gtime))))

! Volume of human fetus (L)
    VFet = 3.50 * (exp(-16.081*exp(-5.67e-4*Gtime))+ exp(-140.178*exp(-7.01e-4*Gtime)))

! Volume of human mammary tissue (L)
    VMam = BWInit*(VMamC+(0.0065*exp(-7.444868477*exp(-0.000678*Gtime))))

! Volume of human placenta (L)
    VPla = 0.85*exp(-9.434*exp(-5.23e-4*Gtime))
```

```
! Volume of human uterus (L)
    VUtr = BWInit*(VUtrC+(0.02*exp(-4.715669973*exp(-0.000376*Gtime))))

! Increase in human body weight (kg)
     ! BW = BWInit + (VFat - VFatI) + VFet + (VMam - VMamI) + VPla + (VUtr - VUtrI)
BW = BW0 + (VFat - VFatI) + (VFet - VFetI) + (VMam - VMamI) + (VPla - VPlaI) + (VUtr - VUtrI)
! Scaled human alveolar ventilation (L/hr)
     QP = QPC * (BW**0.75)
    QAlv = 0.67 * QP

! Increase in human blood flows (L/hr)
    QFat = QFatI * (VFat / VFatI)
    QMam = QMamI * (VMam / VMamI)
    QUtr = QUtrI * (VUtr / VUtrI)

! Human Blood flow to placenta (L/hr)
    QPla = 58.5 * VPla

! Increased human cardiac output (L/hr)
     QC = QCInit + (QFat - QFatI) + (QMam - QMamI) + (QPla - QPlaI) + (QUtr - QUtrI)
                          QSlw5 = Qc - (QFat + QLiv + QRap)
                          VSlw5 = BW - (VFat + VLiv + VRap)

! Scaled permeability-area product
     PAF = PAFC * (VFet**0.75)


! ------------------ HUMAN NMP MODEL -------------------------

! Amount Exhaled (mg)
   RAExh = QAlv * CAlv
    AExh = INTEG(RAExh, 0.0)

CI = concmg*czone + RESLVL(T)
! for a 5 day/wk exposure, change first pulse to pulse(0,7*24,5*24)
! for daily, pulse(0,1e6,24)

TORAL = ODOSE1 - AO   ! AMT ABSORBED ORALLY, MG!
RSTOM = -KAS*AO       ! Change in stomach (umole/hr)
RAO = KaS*AO          ! Rate of absorption (-RSTOM)
AO=ODOSE1+INTEG(Rstom,0.0) ! Amt in stomach (umole)

! Amount in Fat (mg)
   RAFat = QFat * (CArt - CVFat)
```

```
      AFat = INTEG(RAFat, IAFat)
      CFat = AFat / VFat
     CVFat = CFat / PFat

! Amount in Fetus (mg)
     RAFet = PAF * (CPla - CFet)
      AFet = INTEG(RAFet, 0.0)
      CFet = AFet / VFet
   AUCCFet = INTEG(CFet, 0.0)

! Amount in Liver (mg)
     RALiv = (QLiv * (CArt - CVLiv)) + RAO + Drink - RAMet1
      ALiv = INTEG(RALiv, IALiv)
      CLiv = ALiv / VLiv
     CVLiv = CLiv / PLiv

! Amount Metabolised in Liver -- Saturable (mg)
    RAMet1 = VK1 * CVLiv / (1 + af1*CVLiv)
     AMet1 = INTEG(RAMet1, 0.0)

! Amount in Mammary Tissue (mg)
     RAMam = QMam * (CArt - CVMam)
      AMam = INTEG(RAMam, IAMam)
      CMam = AMam / VMam
     CVMam = CMam / PMam

! Amount in Placenta (mg)
     RAPla = (QPla * (CArt - CVPla)) + (PAF * (CFet - CPla))
      APla = INTEG(RAPla, 0.0)
      CPla = APla / VPla
     CVPla = CPla / PPla

! Amount in Rapidly Perfused Tissue (mg)
     RARap = QRap * (CArt - CVRap)
      ARap = INTEG(RARap, IARap)
      CRap = ARap / VRap
     CVRap = CRap / PRap

! ASKl = AMOUNT NMP IN liquid-exposed SKIN TISSUES (MG) AND DERMAL DOSING (from vapor)
! Liquid exposure when czone = 1, otherwise czone = 0. CI = air concentration
czone = pulse(0.0,fullweek,hrsweek)*DZONE
! for a 5 day/wk exposure, use fullweek=7*24, hrsweek=5*24 (Dayswk=5)
! for a single day, fullweek=1e16, hrsweek=24 (Dayswk=1)
PVLU=PVLF(WF)
```

```
RADL = (PVLU*SAL/1000.0)*(CSURF - (CSKL/PSKL))*czone*BRUSH
  ! Net rate of delivery to "L" skin from liquid, when liquid is there
        ADLL = integ(RADL, 0.0)
RADVL = (PV*SAL/1000.0)*(CI - (CSKL/PSKA))*(1.0-Czone*BRUSH)
 ! Net rate of delivery to "L" skin from air, when liquid not present
        ADVL = integ(RADVL, 0.0)
ASURF = INTEG(-RADL, DDN) ! Amount in liquid.  DDN is the initial amount.
VLIQ = (AH20 + ASURF)/DENSITY
CSURF = ASURF/VLIQ
WF = CSURF/DENSITY

RASKL = QSKL*(CArt - CvSKL) + RADL + RADVL     ! Rate of change in "L" skin compartment
ASKL = INTEG(RASKL, 0.0)          ! Amount in "L" skin
CSKL = ASKL/VSKL                  ! Concentration in "L" skin
CvSKL = CSKL/PSKB                 ! Concentration in venous blood exiting "L" skin

! ASKv = AMOUNT NMP IN vapor-exposed SKIN TISSUES (MG) AND DERMAL DOSING (from vapor);
! "SKv" (vapor-only-exposed) skin compartment.  CI = air concentration

RADVv = (PV*SAv/1000.0)*(CI*(1.0 - AMASK/SAVC) - (CSKv/PSKA))   ! Net rate of transfer from air to skin
        ! In above, CI is reduced in proportion to mask fractional coverage (AMASK), so *average*
        ! concentration of air over exposed skin is reduced from CI by AMASK/SAVC.
        ! If the concentration inside the mask is 10% of exposure and the surface area fraction of the
        ! face (covered by the mask) is 'mask' = 0.03, and SAVC is the surface area fraction otherwise
        ! exposed, then the average concentration of vapor-exposed skin (weighted by surface area) is:
                ! [(SA fully exposed)*CI + (SA of mask)*10%*CI]/SAVC =
                ! [(SAVC - mask)*CI     +       mask*0.1*CI]/SAVC = [1 - 0.9*mask/SAVC]*CI
                !                                                 = (1 - AMASK/SAVC)*CI,
! if AMASK = 0.9*mask; i.e., the mask effectively covers 90% of the face, reduces CI by AMASK/SAVC.

 ADVv = INTEG(RADVv,0.0)         !'AMT NMP ABSORBED DERMAL, MG'
RASKv = QSKv*(CArt - CvSKv) + RADVv    ! Rate of change in "V" skin
ASKv = INTEG(RASKv, 0.0)          ! Amount in "V" skin
CSKv = ASKv/VSKv                  ! Concentration in "V" skin
CvSKv = CSKv/PSKb                 ! Concentration in venous blood exiting "V" skin

! Amount in Slowly Perfused Tissue (mg)
    RASlw = QSlw * (CArt - CVSlw)
     ASlw = INTEG(RASlw, IASlw)
     CSlw = ASlw / VSlw
    CVSlw = CSlw / PSlw

! Amount in Uterus (mg)
    RAUtr = QUtr * (CArt - CVUtr)
```

```
     AUtr = INTEG(RAUtr, IAUtr)
     CUtr = AUtr / VUtr
    CVUtr = CUtr / PUtr

! BLOOD VENOUS ARTERIAL (c)
CVEN = (QFAT*CVFat + QLIV*CVLiv + QMAM*CVMam + QPLA*CVPla + QRap*CVRap + QSlw*CVSlw &
        + QUtr*CVUtr + QSKV*CVSKv + QSKL*CVSKL + IV) / QC
Ivtot = INTEG(IV, 0.0)

! Amount in Arterial Blood (mg)
   RAINH = QAlv*(CI*FRACIN - CAlv)
   RABld = RAINH + QC*(CVen-CArt) - RAUNP
   INhaltot = INTEG(RAINH, 0.0)
    ABld = INTEG(RABld, IAArt)
    CArt = ABld / VBL
    CAlv = CArt / PB
  CAlvPPM = CAlv * 24450.0 / MW
  AUCCBld = INTEG(CArt, 0.0)

! Amount in Urine (mg)
  RAUNP = KUMNE*CART          ! FIRST ORDER RATE OF LOSS (URINE
  AUNP = INTEG(RAUNP,0.0)

! ---------- HUMAN 5HNMP MODEL ----------

! Amount in body (mg)
   RA5H = (RAMet1*STOCH) - RAMetM1 - RAUHP
    A5H = INTEG(RA5H, 0.0)
    Cven1 = A5H / VOD5H

! Amount Metabolised [in Liver] -- Saturable (mg)
RAMetM1 = VK2*Cven1
          AMetM1 = INTEG(RAMetM1, 0.0)

! Amount in Urine (mg)
  RAUHP = KME*Cven1
AUHP = INTEG(RAUHP,0.0)

! ---------- CHECK MASS BALANCE ----------
 INTOT=INTEG((QAlv*CI*FRACIN), 0.0)

  TDose = INTOT + AO + InitTot +TORAL +ADLL +ADVL +ADvV
NMPTOT =ABld +AFat +AFet +ALiv +AMam +APla +ARap +ASkl +ASkv +ASlw +AUtr +AExh +AUnp +AMET1
    MassBal = TDose/(NMPTOT+0.000000000001)
```

```
TERMT(T.GT.TSTOP, 'Simulation Finished')
END     ! End of Derivative

TERMINAL
DAUCCBld = AUCCBld * 24.0 / TStop
DAUCCFet = AUCCFet * 24.0 / TStop
END

END     ! End of Dynamic
END     ! End of Program
```

```
% 2020 script to run NMP PBPK analysis for residential exposures, female users
exist cont
if ~ans
        cont=0
end
if cont
        cd ..
        cont=0
end
cont=1
% Files appearing in 'load' statements below should be in sub-folder set by 'cd' below (~ line 23)
sclist=["Paint_Remover_1"; "Paint_Remover_2"; "Adhesives_1"; "Adhesives_2"];
% list of scenario/tab names
fname="Residential_Dec2020.xls"
        res=[];
        use human_params
        use human_avg_params
        TSTOP=24; CINTC=0.01; BWINIT=74; VLIQ0=1e6;
        prepare @clear T CVEN AUCCBLD CI CSURF CZONE RESLVL CART ASURF AUCCBLD
        % Fixed parameters for residential exposure scenarios
        AMASK=0; S2=0; ON3=1; % 2 daily exposures
% PVLF(3)=4.78e-4
        cd 'resid_female'
        load rt @file='Resid2020_time.csv' @format=ascii @separator=comma
        % time array of air concentrations, assuming all are the same, use the 1st one

% Paint_Remover_1
sc=1;   % scenario #
load data @file=Paint_Remover_1b.csv @format=ascii @separator=comma;
RESLVL=[data(:,1)/1000;rt]; aWF=0.6; P2=4.5/60; ON3=1; S3=45/60; P3=5/60;
CONCL=aWF*DENSITY; % CONCL is NMP concentration in liquid mg/L
```

```
BRUSH=1; sal0 = 445; % surface area of hands exposed/no gloves
        cvs = [];
for BWINIT = [74 65.9]
        HT=170.0        % height (or length) of reference man
        start @nocallback
                % Run to calculate TSA for BWINIT
        aglove=890/TSA; % fraction of surface area covered by gloves
        aliq=sal0/TSA; % fraction of surface area covered by liquid

        % Simulations for user
        for gloves = [1 0]
                rexp = [sc aWF BWINIT gloves]
                SAL=sal0/(1+4*gloves); % gloves have PF = 5
                SAVC=0.25-gloves*aglove-(1-gloves)*aliq;
                for GDSTART= [0 8]*30  % Gestation day on which simulations start
                        start @nocallback
                        rexp=[rexp, AUCCBLD, max(_cven), (1 - (AEXH + AUNP + AMET1)/TDOSE)];
                end
                res=[res; rexp]; ci1=_ci; cvs=[cvs,_cven];
        end
end

% Simulations for bystander adult female
BWINIT=74; BRUSH=0; SAL=0.01; SAVC=0.25; rexp=[sc 0 BWINIT 0];
for GDSTART = [0 8]*30 % Gestation day on which simulations start
        start @nocallback
        rexp=[rexp, AUCCBLD, max(_cven), (1 - (AEXH + AUNP + AMET1)/TDOSE)];
end
ci2=_ci; cvs=[cvs,_cven]; res=[res; rexp]

% Simulations for rest-of-house adult female
RESLVL=[data(:,2)/1000;rt]; rexp=[sc 0 BWINIT 0];
for GDSTART=[0 8]*30   % Gestation day on which simulations start
        start @nocallback
        rexp=[rexp, AUCCBLD, max(_cven), (1 - (AEXH + AUNP + AMET1)/TDOSE)];
end
ci3=_ci; cvs=[cvs,_cven]; res=[res; rexp]

% Simulations for rest-of-house child
BWINIT=18.6; HT=105.7; GDSTART=0; rexp=[sc 0 BWINIT 0];
start @nocallback
res = [res; [rexp, AUCCBLD, max(_cven), (1 - (AEXH + AUNP + AMET1)/TDOSE), NaN, NaN, NaN]];
plot(_t,ci1*1000,_t,ci2*1000,_t,ci3*1000,'residential_ci.aps')
plot(_t,[cvs(:,[5 2 6])],'residential_cv.aps')
```

```
% Paint_Remover_2
sc=2;    % scenario #
load data @file=Paint_Remover_2b.csv @format=ascii @separator=comma;
RESLVL=[data(:,1)/1000;rt]; aWF=0.6; P2=18/60; S3=84/60; P3=18/60;
ON4=1; S4=228/60; ON5=1; S5=312/60; % Turning on 3rd and 4th daily exposure
CONCL=aWF*DENSITY; % CONCL is NMP concentration in liquid mg/L
BRUSH=1; sal0 = 445; % surface area of hands exposed/no gloves

        cvs = [];
for BWINIT = [74 65.9]
        HT=170.0        % height (or length) of reference man
        start @nocallback
                % Run to calculate TSA for BWINIT
        aglove=890/TSA; % fraction of surface area covered by gloves
        aliq=sal0/TSA; % fraction of surface area covered by liquid

        % Simulations for user
        for gloves = [1 0]
                rexp = [sc aWF BWINIT gloves]
                SAL=sal0/(1+4*gloves); % gloves have PF = 5
                SAVC=0.25-gloves*aglove-(1-gloves)*aliq;
                for GDSTART=[0 8]*30   % Gestation day on which simulations start
                        start @nocallback
                        rexp=[rexp, AUCCBLD, max(_cven), (1 - (AEXH + AUNP + AMET1)/TDOSE)];
                end
                res=[res; rexp]; ci1=_ci; cvs=[cvs,_cven];
        end
end

% Simulations for bystander adult female
BWINIT=74; BRUSH=0; SAL=0.01; SAVC=0.25; rexp=[sc 0 BWINIT 0];
for GDSTART=[0 8]*30   % Gestation day on which simulations start
        start @nocallback
        rexp=[rexp, AUCCBLD, max(_cven), (1 - (AEXH + AUNP + AMET1)/TDOSE)];
end
ci2=_ci; cvs=[cvs,_cven]; res=[res; rexp]

% Simulations for rest-of-house adult female
RESLVL=[data(:,2)/1000;rt]; rexp=[sc 0 BWINIT 0];
for GDSTART=[0 8]*30   % Gestation day on which simulations start
        start @nocallback
        rexp=[rexp, AUCCBLD, max(_cven), (1 - (AEXH + AUNP + AMET1)/TDOSE)];
```

```
end
ci3=_ci; cvs=[cvs,_cven]; res=[res; rexp]

% Simulations for rest-of-house child
BWINIT=18.6; HT=105.7; GDSTART=0; rexp=[sc 0 BWINIT 0];
start @nocallback
res=[res; [rexp, AUCCBLD, max(_cven), (1 - (AEXH + AUNP + AMET1)/TDOSE), NaN, NaN, NaN]];
plot(_t,ci1*1000,_t,ci2*1000,_t,ci3*1000,'residential_ci.aps')
plot(_t,[cvs(:,[5 2 6])],'residential_cv.aps')

% Turning off 2nd, 3rd, and 4th dermal exposures:
ON3=0; ON4=0; ON5=0;



% Third scenario, Adhesives 1
sc=3;    % scenario #
load data @file=Adhesives_1b.csv @format=ascii @separator=comma;
RESLVL=[data(:,1)/1000;rt]; aWF=0.85; P2=4.25/60;
CONCL=aWF*DENSITY; % CONCL is NMP concentration in liquid mg/L
BRUSH=1; sal0 = 445; % surface area of hands exposed/no gloves

for BWINIT = [74 65.9]
        cvs = []; ci1 = [];
        HT=170.0        % height (or length) of reference man
        start @nocallback
                % Run to calculate TSA for BWINIT
        aglove=890/TSA; % fraction of surface area covered by gloves
        aliq=sal0/TSA; % fraction of surface area covered by liquid

        % Simulations for user
        for gloves = [1 0]
                rexp = [sc aWF BWINIT gloves]
                SAL=sal0/(1+4*gloves); % gloves have PF = 5
                SAVC=0.25-gloves*aglove-(1-gloves)*aliq;
                for GDSTART=[0 8]*30   % Gestation day on which simulations start
                        start @nocallback
                        rexp=[rexp, AUCCBLD, max(_cven), (1 - (AEXH + AUNP + AMET1)/TDOSE)];
                end
                res=[res; rexp]; ci1=_ci; cvs=[cvs,_cven];
        end
end

% Simulations for bystander adult female
BWINIT=74; BRUSH=0; SAL=0.01; SAVC=0.25; rexp=[sc 0 BWINIT 0];
```

```
for GDSTART=[0 8]*30   % Gestation day on which simulations start
        start @nocallback
        rexp=[rexp, AUCCBLD, max(_cven), (1 - (AEXH + AUNP + AMET1)/TDOSE)];
end
res=[res; rexp]

% Simulations for bystander child
BWINIT=18.6; HT=105.7; GDSTART=0; rexp=[sc 0 BWINIT 0];
start @nocallback
res=[res; [rexp, AUCCBLD, max(_cven), (1 - (AEXH + AUNP + AMET1)/TDOSE), NaN, NaN, NaN]];
plot(_t,ci1*1000,_t,_ci*1000,_t,_czone,'residential_ci.aps')
plot(_t,[cvs(:,[2 1]),_cven],'residential_cv.aps')


% Fourth scenario, Adhesives 2
sc=4;    % scenario #
load data @file=Adhesives_2b.csv @format=ascii @separator=comma;
RESLVL=[data(:,1)/1000;rt]; aWF=0.85; P2=60/60;
CONCL=aWF*DENSITY; % CONCL is NMP concentration in liquid mg/L
BRUSH=1; sal0 = 445; % surface area of hands exposed/no gloves

for BWINIT = [74 65.9]
        cvs = []; ci1 = [];
        HT=170.0        % height (or length) of reference man
        start @nocallback
                % Run to calculate TSA for BWINIT
        aglove=890/TSA; % fraction of surface area covered by gloves
        aliq=sal0/TSA; % fraction of surface area covered by liquid

        % Simulations for user
        for gloves = [1 0]
                rexp = [sc aWF BWINIT gloves]
                SAL=sal0/(1+4*gloves); % gloves have PF = 5
                SAVC=0.25-gloves*aglove-(1-gloves)*aliq;
                for GDSTART=[0 8]*30   % Gestation day on which simulations start
                        start @nocallback
                        rexp=[rexp, AUCCBLD, max(_cven), (1 - (AEXH + AUNP + AMET1)/TDOSE)];
                end
                res=[res; rexp]; ci1=_ci; cvs=[cvs,_cven];
        end
end

% Simulations for bystander adult female
BWINIT=74; BRUSH=0; SAL=0.01; SAVC=0.25; rexp=[sc 0 BWINIT 0];
```

```
for GDSTART=[0 8]*30   % Gestation day on which simulations start
        start @nocallback
        rexp=[rexp, AUCCBLD, max(_cven), (1 - (AEXH + AUNP + AMET1)/TDOSE)];
end
res=[res; rexp]

% Simulations for bystander child
BWINIT=18.6; HT=105.7; GDSTART=0; rexp=[sc 0 BWINIT 0];
start @nocallback
res=[res; [rexp, AUCCBLD, max(_cven), (1 - (AEXH + AUNP + AMET1)/TDOSE), NaN, NaN, NaN]];
plot(_t,ci1*1000,_t,_ci*1000,_t,_czone,'residential_ci.aps')
plot(_t,[cvs(:,[2 1]),_cven],'residential_cv.aps')


xlsWrite(fname, "results", "A3:J30",res)
save res @file=Residential2020.csv @format=ascii @separator=comma
cont=0
cd ..
```

3 References

Poet, TS; Kirman, CR; Bader, M; van Thriel, C; Gargas, ML; Hinderliter, PM. (2010). Quantitative risk analysis for N-methyl pyrrolidone using physiologically based pharmacokinetic and benchmark dose modeling. Toxicol Sci 113: 468-482. http://dx.doi.org/10.1093/toxsci/kfp264.

U.S. EPA. (2013). TSCA workplan chemical risk assessment n-Methylpyrrolidone: Paint stripping use CASRN: 872-50-4. Draft. Washington, DC: Office of Pollution Prevention and Toxics, US Environmental Protection Agency.

U.S. EPA. (2018). An umbrella Quality Assurance Project Plan (QAPP) for PBPK models. Research Triangle Park: U.S. Environmental Protection Agency.