Online Resource 3: NONMEM control stream

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$SIZES LIM6=5000
$PROBLEM PK NICOTINE (AND COTININE)
$INPUT ID TIME DV CMT AMT EVID BQL WT CO
; TIME (minutes)
; AMT is not real amount of drug. AMT is the airflow values after processing.
; We assumed the real amount is proportional.
; F to scale the dose
$SUBROUTINES ADVAN13 TOL=6
$MODEL
        COMP(PARENT)          ; 1 CENTRAL CMT nicotine
        COMP(MET1)            ; 2 METABOLITE 1 cotinine (COT)

$PK
        ; nicotine original juice (18mg/mL)
        F1=18*THETA(1)*EXP(ETA(1))   ; Bioavailability (Prop factor Airflow -> real dose)
        VC=THETA(2)*EXP(ETA(2))              ; V CENTRAL NICOTINE(L) fix from the literature
        VM=THETA(3)*EXP(ETA(3))              ; V CENTRAL COTININE(L) fix from the literature

        ; CLtotal NICOTINE CLEARANCE(L/min) = CLEX + CL2COT + CL2METO
        CLEX =THETA(4)*EXP(ETA(4)) ; Fix from literature
        CL2COT = THETA(5)*EXP(ETA(5))        ; Fix from literature
        CLCOT= THETA(6)*EXP(ETA(6))          ; Fix from literature

        ; Initialization
        A_0(1)=((1+CO)**THETA(12))*THETA(8)*EXP(ETA(8))
        A_0(2)=((1+CO)**THETA(13))*THETA(9)*EXP(ETA(9))
        ;--------  scales --------
        S1=VC           ;AMT= arbitary units in micrograms,  DV= ng/mL (==microg/L)
        S2=VM

$DES
;---------------------------------pk ODEs Morphine-------------------------------------
DADT(2) =  - (CLEX/VC)*A(1) - (CL2COT/VC)*A(1)        ; Nicotine
DADT(3) = (CL2COT/VC)*A(1) - (CLCOT/VM)*A(2)         ; Cotinine

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