

NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) VERSION 7.4.1  
ORIGINALLY DEVELOPED BY STUART BEAL, LEWIS SHEINER, AND ALISON BOECKMANN  
CURRENT DEVELOPERS ARE ROBERT BAUER, ICON DEVELOPMENT SOLUTIONS,  
AND ALISON BOECKMANN. IMPLEMENTATION, EFFICIENCY, AND STANDARDIZATION  
PERFORMED BY NOUS INFOSYSTEMS.

PROBLEM NO.: 1  
PHENOBARBITAL IV P:ROOT F:BASE

DATA CHECKOUT RUN: NO  
DATA SET LOCATED ON UNIT NO.: 2  
THIS UNIT TO BE REWOUND: NO  
NO. OF DATA RECS IN DATA SET: 744  
NO. OF DATA ITEMS IN DATA SET: 8  
ID DATA ITEM IS DATA ITEM NO.: 1  
DEP VARIABLE IS DATA ITEM NO.: 6  
MDV DATA ITEM IS DATA ITEM NO.: 7

INDICES PASSED TO SUBROUTINE PRED:  
8 2 3 0 0 0 0 0 0 0 0

LABELS FOR DATA ITEMS:  
ID TIME AMT BWT APGA DV MDV EVID

(NONBLANK) LABELS FOR PRED-DEFINED ITEMS:  
CL V K HALF IPRE IWRE

FORMAT FOR DATA:  
(8E6.0)

TOT. NO. OF OBS RECS: 155  
TOT. NO. OF INDIVIDUALS: 59

LENGTH OF THETA: 4

DEFAULT THETA BOUNDARY TEST OMITTED: YES

OMEGA HAS BLOCK FORM:  
1  
1 1

DEFAULT OMEGA BOUNDARY TEST OMITTED: YES

SIGMA HAS SIMPLE DIAGONAL FORM WITH DIMENSION: 1

DEFAULT SIGMA BOUNDARY TEST OMITTED: YES

INITIAL ESTIMATE OF THETA:  
LOWER BOUND INITIAL EST UPPER BOUND  
0.0000E+00 0.1000E-01 0.1000E+07  
0.0000E+00 0.1000E+01 0.1000E+07  
0.0000E+00 0.1000E+01 0.1000E+07  
0.0000E+00 0.1000E+00 0.1000E+07

INITIAL ESTIMATE OF OMEGA:

BLOCK SET NO.	BLOCK	FIXED
1		NO
	0.2000E+00	
	0.1000E+00 0.2000E+00	

INITIAL ESTIMATE OF SIGMA:

0.1000E+01

SIGMA CONSTRAINED TO BE THIS INITIAL ESTIMATE

COVARIANCE STEP OMITTED: NO  
EIGENVLS. PRINTED: NO  
SPECIAL COMPUTATION: NO  
COMPRESSED FORMAT: NO  
GRADIENT METHOD USED: NOSLOW  
SIGDIGITS ETAHAT (SIGLO): -1  
SIGDIGITS GRADIENTS (SIGL): -1  
EXCLUDE COV FOR FOCE (NOFCOV): NO  
TURN OFF Cholesky Transposition of R Matrix (CHOLROFF): NO  
KNUTHSUMOFF: -1  
RESUME COV ANALYSIS (RESUME): NO  
SIR SAMPLE SIZE (SIRSAMPLE): -1  
NON-LINEARLY TRANSFORM THETAS DURING COV (THBND): 1  
PRECONDITIONING CYCLES (PRECOND): 0  
PRECONDITIONING TYPES (PRECONDS): TOS

FORCED PRECONDITIONING CYCLES (PFCOND):0  
PRECONDITIONING TYPE (PRETYPE): 0  
FORCED POS. DEFINITE SETTING: (FPOSDEF):0

TABLES STEP OMITTED: NO  
NO. OF TABLES: 4  
SEED NUMBER (SEED): 11456  
RANMETHOD: 3U  
MC SAMPLES (ESAMPLE): 300  
WRES SQUARE ROOT TYPE (WRESCHOL): EIGENVALUE

-- TABLE 1 --

RECORDS ONLY: ALL

4 COLUMNS APPENDED: YES  
PRINTED: NO  
HEADER: YES  
FILE TO BE FORWARDED: NO  
FORMAT: S1PE11.4  
LFORMAT:  
RFORMAT:  
FIXED\_EFFECT\_ETAS:

USER-CHOSEN ITEMS:  
ID TIME MDV IPRE IWRE CWRES

-- TABLE 2 --

RECORDS ONLY: ALL

4 COLUMNS APPENDED: NO  
PRINTED: NO  
HEADER: YES  
FILE TO BE FORWARDED: NO  
FORMAT: S1PE11.4  
LFORMAT:  
RFORMAT:  
FIXED\_EFFECT\_ETAS:

USER-CHOSEN ITEMS:  
ID CL V K HALF ETA1 ETA2

-- TABLE 3 --

RECORDS ONLY: ALL

4 COLUMNS APPENDED: NO  
PRINTED: NO  
HEADER: YES  
FILE TO BE FORWARDED: NO  
FORMAT: S1PE11.4  
LFORMAT:  
RFORMAT:  
FIXED\_EFFECT\_ETAS:

USER-CHOSEN ITEMS:  
ID BWT APGA

-- TABLE 4 --

RECORDS ONLY: ALL

4 COLUMNS APPENDED: NO  
PRINTED: NO  
HEADER: YES  
FILE TO BE FORWARDED: NO  
FORMAT: S1PE11.4  
LFORMAT:  
RFORMAT:  
FIXED\_EFFECT\_ETAS:

USER-CHOSEN ITEMS:  
ID APGA  
DOUBLE PRECISION PREDPP VERSION 7.4.1

ONE COMPARTMENT MODEL (ADVAN1)

MAXIMUM NO. OF BASIC PK PARAMETERS: 2

BASIC PK PARAMETERS (AFTER TRANSLATION):  
ELIMINATION RATE (K) IS BASIC PK PARAMETER NO.: 1

TRANSLATOR WILL CONVERT PARAMETERS  
CLEARANCE (CL) AND VOLUME (V) TO K (TRANS2)

COMPARTMENT ATTRIBUTES						
COMPT. NO.	FUNCTION	INITIAL STATUS	ON/OFF ALLOWED	DOSE ALLOWED	DEFAULT FOR DOSE	DEFAULT FOR OBS.
1	CENTRAL	ON	NO	YES	YES	YES
2	OUTPUT	OFF	YES	NO	NO	NO

ADDITIONAL PK PARAMETERS - ASSIGNMENT OF ROWS IN GG						
COMPT. NO.	INDICES					
	SCALE	BIOAVAIL. FRACTION	ZERO-ORDER RATE	ZERO-ORDER DURATION	ABSORB LAG	
1	3	*	*	*	*	
2	*	-	-	-	-	
- PARAMETER IS NOT ALLOWED FOR THIS MODEL						
* PARAMETER IS NOT SUPPLIED BY PK SUBROUTINE;						
WILL DEFAULT TO ONE IF APPLICABLE						

DATA ITEM INDICES USED BY PRED ARE:  
EVENT ID DATA ITEM IS DATA ITEM NO.: 8  
TIME DATA ITEM IS DATA ITEM NO.: 2  
DOSE AMOUNT DATA ITEM IS DATA ITEM NO.: 3

PK SUBROUTINE CALLED WITH EVERY EVENT RECORD.  
PK SUBROUTINE NOT CALLED AT NONEVENT (ADDITIONAL OR LAGGED) DOSE TIMES.

ERROR SUBROUTINE CALLED WITH EVERY EVENT RECORD.

#TBLN: 1  
#METH: First Order Conditional Estimation with Interaction

ESTIMATION STEP OMITTED: NO  
ANALYSIS TYPE: POPULATION  
NUMBER OF SADDLE POINT RESET ITERATIONS: 0  
GRADIENT METHOD USED: NOSLOW  
CONDITIONAL ESTIMATES USED: YES  
CENTERED ETA: NO  
EPS-ETA INTERACTION: YES  
LAPLACIAN OBJ. FUNC.: NO  
NO. OF FUNCT. EVALS. ALLOWED: 9999  
NO. OF SIG. FIGURES REQUIRED: 3  
INTERMEDIATE PRINTOUT: YES  
ESTIMATE OUTPUT TO MSF: YES  
ABORT WITH PRED EXIT CODE 1: NO  
IND. OBJ. FUNC. VALUES SORTED: NO  
NUMERICAL DERIVATIVE  
FILE REQUEST (NUMBER): NONE  
MAP (ETAHAT) ESTIMATION METHOD (OPTMAP): 0  
ETA HESSIAN EVALUATION METHOD (ETADER): 0  
INITIAL ETA FOR MAP ESTIMATION (MCETA): 0  
SIGDIGITS FOR MAP ESTIMATION (SIGLO): 100  
GRADIENT SIGDIGITS OF  
FIXED EFFECTS PARAMETERS (SIGL): 100  
NOPRIOR SETTING (NOPRIOR): OFF  
NOCOV SETTING (NOCOV): OFF  
DERCONT SETTING (DERCONT): OFF  
FINAL ETA RE-EVALUATION (FNLETA): ON  
EXCLUDE NON-INFLUENTIAL (NON-INFL.) ETAS  
IN SHRINKAGE (ETATYPE): NO  
NON-INFL. ETA CORRECTION (NONINFETA): OFF  
RAW OUTPUT FILE (FILE): 2005.ext  
EXCLUDE TITLE (NOTITLE): NO  
EXCLUDE COLUMN LABELS (NOLABEL): NO  
FORMAT FOR ADDITIONAL FILES (FORMAT): S1PE12.5  
PARAMETER ORDER FOR OUTPUTS (ORDER): TSOL  
WISHART PRIOR DF INTERPRETATION (WISHTYPE): 0  
KNUTHSUMOFF: 0  
INCLUDE LNTWOPI: NO  
INCLUDE CONSTANT TERM TO PRIOR (PRIORC): NO  
INCLUDE CONSTANT TERM TO OMEGA (ETA) (OLNTWOPI): NO  
ADDITIONAL CONVERGENCE TEST (CTYPE=4)? : NO  
EM OR BAYESIAN METHOD USED: NONE

THE FOLLOWING LABELS ARE EQUIVALENT

PRED=PREDI  
RES=RESI  
WRES=WRESI  
IWSR=IWRESI  
IPRD=IPREDI  
IRS=IRESI

MONITORING OF SEARCH:

ITERATION NO.: 0 OBJECTIVE VALUE: 816.766780836366 NO. OF FUNC. EVALS.: 6  
CUMULATIVE NO. OF FUNC. EVALS.: 6  
NPARAMETR: 1.0000E-02 1.0000E+00 1.0000E+00 1.0000E-01 2.0000E-01 1.0000E-01 2.0000E-01  
PARAMETER: 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01 1.0000E-01  
GRADIENT: 2.4981E+02 -2.8823E+02 -1.2480E+01 -4.3411E+01 -6.8937E+01 1.7895E+02 -6.6195E+01

ITERATION NO.: 5 OBJECTIVE VALUE: 711.060586376867 NO. OF FUNC. EVALS.: 36  
CUMULATIVE NO. OF FUNC. EVALS.: 42  
NPARAMETR: 5.7830E-03 1.2408E+00 1.0885E+00 1.0361E-01 3.1108E-01 3.0060E-01 3.7372E-01  
PARAMETER: -4.4767E-01 3.1572E-01 1.8480E-01 1.3549E-01 3.2087E-01 2.4103E-01 -1.9434E-01  
GRADIENT: -1.3738E+01 -2.8376E+01 -8.2527E-01 8.9304E+00 -3.8046E+00 1.6895E+02 2.6953E+01

ITERATION NO.: 10 OBJECTIVE VALUE: 691.131417646534 NO. OF FUNC. EVALS.: 41  
CUMULATIVE NO. OF FUNC. EVALS.: 83  
NPARAMETR: 6.4184E-03 1.4135E+00 1.5510E+00 8.7660E-02 2.5957E-01 1.7183E-01 1.5939E-01  
PARAMETER: -3.4342E-01 4.4607E-01 5.3889E-01 -3.1705E-02 2.3036E-01 1.5083E-01 -4.9500E-01  
GRADIENT: -1.2992E+01 1.4579E+01 -5.6559E-01 4.0019E+00 3.8721E+00 -5.4048E+01 1.2411E+01

ITERATION NO.: 15 OBJECTIVE VALUE: 685.704738210397 NO. OF FUNC. EVALS.: 35  
CUMULATIVE NO. OF FUNC. EVALS.: 118  
NPARAMETR: 6.7077E-03 1.3923E+00 2.1541E+00 7.0195E-02 2.4720E-01 1.9228E-01 1.5709E-01  
PARAMETER: -2.9933E-01 4.3097E-01 8.6738E-01 -2.5390E-01 2.0594E-01 1.7295E-01 -1.3957E+00  
GRADIENT: 1.1456E+00 -4.9066E+00 2.2781E+00 1.9320E+00 -2.5448E+00 9.6489E+00 7.0085E-01

ITERATION NO.: 20 OBJECTIVE VALUE: 685.540731915364 NO. OF FUNC. EVALS.: 37  
CUMULATIVE NO. OF FUNC. EVALS.: 155  
NPARAMETR: 6.7378E-03 1.3990E+00 2.2549E+00 6.4481E-02 2.5411E-01 1.9624E-01 1.5548E-01  
PARAMETER: -2.9485E-01 4.3576E-01 9.1311E-01 -3.3880E-01 2.1972E-01 1.7410E-01 -1.7213E+00  
GRADIENT: 1.6232E-01 -2.9880E-01 1.3122E-01 -6.5885E-02 -3.3396E-02 3.0320E-01 7.5507E-02

ITERATION NO.: 25 OBJECTIVE VALUE: 685.535279891691 NO. OF FUNC. EVALS.: 38  
CUMULATIVE NO. OF FUNC. EVALS.: 193  
NPARAMETR: 6.7408E-03 1.3992E+00 2.2728E+00 6.4135E-02 2.5384E-01 1.9655E-01 1.5510E-01  
PARAMETER: -2.9441E-01 4.3588E-01 9.2101E-01 -3.4418E-01 2.1920E-01 1.7447E-01 -1.8714E+00  
GRADIENT: 5.0171E-03 -2.9098E-02 9.3757E-02 1.0926E-02 -8.4871E-03 9.9333E-02 1.7816E-03

ITERATION NO.: 29 OBJECTIVE VALUE: 685.525192050602 NO. OF FUNC. EVALS.: 52  
CUMULATIVE NO. OF FUNC. EVALS.: 245  
NPARAMETR: 6.7834E-03 1.4066E+00 2.2768E+00 6.4010E-02 2.5381E-01 1.9657E-01 1.5507E-01  
PARAMETER: -2.8811E-01 4.4120E-01 9.2279E-01 -3.4613E-01 2.1914E-01 1.7449E-01 -1.8864E+00  
GRADIENT: 3.6549E-02 -4.1369E-02 -2.6860E-03 -1.4247E-03 -9.3274E-04 1.1162E-01 1.7977E-04

#TERM:

MINIMIZATION SUCCESSFUL  
NO. OF FUNCTION EVALUATIONS USED: 245  
NO. OF SIG. DIGITS IN FINAL EST.: 3.6

ETABAR IS THE ARITHMETIC MEAN OF THE ETA-ESTIMATES,  
AND THE P-VALUE IS GIVEN FOR THE NULL HYPOTHESIS THAT THE TRUE MEAN IS 0.

ETABAR: -4.6538E-03 -3.9029E-03  
SE: 6.4054E-02 5.0241E-02  
N: 59 59  
P VAL.: 9.4208E-01 9.3808E-01

ETASHRINKSD(%) 1.5020E+00 1.1579E+00  
ETASHRINKVR(%) 2.9815E+00 2.3023E+00  
EBVSHRINKSD(%) 2.2370E+00 1.8965E+00  
EBVSHRINKVR(%) 4.4239E+00 3.7570E+00

EPSSHRINKSD(%) 2.1211E+01  
EPSSHRINKVR(%) 3.7922E+01

TOTAL DATA POINTS NORMALLY DISTRIBUTED (N): 155  
N\*LOG(2PI) CONSTANT TO OBJECTIVE FUNCTION: 284.87094529344853  
OBJECTIVE FUNCTION VALUE WITHOUT CONSTANT: 685.52519205060185  
OBJECTIVE FUNCTION VALUE WITH CONSTANT: 970.39613734405043  
REPORTED OBJECTIVE FUNCTION DOES NOT CONTAIN CONSTANT

TOTAL EFFECTIVE ETAS (NIND\*NETA): 118

#TERE:  
Elapsed estimation time in seconds: 1.07  
Elapsed covariance time in seconds: 0.39  
Elapsed postprocess time in seconds: 0.02

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\*\*\*\*\*  
\*\*\*\*\* FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION \*\*\*\*\*  
#OBJT:\*\*\*\*\* MINIMUM VALUE OF OBJECTIVE FUNCTION \*\*\*\*\*  
\*\*\*\*\*  
\*\*\*\*\*

#OBJV:\*\*\*\*\* 685.525 \*\*\*\*\*

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\*\*\*\*\*  
\*\*\*\*\* FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION \*\*\*\*\*  
\*\*\*\*\* FINAL PARAMETER ESTIMATE \*\*\*\*\*  
\*\*\*\*\*  
\*\*\*\*\*

THETA - VECTOR OF FIXED EFFECTS PARAMETERS \*\*\*\*\*

TH 1	TH 2	TH 3	TH 4
6.78E-03	1.41E+00	2.28E+00	6.40E-02

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS \*\*\*\*\*

ETA1	ETA2
ETA1 2.54E-01	
ETA2 1.97E-01	1.55E-01

SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS \*\*\*\*

EPS1  
EPS1 1.00E+00

OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS \*\*\*\*\*

ETA1      ETA2  
ETA1 5.04E-01  
ETA2 9.91E-01 3.94E-01

SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS \*\*\*

EPS1  
EPS1 1.00E+00

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\*\*\*\*\*  
\*\*\*\*\* FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION \*\*\*\*\*  
\*\*\*\*\* STANDARD ERROR OF ESTIMATE \*\*\*\*\*  
\*\*\*\*\*  
\*\*\*\*\*

THETA - VECTOR OF FIXED EFFECTS PARAMETERS \*\*\*\*\*

TH 1      TH 2      TH 3      TH 4  
5.17E-04 7.47E-02 7.39E-01 3.13E-02

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS \*\*\*\*\*

ETA1      ETA2  
ETA1 7.61E-02  
ETA2 5.06E-02 3.98E-02

SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS \*\*\*\*

EPS1  
EPS1 .....

OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS \*\*\*\*\*

ETA1      ETA2  
ETA1 7.55E-02  
ETA2 4.96E-02 5.05E-02

SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS \*\*\*

EPS1

EPS1 .....

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*****
*****
***** FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION *****
***** COVARIANCE MATRIX OF ESTIMATE *****
*****
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	TH 1	TH 2	TH 3	TH 4	OM11	OM12	OM22	SG11
TH 1	2.67E-07							
TH 2	2.94E-05	5.59E-03						
TH 3	-7.35E-05	-2.70E-03	5.46E-01					
TH 4	2.22E-06	-1.35E-04	-2.02E-02	9.77E-04				
OM11	5.96E-06	2.82E-03	9.89E-03	-5.14E-04	5.79E-03			
OM12	9.34E-06	2.24E-03	4.19E-03	-2.21E-04	3.63E-03	2.56E-03		
OM22	1.18E-05	1.61E-03	-7.97E-03	2.84E-04	1.93E-03	1.66E-03	1.58E-03	
SG11	.....	.....	.....	.....	.....	.....	.....	.....

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*****
*****
***** FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION *****
***** CORRELATION MATRIX OF ESTIMATE *****
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	TH 1	TH 2	TH 3	TH 4	OM11	OM12	OM22	SG11
TH 1	5.17E-04							
TH 2	7.62E-01	7.47E-02						
TH 3	-1.92E-01	-4.89E-02	7.39E-01					
TH 4	1.38E-01	-5.76E-02	-8.76E-01	3.13E-02				
OM11	1.51E-01	4.97E-01	1.76E-01	-2.16E-01	7.61E-02			
OM12	3.57E-01	5.93E-01	1.12E-01	-1.40E-01	9.42E-01	5.06E-02		
OM22	5.74E-01	5.42E-01	-2.71E-01	2.28E-01	6.38E-01	8.26E-01	3.98E-02	
SG11	.....	.....	.....	.....	.....	.....	.....	.....

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*****
*****
***** FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION *****
***** INVERSE COVARIANCE MATRIX OF ESTIMATE *****
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*****
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	TH 1	TH 2	TH 3	TH 4	OM11	OM12	OM22	SG11
TH 1	1.90E+07							
TH 2	-1.04E+05	9.04E+02						
TH 3	-3.19E+03	3.80E+01	1.20E+01					
TH 4	-2.21E+04	4.19E+02	1.84E+02	4.83E+03				
OM11	3.78E+04	2.28E+02	1.06E+02	6.71E+02	5.28E+03			

OM12    1.02E+05 -1.77E+03 -3.13E+02 -1.45E+03 -1.16E+04  2.94E+04  
OM22    -2.01E+05  1.55E+03  2.12E+02  5.00E+02  5.61E+03 -1.70E+04  1.26E+04  
SG11    .....  
Elapsed finaloutput time in seconds:        0.34  
#CPUT: Total CPU Time in Seconds,        1.872