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NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) DOUBLE PRECISION NONMEM VERSION VI LEVEL 2.0
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DEVELOPED AND PROGRAMMED BY STUART BEAL AND LEWIS SHEINER

PROBLEM NO.: 1

THEOPHYLLINE ORAL 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: 144

NO. OF DATA ITEMS IN DATA SET: 8

ID DATA ITEM IS DATA ITEM NO.: 1

DEP VARIABLE IS DATA ITEM NO.: 5

MDV DATA ITEM IS DATA ITEM NO.: 6

INDICES PASSED TO SUBROUTINE PRED:

8 4 2 0 0 0 0 0 0

0 0

LABELS FOR DATA ITEMS:

ID AMT DOSE TIME DV MDV BWT EVID

(NONBLANK) LABELS FOR PRED-DEFINED ITEMS:

CL V KA K IPRE IWRE G11 G21 G31

FORMAT FOR DATA: (7E6.0,1F2.0)

TOT. NO. OF OBS RECS: 132
TOT. NO. OF INDIVIDUALS: 12

LENGTH OF THETA: 5

DEFAULT THETA BOUNDARY TEST OMITTED: YES

OMEGA HAS BLOCK FORM:

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+07 0.0000E+00 0.1000E+07 0.0000E+00 0.1000E+01 0.1000E+07 0.0000E+00 0.5000E+00 0.1000E+07

INITIAL ESTIMATE OF OMEGA:

BLOCK SET NO. BLOCK FIXED 1 NO

0.2000E+00

0.1000E+00 0.2000E+00

0.1000E+00 0.1000E+00 0.2000E+00

INITIAL ESTIMATE OF SIGMA:

0.1000E+01

SIGMA CONSTRAINED TO BE THIS INITIAL ESTIMATE

ESTIMATION STEP OMITTED: NO CONDITIONAL ESTIMATES USED: YES CENTERED ETA: NO EPS-ETA INTERACTION: YES LAPLACIAN OBJ. FUNC.: NO 9999 NO. OF FUNCT. EVALS. ALLOWED: NO. OF SIG. FIGURES REQUIRED: 3 INTERMEDIATE PRINTOUT: YES ESTIMATE OUTPUT TO MSF: ABORT WITH PRED EXIT CODE 1: MO IND. OBJ. FUNC. VALUES SORTED: NO

COVARIANCE STEP OMITTED: NO

R MATRIX PRINTED: S MATRIX PRINTED: YES EIGENVLS. PRINTED: YES SPECIAL COMPUTATION: COMPRESSED FORMAT: NO TABLES STEP OMITTED: NO NO. OF TABLES: 6 -- TABLE 1 --PRINTED: NO HEADER: YES FILE TO BE FORWARDED: NO USER-CHOSEN ITEMS IN THE ORDER THEY WILL APPEAR IN THE TABLE: ID TIME MDV IPRE IWRE G11 G21 G31 н11 -- TABLE 2 --4 COLUMNS APPENDED: NO HEADER: YES FILE TO BE FORWARDED: NO USER-CHOSEN ITEMS IN THE ORDER THEY WILL APPEAR IN THE TABLE: V CL KA K ETA1 ETA2 ETA3 -- TABLE 3 --4 COLUMNS APPENDED: NO PRINTED: NO FILE TO BE FORWARDED: NO USER-CHOSEN ITEMS IN THE ORDER THEY WILL APPEAR IN THE TABLE: ID BWT -- TABLE 4 --4 COLUMNS APPENDED: PRINTED: NO HEADER: YES FILE TO BE FORWARDED: NO USER-CHOSEN ITEMS IN THE ORDER THEY WILL APPEAR IN THE TABLE: ID -- TABLE 5 --FIRST RECORDS ONLY: YES 4 COLUMNS APPENDED: NO PRINTED: NO HEADER: YES FILE TO BE FORWARDED: NO USER-CHOSEN ITEMS IN THE ORDER THEY WILL APPEAR IN THE TABLE: BWT ETA1 ETA2 -- TABLE 6 --FIRST RECORDS ONLY: YES 4 COLUMNS APPENDED: NO PRINTED: NO HEADER: YES FILE TO BE FORWARDED: NO USER-CHOSEN ITEMS IN THE ORDER THEY WILL APPEAR IN THE TABLE: ID CL K V KA

ONE COMPARTMENT MODEL WITH FIRST-ORDER ABSORPTION (ADVAN2)

DOUBLE PRECISION PREDPP VERSION V LEVEL 2.0

BASIC PK PARAMETERS (AFTER TRANSLATION):

ELIMINATION RATE (K) IS BASIC PK PARAMETER NO.: 1 ABSORPTION RATE (KA) IS BASIC PK PARAMETER NO.: 3

TRANSLATOR WILL CONVERT PARAMETERS

CLEARANCE (CL) AND VOLUME (V) TO K (TRANS2)

COMPARTMENT ATTRIBUTES

| COMPT. NO. | FUNCTION | INITIAL | ON/OFF | DOSE | DEFAULT | DEFAULT |
|------------|----------|---------|---------|---------|----------|---------|
| | | STATUS | ALLOWED | ALLOWED | FOR DOSE | FOR OBS |
| 1 | DEPOT | OFF | YES | YES | YES | NO |
| 2 | CENTRAL | ON | NO | YES | NO | YES |
| 3 | OUTPUT | OFF | YES | NO | NO | NO |

ADDITIONAL PK PARAMETERS - ASSIGNMENT OF ROWS IN GG INDICES

COMPT. NO.

1 2

3

SCALE BIOAVAIL. ZERO-ORDER ZERO-ORDER ABSORB FRACTION RATE DURATION LAG 4

- 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.: 4 DOSE AMOUNT DATA ITEM IS DATA ITEM NO.: 2

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.

MONITORING OF SEARCH:

ITERATION NO.: 0 OBJECTIVE VALUE: 0.11716E+04 NO. OF FUNC. EVALS.: 7

CUMULATIVE NO. OF FUNC. EVALS.:

PARAMETER: 0.1000E+00 0.1000E+00

GRADIENT: -0.2546E+03 -0.5245E+02 -0.2309E+01 0.2170E+02 -0.2264E+03 -0.5762E+03 -0.6262E+03 -0.2617E+02 -0.6178E+02 -0.4997E+00 -0.3231E-01

NUMSIGDIG: 0.0000E+00 0.0000E+00

ITERATION NO.: 5 OBJECTIVE VALUE: 0.30570E+03 NO. OF FUNC. EVALS.:10

CUMULATIVE NO. OF FUNC. EVALS.: 51

PARAMETER: 0.1444E+01 0.5708E+00 -0.3166E+00 -0.8717E+00 0.5773E-01 0.1973E+01 0.2118E+01 -0.6763E+00 0.2080E+00 0.8985E-01 0.9005E-01

GRADIENT: -0.1533E+02 0.1095E+02 0.1473E+02 0.2083E+02 0.1253E+03 -0.2710E+02 0.2473E+02 0.2038E+02 0.6009E+01 0.2063E+01 -0.3844E+01

NUMSIGDIG: -0.1521E+01 -0.1377E+01 -0.1143E+01 -0.9149E+00 -0.1806E+01 -0.1650E+01 -0.7014E+00 -0.1148E+01 -0.9639E+00 -0.1259E+01 -0.1548E+01

ITERATION NO.: 10 OBJECTIVE VALUE: 0.25480E+03 NO. OF FUNC. EVALS.: 8

CUMULATIVE NO. OF FUNC. EVALS.: 94

PARAMETER: 0.3253E+01 0.3723E+01 -0.5266E+00 -0.1054E+01 -0.2619E+00 0.1732E+01 0.1184E+01 -0.1286E+01 -0.1821E+01 -0.1167E+00

0.1151E+01

GRADIENT: -0.5684E+02 0.6931E+02 0.1598E+02 0.1513E+02 0.1044E+03 -0.5436E+01 0.2423E+02 -0.3980E+00 0.4970E-01 -0.1349E+01

-0.5601E+01

NUMSIGDIG: 0.6527E-01 -0.1227E+00 -0.5265E+00 -0.8409E+00 0.4583E+00 0.6177E+00 0.8016E-01 0.1363E+01 -0.1628E+00 0.6163E+00

-0.5029E+00

ITERATION NO.: 15 OBJECTIVE VALUE: 0.15931E+03 NO. OF FUNC. EVALS.: 8

CUMULATIVE NO. OF FUNC. EVALS.: 137

PARAMETER: 0.3935E+01 0.3810E+01 -0.1775E+01 -0.1276E+01 -0.8842E+00 0.9476E+00 0.2569E+00 -0.5717E+00 -0.4085E+00 -0.1121E+01

0.1872E+00

GRADIENT: 0.1901E+02 0.1877E+02 0.8663E+01 0.4810E+01 0.4959E+02 0.1858E+02 -0.4277E+02 -0.1636E+02 0.1507E+02 -0.9892E+00

-0.2897E+01

NUMSIGDIG: 0.9527E+00 0.7783E+00 0.2090E+00 0.8978E+00 0.5691E+00 0.7194E+00 -0.4490E-01 0.1659E+00 -0.3729E+00 0.6628E+00

-0.4239E+00

ITERATION NO.: 20 OBJECTIVE VALUE: 0.12623E+03 NO. OF FUNC. EVALS.: 8

CUMULATIVE NO. OF FUNC. EVALS.: 179

PARAMETER: 0.3223E+01 0.3497E+01 -0.1820E+01 -0.1099E+01 -0.1272E+01 0.1087E+01 0.1924E+00 -0.7811E-01 -0.2603E+01 0.2105E+00

0.9973E+00

GRADIENT: 0.1226E+02 -0.1678E+02 0.1410E+00 -0.3031E+01 -0.6573E+01 0.2910E+02 -0.3933E+02 -0.3774E+01 -0.1376E+01 0.2015E+01

0.1320E+02

NUMSIGDIG: 0.1093E+01 0.1551E+01 0.1353E+01 0.1379E+01 0.1255E+01 0.1952E+01 0.1265E+01 -0.1836E+00 0.4664E+00 -0.7539E+00

-0.3636E+00

ITERATION NO.: 25 OBJECTIVE VALUE: 0.11274E+03 NO. OF FUNC. EVALS.:10

CUMULATIVE NO. OF FUNC. EVALS.: 224

PARAMETER: 0.3298E+01 0.3510E+01 -0.1872E+01 -0.1071E+01 -0.1263E+01 0.8405E+00 0.1859E+00 0.3486E+00 -0.1678E+01 0.4165E+00

0.3384E-01

GRADIENT: 0.9005E+01 -0.1562E+02 0.7189E+01 0.1386E+01 0.3224E+01 0.2162E+02 -0.8114E+01 0.3447E+01 0.4259E+00 -0.8391E+00

-0.1625E+00

NUMSIGDIG: 0.1544E+01 0.2382E+01 0.2355E+01 0.2795E+01 0.1898E+01 0.1062E+01 0.1007E+01 0.1319E+01 0.5984E+00 0.5316E+00

0.9974E-01

ITERATION NO.: 30 OBJECTIVE VALUE: 0.98442E+02 NO. OF FUNC. EVALS.: 8

CUMULATIVE NO. OF FUNC. EVALS.: 265

PARAMETER: 0.3489E+01 0.3568E+01 -0.1850E+01 -0.7274E+00 -0.1524E+01 -0.1064E+00 0.7151E-01 0.6274E-01 -0.2228E+01 0.3981E+00

0.4305E-01

GRADIENT: 0.3594E+02 -0.4106E+02 0.1230E+01 0.4437E+00 -0.6408E+01 0.9922E+01 0.1986E+02 -0.1116E+02 -0.2319E+01 0.3965E+01

0.1710E+01

NUMSIGDIG: 0.2513E+01 0.2383E+01 0.1456E+01 0.1464E+01 0.1318E+01 -0.3279E+00 0.6856E+00 0.8252E-01 0.8574E+00 0.8335E+00

0.8318E+00

ITERATION NO.: 35 OBJECTIVE VALUE: 0.93790E+02 NO. OF FUNC. EVALS.: 9

CUMULATIVE NO. OF FUNC. EVALS.: 306

PARAMETER: 0.3399E+01 0.3554E+01 -0.1878E+01 -0.9800E+00 -0.1297E+01 -0.3933E+00 0.6089E-01 0.8888E-01 -0.2008E+01 0.3785E+00

-0.1390E+00

GRADIENT: -0.2897E+01 0.6730E+01 -0.1368E+01 0.3905E+01 0.2252E+01 0.1668E+01 0.2126E+02 -0.5453E+01 -0.2711E+00 -0.6166E+01

-0.7195E+00

NUMSIGDIG: 0.3088E+01 0.4392E+01 0.1648E+01 0.6645E+00 0.9725E+00 0.1092E+01 0.2648E+01 0.6298E+00 0.1056E+01 0.1916E+01

0.5763E+00

ITERATION NO.: 40 OBJECTIVE VALUE: 0.93182E+02 NO. OF FUNC. EVALS.: 8

CUMULATIVE NO. OF FUNC. EVALS.: 346

PARAMETER: 0.3408E+01 0.3554E+01 -0.1879E+01 -0.1137E+01 -0.1242E+01 -0.4622E+00 0.5702E-01 0.9440E-01 -0.1863E+01 0.4361E+00

-0.2170E+00

GRADIENT: 0.9969E+00 -0.1574E+01 0.6634E-02 0.1234E+00 0.5947E+00 -0.2192E+00 0.2820E+01 0.3847E-01 -0.2601E+00 -0.1310E+00

-0.6119E-01

NUMSIGDIG: 0.4075E+01 0.3880E+01 0.2976E+01 0.2632E+01 0.2737E+01 0.2602E+01 0.2613E+01 0.1724E+01 0.1958E+01 0.2387E+01

0.1668E+01

ITERATION NO.: 45 OBJECTIVE VALUE: 0.92862E+02 NO. OF FUNC. EVALS.:13

CUMULATIVE NO. OF FUNC. EVALS.: 414

PARAMETER: 0.3446E+01 0.3579E+01 -0.1805E+01 -0.1133E+01 -0.1244E+01 -0.4705E+00 0.5600E-01 0.8769E-01 -0.1838E+01 0.4395E+00

-0.2054E+00

GRADIENT: 0.1279E+01 -0.1171E+01 -0.2422E-01 0.3515E-01 -0.1231E+00 -0.2251E+00 0.5691E+01 -0.8994E+00 -0.7296E-01 0.7424E-01

-0.9706E-01

NUMSIGDIG: 0.2866E+01 0.3245E+01 0.3323E+01 0.2100E+01 0.2564E+01 0.1650E+01 0.1797E+01 0.1179E+01 0.1727E+01 0.1932E+01

0.1644E+01

ITERATION NO.: 50 OBJECTIVE VALUE: 0.92833E+02 NO. OF FUNC. EVALS.:13

CUMULATIVE NO. OF FUNC. EVALS.: 482

PARAMETER: 0.3443E+01 0.3580E+01 -0.1800E+01 -0.1146E+01 -0.1242E+01 -0.4696E+00 0.5533E-01 0.8823E-01 -0.1729E+01 0.4060E+00

0.6727E-01

GRADIENT: -0.4029E+00 0.5767E+00 0.1020E+00 -0.2998E-02 0.1001E+00 0.2231E+00 -0.4178E+01 0.2014E+00 -0.1038E-01 0.3396E+00

GRADIENT: -0.4029E+00 0.4530E-01

NUMSIGDIG: 0.3827E+01 0.4215E+01 0.3267E+01 0.2931E+01 0.5732E+01 0.2161E+01 0.2715E+01 0.2157E+01 0.3043E+01 0.1897E+01

0.7644E+00

ITERATION NO.: 55 OBJECTIVE VALUE: 0.92831E+02 NO. OF FUNC. EVALS.:13

CUMULATIVE NO. OF FUNC. EVALS.: 549

PARAMETER: 0.3444E+01 0.3580E+01 -0.1803E+01 -0.1145E+01 -0.1243E+01 -0.4713E+00 0.5574E-01 0.8928E-01 -0.1730E+01 0.3993E+00 0.8402E-01

GRADIENT: 0.3004E-02 -0.9087E-02 0.9709E-03 0.3069E-03 0.1028E-02 -0.1124E-02 0.1177E-01 -0.1328E-02 -0.1388E-03 0.1311E-02

-0.3115E-03

NUMSIGDIG: 0.6464E+01 0.5608E+01 0.5300E+01 0.4516E+01 0.5566E+01 0.4164E+01 0.4699E+01 0.4924E+01 0.3677E+01 0.3490E+01

0.2513E+01

ITERATION NO.: 58 OBJECTIVE VALUE: 0.92831E+02 NO. OF FUNC. EVALS.:10

585

CUMULATIVE NO. OF FUNC. EVALS.: 585

PARAMETER: 0.3444E+01 0.3580E+01 -0.1803E+01 -0.1145E+01 -0.1243E+01 -0.4712E+00 0.5574E-01 0.8929E-01 -0.1729E+01 0.3992E+00

0.8445E-01

GRADIENT: 0.9893E-05 0.2714E-05 0.4942E-05 0.8275E-05 0.3945E-04 0.2272E-05 -0.9890E-04 0.1341E-04 0.3307E-04 -0.9278E-04

-0.3285E-04

NUMSIGDIG: 0.7558E+01 0.8077E+01 0.7615E+01 0.6765E+01 0.6745E+01 0.6834E+01 0.6376E+01 0.5781E+01 0.5513E+01 0.6502E+01

0.5384E+01

MINIMIZATION SUCCESSFUL

NO. OF FUNCTION EVALUATIONS USED:

NO. OF SIG. DIGITS IN FINAL EST.: 5.4

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: -0.73E-03 -0.22E-02 -0.12E-01

SE: 0.70E-01 0.38E-01 0.18E+00

P VAL.: 0.99E+00 0.95E+00 0.95E+00

| ******* | | | | ****** |
|------------|---------------|----------------|----------|--------|
| ******* | MINIMUM VALUE | OF OBJECTIVE F | FUNCTION | ****** |
| ******* | | | | ****** |
| ********** | ****** | ****** | ****** | ****** |
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| ********* | ******* 92 | .831 ***** | ****** | ****** |
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| ********** | ****** | ***** | ****** | ****** |
| ****** | | | | ***** |
| ****** | FINAL P | ARAMETER ESTIM | MATE | ****** |
| ******* | | | | ***** |
| ********** | | | | |

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

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

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

ETA1 ETA2 ETA3

5.04E-02 5.69E-02 4.35E-01

TH 1 TH 2 TH 3 TH 4 TH 5

2.83E+00 3.24E+01 1.49E+00 2.88E-01 1.31E-01

EPS1

6.38E-02

3.15E-02 1.94E-02

ETA1

ETA2 ETA3

EPS1 1.00E+00

| ******* | ********** ************ *********** | | | | STANDARI | ERROR OF | ESTIMATE | | | ****** ****** | ********** ********* | ** |
|---|--|---|--|--|--|---|---|--|---|---|---|-----------------------|
| | | | | | | | | | | | | • • • |
| | | | | | | | | | | | | |
| THETA - V | VECTOR OF FI | XED EFF | ECTS PARAM | METERS ** | ***** | | | | | | | |
| | TH 1 | TH 2 | TH 3 | TH 4 | TH 5 | | | | | | | |
| 2 | 2.20E-01 1. | 69E+00 | 3.02E-01 | 2.07E-01 | 4.64E-02 | | | | | | | |
| | | | | | | | | | | | | |
| OMEGA - C | COV MATRIX F | UNVE AU | OM FEFFCTS | S - FTAS * | ***** | | | | | | | |
| OMEGA - C | COV MAIRIA P | OK KAND | OM EFFECT. | J - EIRD | | | | | | | | |
| | ETA1 | ETA2 | ETA3 | | | | | | | | | |
| ETA1 2 | 2.95E-02 | | | | | | | | | | | |
| ETA2 8 | 8.74E-03 8. | 62E-03 | | | | | | | | | | |
| ETA3 3 | 3.99E-02 3. | 60E-02 | 2.23E-01 | | | | | | | | | |
| | | | | | | | | | | | | |
| SIGMA - C | COV MATRIX F | OR RAND | OM EFFECTS | S - EPSILON | IS **** | | | | | | | |
| | | | | | | | | | | | | |
| | EPS1 | | | | | | | | | | | |
| EPS1 | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| ****** | *********** ************** | | ****** | | | MATRIX OF | | ***** | ***** | ***** | ****** | ** |
| ****** | ****** | | | C | COVARIANCE | MATRIX OF | ESTIMATE | | | ****** ****** | ********* ******* | ** |
| ****** | *********** ******** | | | C | COVARIANCE | MATRIX OF | ESTIMATE | | | ****** ****** | ********* ******* | ** |
| ********* ********* ******** | *********************************** | ***** | ***** | C | COVARIANCE | MATRIX OF | ESTIMATE | ***** | ***** | ****** ****** ****** | ********** ********** ********* | ** |
| ********* ******** ********* TH 1 4 | *********** *********** ************ TH 1 | ***** TH 2 | ***** | C | COVARIANCE | MATRIX OF | ESTIMATE | ***** | ***** | ****** ****** ****** | ********** ********** ********* | ** |
| ********* ******** TH 1 4 TH 2 2 | *********** ********* ********* TH 1 4.82E-02 | ****** TH 2 | ******** TH 3 | C | COVARIANCE | MATRIX OF | ESTIMATE | ***** | ***** | ****** ****** ****** | ********** ********** ********* | ** |
| ********* ******** TH 1 4 TH 2 2 TH 3 1 | *********** ********* ********* TH 1 4.82E-02 2.92E-01 2. | ****** TH 2 85E+00 71E-01 | ************************************** | C************************************* | COVARIANCE | MATRIX OF | ESTIMATE | ***** | ***** | ****** ****** ****** | ********** ********** ********* | ** |
| ********* ******** TH 1 4 TH 2 2 TH 3 1 TH 4 -3 | *********** ********* ******* TH 1 4.82E-02 2.92E-01 2. 1.49E-02 2. | ****** TH 2 85E+00 71E-01 55E-01 | *********** TH 3 9.12E-02 -4.23E-03 | TH 4 | COVARIANCE | MATRIX OF | ESTIMATE | ***** | ***** | ****** ****** ****** | ********** ********** ********* | ** |
| ********* ******** TH 1 4 TH 2 2 TH 3 1 TH 4 -3 TH 5 5 | *********** ********* TH 1 4.82E-02 2.92E-01 2. 1.49E-02 2. 3.35E-02 -1. | ****** TH 2 85E+00 71E-01 55E-01 13E-02 | ********* TH 3 9.12E-02 -4.23E-03 -7.47E-04 | TH 4 4.27E-02 -8.56E-03 | COVARIANCE ********* TH 5 2.15E-03 | MATRIX OF | ESTIMATE | ***** | ***** | ****** ****** ****** | ********** ********** ********* | ** |
| ********** TH 1 4 TH 2 2 TH 3 1 TH 4 -3 TH 5 5 OM11 -4 | ********** ********* TH 1 4.82E-02 2.92E-01 2. 1.49E-02 2. 3.35E-02 -1. 5.83E-03 2. | ****** TH 2 85E+00 71E-01 55E-01 13E-02 06E-02 | ********* TH 3 9.12E-02 -4.23E-03 -7.47E-04 1.76E-04 | TH 4 4.27E-02 -8.56E-03 5.14E-03 | TH 5 2.15E-03 -1.03E-03 | MATRIX OF *********************************** | ESTIMATE *********** OM12 | ***** | ***** | ****** ****** ****** | ********** ********** ********* | ** |
| ********** ********* TH 1 4 TH 2 2 TH 3 1 TH 4 -3 TH 5 5 OM11 -4 OM12 -2 | *********** ********* TH 1 4.82E-02 2.92E-01 2. 1.49E-02 2. 3.35E-02 -1. 5.83E-03 2. 4.22E-03 -1. | ****** TH 2 85E+00 71E-01 55E-01 13E-02 06E-02 44E-04 | ********** TH 3 9.12E-02 -4.23E-03 -7.47E-04 1.76E-04 -1.89E-04 | TH 4 4.27E-02 -8.56E-03 5.14E-03 2.79E-04 | TH 5 2.15E-03 -1.03E-03 | MATRIX OF *********************************** | *********** OM12 7.64E-05 | ************************************** | ***** | ****** ****** ****** | ********** ********** ********* | ** |
| ********** ********* TH 1 4 TH 2 2 TH 3 1 TH 4 -3 TH 5 5 OM11 -4 OM12 -2 OM13 -3 | *********** ********** TH 1 4.82E-02 2.92E-01 2. 1.49E-02 2. 3.35E-02 -1. 5.83E-03 2. 4.22E-03 -1. 2.91E-04 6. | ******* TH 2 85E+00 71E-01 55E-01 13E-02 06E-02 44E-04 73E-03 | ********** TH 3 9.12E-02 -4.23E-03 -7.47E-04 1.76E-04 -1.89E-04 5.80E-03 | TH 4 4.27E-02 -8.56E-03 5.14E-03 2.79E-04 -1.94E-03 | 2.15E-03 -1.03E-03 -1.19E-04 3.88E-05 | MATRIX OF ********** OM11 8.71E-04 1.41E-04 -1.16E-04 | ********** OM12 7.64E-05 | *********** OM13 | ************************************** | ****** ****** ****** | ********** ********** ********* | ** |
| ********** TH 1 4 TH 2 2 TH 3 3 TH 4 -3 TH 5 5 OM11 -4 OM12 -2 OM13 -3 OM22 4 | *********** ********** TH 1 4.82E-02 2.92E-01 2. 1.49E-02 2. 3.35E-02 -1. 5.83E-03 2. 4.22E-03 -1. 2.91E-04 6. 3.96E-04 -2. | ******* TH 2 85E+00 71E-01 13E-02 06E-02 44E-04 73E-03 23E-04 | ********** TH 3 9.12E-02 -4.23E-03 -7.47E-04 1.76E-04 -1.89E-04 5.80E-03 -3.38E-04 | TH 4 4.27E-02 -8.56E-03 5.14E-03 2.79E-04 -1.94E-03 -5.44E-04 | 2.15E-03 -1.03E-03 -1.19E-04 3.88E-05 4.05E-05 | MATRIX OF ********** OM11 8.71E-04 1.41E-04 -1.16E-04 -4.94E-05 | *********** OM12 7.64E-05 9.44E-05 4.53E-05 | *********** OM13 1.59E-03 1.20E-04 | ************************************** | ****** ****** ******* OM23 | ********** ********** ********* | ** |
| *********** ********* TH 1 | *********** ********** TH 1 4.82E-02 2.92E-01 2. 1.49E-02 2. 3.35E-02 -1. 5.83E-03 2. 4.22E-03 -1. 2.91E-04 6. 3.96E-04 -2. 4.52E-04 -2. | ******* TH 2 85E+00 71E-01 55E-01 13E-02 06E-02 44E-04 73E-03 23E-04 16E-03 | ********** TH 3 9.12E-02 -4.23E-03 -7.47E-04 1.76E-04 -1.89E-04 5.80E-03 -3.38E-04 5.55E-03 | TH 4 4.27E-02 -8.56E-03 5.14E-03 2.79E-04 -1.94E-03 -5.44E-04 -6.16E-04 | 2.15E-03 -1.03E-03 -1.19E-04 3.88E-05 4.05E-05 | MATRIX OF ********** OM11 8.71E-04 1.41E-04 -1.16E-04 -4.94E-05 -1.69E-04 | ********** OM12 7.64E-05 9.44E-05 4.53E-05 3.18E-05 | *********** OM13 1.59E-03 1.20E-04 1.20E-03 | ************ OM22 7.43E-05 1.35E-04 | ****** ****** OM23 1.30E-03 | ********** ********* ********** OM33 | ** |
| ********** TH 1 4 TH 2 2 TH 3 1 TH 4 -3 TH 5 5 OM11 -4 OM12 -2 OM13 -3 OM22 4 OM23 -1 OM33 3 | *********** ********** TH 1 4.82E-02 2.92E-01 2. 1.49E-02 2. 3.35E-02 -1. 5.83E-03 2. 4.22E-03 -1. 2.91E-04 6. 3.96E-04 -2. 4.52E-04 -2. 1.91E-04 -6. 1.30E-02 1. | ******* TH 2 85E+00 71E-01 55E-01 13E-02 06E-02 44E-04 73E-03 23E-04 16E-03 20E-01 | ********** TH 3 9.12E-02 -4.23E-03 -7.47E-04 1.76E-04 -1.89E-04 5.80E-03 -3.38E-04 5.55E-03 4.24E-02 | TH 4 4.27E-02 -8.56E-03 5.14E-03 2.79E-04 -1.94E-03 -5.44E-04 -6.16E-04 | 2.15E-03 -1.03E-03 -1.19E-04 3.88E-05 4.05E-05 -2.18E-04 -1.01E-03 | MATRIX OF ********** OM11 8.71E-04 1.41E-04 -1.16E-04 -4.94E-05 -1.69E-04 -1.10E-03 | ********** OM12 7.64E-05 9.44E-05 4.53E-05 3.18E-05 1.27E-04 | ********** OM13 1.59E-03 1.20E-04 1.20E-03 5.26E-03 | *********** OM22 7.43E-05 1.35E-04 5.58E-04 | ******* ****** OM23 1.30E-03 6.64E-03 | *********** ********** OM33 | *** ** ** ** ** ** ** |
| ********** TH 1 4 TH 2 2 TH 3 1 TH 4 -3 TH 5 5 OM11 -4 OM12 -2 OM13 -3 OM22 4 OM23 -1 OM33 3 | *********** ********** TH 1 4.82E-02 2.92E-01 2. 1.49E-02 2. 3.35E-02 -1. 5.83E-03 2. 4.22E-03 -1. 2.91E-04 6. 3.96E-04 -2. 4.52E-04 -2. 1.91E-04 -6. | ******* TH 2 85E+00 71E-01 55E-01 13E-02 06E-02 44E-04 73E-03 23E-04 16E-03 20E-01 | ********** TH 3 9.12E-02 -4.23E-03 -7.47E-04 1.76E-04 -1.89E-04 5.80E-03 -3.38E-04 5.55E-03 4.24E-02 | TH 4 4.27E-02 -8.56E-03 5.14E-03 2.79E-04 -1.94E-03 -5.44E-04 -6.16E-04 | 2.15E-03 -1.03E-03 -1.19E-04 3.88E-05 4.05E-05 -2.18E-04 -1.01E-03 | MATRIX OF ********** OM11 8.71E-04 1.41E-04 -1.16E-04 -4.94E-05 -1.69E-04 -1.10E-03 | ********** OM12 7.64E-05 9.44E-05 4.53E-05 3.18E-05 1.27E-04 | ********** OM13 1.59E-03 1.20E-04 1.20E-03 5.26E-03 | *********** OM22 7.43E-05 1.35E-04 5.58E-04 | ******* ****** OM23 1.30E-03 6.64E-03 | *********** ********** OM33 | *** ** ** ** ** ** ** |
| ************************************** | *********** ********** TH 1 4.82E-02 2.92E-01 2. 1.49E-02 2. 3.35E-02 -1. 5.83E-03 2. 4.22E-03 -1. 2.91E-04 6. 3.96E-04 -2. 4.52E-04 -2. 1.91E-04 -6. 1.30E-02 1. | ******* TH 2 85E+00 71E-01 55E-01 13E-02 06E-02 44E-04 73E-03 23E-04 16E-03 20E-01 | ********* TH 3 9.12E-02 -4.23E-03 -7.47E-04 1.76E-04 -1.89E-04 5.80E-03 -3.38E-04 5.55E-03 4.24E-02 | TH 4 4.27E-02 -8.56E-03 5.14E-03 2.79E-04 -1.94E-03 -5.44E-04 -6.16E-04 -7.51E-03 | 2.15E-03 -1.03E-03 -1.19E-04 3.88E-05 4.05E-05 -2.18E-04 -1.01E-03 | MATRIX OF ********** OM11 8.71E-04 1.41E-04 -1.16E-04 -4.94E-05 -1.69E-04 -1.10E-03 | *********** OM12 7.64E-05 9.44E-05 4.53E-05 3.18E-05 1.27E-04 | ********** OM13 1.59E-03 1.20E-04 1.20E-03 5.26E-03 | ********** OM22 7.43E-05 1.35E-04 5.58E-04 | ******* ****** OM23 1.30E-03 6.64E-03 | *********** ********** OM33 | *** *** *** SG11 |

TH 1 1.00E+00

TH 2 7.88E-01 1.00E+00

TH 3 2.25E-01 5.32E-01 1.00E+00

TH 4 -7.39E-01 -4.45E-01 -6.78E-02 1.00E+00

TH 5 5.72E-01 2.72E-01 -5.33E-02 -8.93E-01 1.00E+00

OM11 -6.52E-01 -2.13E-01 1.97E-02 8.42E-01 -7.52E-01 1.00E+00

OM12 -1.52E-01 4.37E-02 -7.15E-02 1.54E-01 -2.94E-01 5.46E-01 1.00E+00

OM13 -4.52E-02 -4.05E-02 4.82E-01 -2.35E-01 2.10E-02 -9.89E-02 2.71E-01 1.00E+00

 $\texttt{OM22} \qquad 2.39 \texttt{E} - 01 \ -1.54 \texttt{E} - 02 \ -1.30 \texttt{E} - 01 \ -3.06 \texttt{E} - 01 \ 1.01 \texttt{E} - 01 \ -1.94 \texttt{E} - 01 \ 6.02 \texttt{E} - 01 \ 3.49 \texttt{E} - 01 \ 1.00 \texttt{E} + 00$

OM33 2.66E-01 3.20E-01 6.31E-01 -1.63E-01 -9.77E-02 -1.68E-01 6.52E-02 5.92E-01 2.91E-01 8.28E-01 1.00E+00

SG11

TH 1 TH 2 TH 3 TH 4 TH 5 0M11 0M12 0M13 0M22 0M23 0M33 SG11

TH 1 4.48E+02

TH 2 -6.93E+01 1.67E+01

TH 3 3.10E+02 -7.74E+01 4.68E+02

TH 4 2.47E+03 -5.16E+02 3.60E+03 3.71E+04

TH 5 3.55E+03 -7.25E+02 5.20E+03 5.60E+04 8.66E+04

OM11 -1.74E+04 3.40E+03 -2.45E+04 -2.46E+05 -3.66E+05 1.74E+06

OM12 4.30E+04 -7.04E+03 5.24E+04 5.25E+05 7.78E+05 -4.00E+06 1.01E+07

OM13 1.65E+03 -7.39E+02 3.94E+03 3.83E+04 5.81E+04 -1.70E+05 9.16E+04 1.22E+05

OM22 -2.04E+04 2.18E+03 -1.89E+04 -2.00E+05 -2.95E+05 1.77E+06 -5.18E+06 1.96E+05 3.19E+06

OM33 4.11E+02 -1.57E+02 8.30E+02 7.43E+03 1.12E+04 -3.86E+04 4.63E+04 1.87E+04 1.42E+04 -4.01E+04 3.18E+03

SG11

EIGENVALUES OF COR MATRIX OF ESTIMATE 10 2.30E-04 1.01E-03 1.84E-02 6.29E-02 1.73E-01 1.85E-01 5.96E-01 1.40E+00 1.67E+00 3.02E+00 3.87E+00 R MATRIX TH 1 TH 2 TH 3 TH 4 TH 5 OM11 OM12 OM13 OM22 OM23 OM33 SG11 TH 1 4.15E+01 TH 2 -4.76E+00 1.20E+00 TH 3 7.37E+00 -2.94E+00 1.93E+01 TH 4 1.45E+00 -4.04E-01 -2.57E-01 3.05E+02 TH 5 2.60E+01 -9.79E+00 2.99E+01 1.01E+03 6.29E+03 -3.08E+01 4.90E+00 -6.29E+00 1.92E+02 8.76E+02 5.87E+03 OM11 OM12 4.35E+01 -3.20E+00 -6.72E-01 -9.70E+02 -3.85E+03 -1.62E+04 6.20E+04 2.05E+01 -4.85E+00 7.91E+00 9.41E+01 3.20E+02 1.19E+03 -5.72E+03 1.32E+03 OM13 $6.53{\text{E}} + 01 - 2.05{\text{E}} + 01 - 4.00{\text{E}} + 01 - 1.21{\text{E}} + 03 - 4.70{\text{E}} + 03 - 1.10{\text{E}} + 04 - 5.08{\text{E}} + 04 - 4.90{\text{E}} + 03 - 6.15{\text{E}} + 04 - 6.08{\text{E}} + 04 - 6.08{\text{E}} + 04 - 6.08{\text{E}} + 03 - 6.08{\text{E}}$ OM22 OM23 $-6.92E + 01 \quad 1.57E + 01 \quad -2.37E + 01 \quad -2.38E + 02 \quad -8.48E + 02 \quad -1.67E + 03 \quad 8.74E + 03 \quad -1.90E + 03 \quad -1.26E + 04 \quad 5.74E + 03 \quad -1.26E + 04 \quad -1.$ OM 3.3 5.11E+00 -1.01E+00 2.14E-01 1.57E+01 5.20E+01 6.57E+01 -3.68E+02 1.08E+02 6.97E+02 -4.74E+02 7.02E+01 SG11 S MATRIX TH 1 TH 2 TH 3 TH 4 TH 5 OM11 OM12 OM13 OM22 OM23 OM33 SG11 TH 1 4 06E+01 TH 2 -4.60E+00 1.17E+00 TH 3 7.09E+00 -2.87E+00 1.91E+01 TH 4 -9.39E+01 2.12E+00 -1.74E+01 8.69E+02 3.14E+02 -7.33E+01 1.02E+02 1.78E+03 1.96E+04 TH 5 OM11 -4.94E+02 3.75E+01 -4.61E+01 2.50E+03 -4.42E+02 9.71E+03 8.04E+02 -1.81E+01 2.73E+01 -6.22E+03 -5.58E+03 -2.07E+04 5.14E+04 OM12 OM13 -2.37E+01 -3.37E+00 2.06E+01 1.82E+02 4.03E+02 6.87E+02 -1.65E+03 1.52E+02 OM22

-4.95E+01 -1.45E+01 1.21E+02 -1.49E+02 -1.77E+03 3.47E+02 -4.86E+02 2.29E+02 -5.25E+03 2.06E+03

OM23