```
      SUBROUTINE PRED (ICALL,NEWIND,THETA,DATREC,INDXS,F,G,H)
C
C     THETA(1)=ABSORPTION RATE CONSTANT (1/HR)
C     THETA(2)=ELIMINATION RATE CONSTANT (1/HR)
C     THETA(3)=VOLUME OF DISTRIBUTION (LITERS)
C     DATREC(1)=DOSE (MG)
C     DATREC(2)=TIME (HR)
C
      DIMENSION THETA(*),DATREC(*),INDXS(*),G(*),H(*)
      DOUBLE PRECISION THETA,F,G,H,A,B,C,D
C
      A=EXP(-THETA(2)*DATREC(2))
      B=EXP(-THETA(1)*DATREC(2))
      C=THETA(1)-THETA(2)
      D=A-B
      F=((DATREC(1)*THETA(1))/(THETA(3)*C))*D
      G(1)=1.
      RETURN
      END
```

```
FILE     NULL
PROB     SIMPLE NONLINEAR REGRESSION OF CP VS TIME DATA FROM ONE SUBJECT
DATA        0    0  10    3
ITEM        0    3   0    0   1
LABL     DOSE     TIME        CP
FORM
(3F10.0)
        320         .27        1.71
        320         .52        7.91
        320        1.0         8.31
        320        1.92        8.33
        320        3.5         6.85
        320        5.02        6.08
        320        7.03        5.4
        320        9.0         4.55
        320       12.0         3.01
        320       24.3          .90
STRC        3    1                   1
THCN        1
THTA          1.7      .102       29.
LOWR           .4      .025       10.
UPPR          7.        .4        80.
DIAG    2
ESTM        0 240    4    2
COVR        0
TABL        0    1
TABL        1    2
SCAT        0    4
SCAT        2    3
SCAT        2    4
SCAT        2    5
SCAT        3    4                   1
```

```
NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM)    DOUBLE PRECISION NONMEM    VERSION III LEVEL 1.0
DEVELOPED AND PROGRAMMED BY STUART BEAL AND LEWIS SHEINER

PROBLEM NO.  1
SIMPLE NONLINEAR REGRESSION OF CP VS TIME DATA FROM ONE SUBJECT

NO. OF DATA RECS IN DATA SET:   10
NO. OF DATA ITEMS IN DATA SET:   3
DEP VARIABLE IS DATA ITEM NO.:   3

LABELS TO BE USED FOR ITEMS APPEARING
       IN TABLES AND SCATTERPLOTS ARE:
DOSE    TIME      CP    PRED    RES     WRES

FORMAT FOR DATA IS:
(3F10.0)

TOT. NO. OF OBS RECS:      10
TOT. NO. OF INDIVIDUALS:   10

LENGTH OF THETA:  3

OMEGA HAS SIMPLE DIAGONAL FORM WITH DIMENSION:  1

INITIAL ESTIMATE OF THETA:
LOWER BOUND    INITIAL EST    UPPER BOUND
 0.4000e+00     0.1700e+01     0.7000e+01
 0.2500e-01     0.1020e+00     0.4000e+00
 0.1000e+02     0.2900e+02     0.8000e+02

ESTIMATION STEP OMITTED:    NO
NO. OF FUNCT. EVALS. ALLOWED:  240
NO. OF SIG. FIGURES REQUIRED:    4
INTERMEDIATE PRINTOUT:   YES
CONVERGENCE REPEATED:     NO
MSF OUTPUT:               NO

COVARIANCE STEP OMITTED:    NO
EIGENVLS. PRINTED:    NO
SPECIAL COMPUTATION:  NO

TABLES STEP OMITTED:    NO
NO. OF TABLES:       1
TABLES PRINTED:    YES
TABLES FILE USED:   NO

USER CHOSEN DATA ITEMS FOR TABLE  1,
IN THE ORDER THEY WILL APPEAR IN THE TABLE, ARE:
TIME

SCATTERPLOT STEP OMITTED:    NO
NO. OF PAIRS OF ITEMS GENERATING
        FAMILIES OF SCATTERPLOTS:  4
```

Fig. 3a

```
ITEMS TO BE SCATTERED ARE:     TIME       CP
ITEMS TO BE SCATTERED ARE:     TIME     PRED
ITEMS TO BE SCATTERED ARE:     TIME      RES
ITEMS TO BE SCATTERED ARE:       CP     PRED
    UNIT SLOPE LINE INCLUDED
```

Fig. 3b

```
********************************************************************************************************************************
**********                                                                                                          **********
**********                                    INITIAL PARAMETER ESTIMATE                                            **********
**********                                                                                                          **********
********************************************************************************************************************************
```

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

TH 1	TH 2	TH 3
1.70e+00	1.02e-01	2.90e+01

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

	ETA1
ETA1	1.17e+00

Fig. 4

```
MONITORING OF SEARCH:


ITERATION NO.:    0     OBJECTIVE VALUE:  0.1157e+02     NO. OF FUNC. EVALS.: 5
PARAMETER:  0.1000e+00  0.1000e+00  0.1000e+00  0.1000e+00
GRADIENT:   0.2395e+02 -0.2631e+03 -0.6027e+03  0.3695e-04

ITERATION NO.:    2     OBJECTIVE VALUE:  0.9807e+01     NO. OF FUNC. EVALS.: 6
PARAMETER:  0.1102e+00  0.1059e+00  0.1031e+00  0.9106e-01
GRADIENT:   0.1051e+03 -0.3883e+02 -0.3453e+03 -0.2402e+01

ITERATION NO.:    4     OBJECTIVE VALUE:  0.9577e+01     NO. OF FUNC. EVALS.: 7
PARAMETER:  0.1153e+00  0.9850e-01  0.1079e+00  0.7942e-01
GRADIENT:   0.9697e+02 -0.6965e+02 -0.2652e+03 -0.6587e+02

ITERATION NO.:    6     OBJECTIVE VALUE:  0.8943e+01     NO. OF FUNC. EVALS.: 6
PARAMETER:  0.1098e+00  0.9997e-01  0.1085e+00  0.8684e-01
GRADIENT:   0.4124e+01 -0.5664e+00 -0.1038e+02 -0.4515e+01

ITERATION NO.:    8     OBJECTIVE VALUE:  0.8940e+01     NO. OF FUNC. EVALS.: 6
PARAMETER:  0.1097e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:   0.5923e-01  0.4162e-01 -0.5070e-01  0.1247e-01

ITERATION NO.:   10     OBJECTIVE VALUE:  0.8940e+01     NO. OF FUNC. EVALS.: 6
PARAMETER:  0.1096e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:  -0.2348e-03  0.4554e-03  0.5354e-03  0.3576e-04

ITERATION NO.:   12     OBJECTIVE VALUE:  0.8940e+01     NO. OF FUNC. EVALS.: 6
PARAMETER:  0.1096e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:  -0.5436e-05  0.0000e+00 -0.2194e-05  0.0000e+00

ITERATION NO.:   14     OBJECTIVE VALUE:  0.8940e+01     NO. OF FUNC. EVALS.: 9
PARAMETER:  0.1096e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:   0.1359e-04 -0.2861e-04 -0.6857e-04 -0.6557e-05

ITERATION NO.:   16     OBJECTIVE VALUE:  0.8940e+01     NO. OF FUNC. EVALS.: 1
PARAMETER:  0.1096e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:  -0.1087e-05  0.2384e-05 -0.2194e-05  0.0000e+00

MINIMIZATION ROUTINE SUCCESSFULLY TERMINATED
NO. OF FUNCTION EVALUATIONS USED:  114
NO. OF SIG. DIGITS IN FINAL EST.:  8.5
```

Fig. 5

****

****

****

****

MINIMUM VALUE OF OBJECTIVE FUNCTION

****

****

****

****

****

8.940

****

Fig. 6

```
********************************************************************************************************************************
**********                                                                                                          **********
**********                                      FINAL PARAMETER ESTIMATE                                            **********
**********                                                                                                          **********
********************************************************************************************************************************


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

           TH 1      TH 2      TH 3

        1.94e+00  1.02e-01  3.20e+01


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

           ETA1

ETA1     8.99e-01
```

Fig. 7

****
****
****
****
****

STANDARD ERROR OF ESTIMATE

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

TH 1	TH 2	TH 3
6.28e-01	7.37e-03	1.25e+00

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

	ETA1
ETA1	5.45e-01

Fig. 8

****
****
****
****
****

COVARIANCE MATRIX OF ESTIMATE

	TH 1	TH 2	TH 3	OM11
TH 1	3.95e-01			
TH 2	-3.37e-03	5.43e-05		
TH 3	4.91e-01	-7.90e-03	1.57e+00	
OM11	-1.53e-01	2.64e-03	-4.56e-01	2.97e-01

Fig. 9

****
****
****
****

CORRELATION MATRIX OF ESTIMATE

****
****
****
****

	TH 1	TH 2	TH 3	OM11
TH 1	1.00e+00			
TH 2	-7.27e-01	1.00e+00		
TH 3	6.24e-01	-8.55e-01	1.00e+00	
OM11	-4.48e-01	6.59e-01	-6.67e-01	1.00e+00

Fig. 10

Fig. 11

INVERSE COVARIANCE MATRIX OF ESTIMATE

	TH 1	TH 2	TH 3	OM11
TH 1	5.40e+00			
TH 2	3.42e+02	9.41e+04		
TH 3	-7.86e-02	3.14e+02	2.55e+00	
OM11	-3.83e-01	-1.80e+02	1.08e+00	6.44e+00

TABLES OF DATA AND PREDICTIONS

Fig. 12

TABLE NO. 1

LINE NO.	TIME	CP	PRED	RES	WRES
1	2.70e-01	1.71e+00	4.02e+00	-2.31e+00	-2.43e+00
2	5.20e-01	7.91e+00	6.16e+00	1.75e+00	1.85e+00
3	1.00e+00	8.31e+00	8.01e+00	2.98e-01	3.15e-01
4	1.92e+00	8.33e+00	8.42e+00	-9.15e-02	-9.65e-02
5	3.50e+00	6.85e+00	7.38e+00	-5.26e-01	-5.55e-01
6	5.02e+00	6.08e+00	6.33e+00	-2.49e-01	-2.63e-01
7	7.03e+00	5.40e+00	5.16e+00	2.40e-01	2.53e-01
8	9.00e+00	4.55e+00	4.22e+00	3.27e-01	3.45e-01
9	1.20e+01	3.01e+00	3.11e+00	-1.03e-01	-1.08e-01
10	2.43e+01	9.00e-01	8.91e-01	8.82e-03	9.29e-03

Fig. 13

Fig. 14

Fig. 15

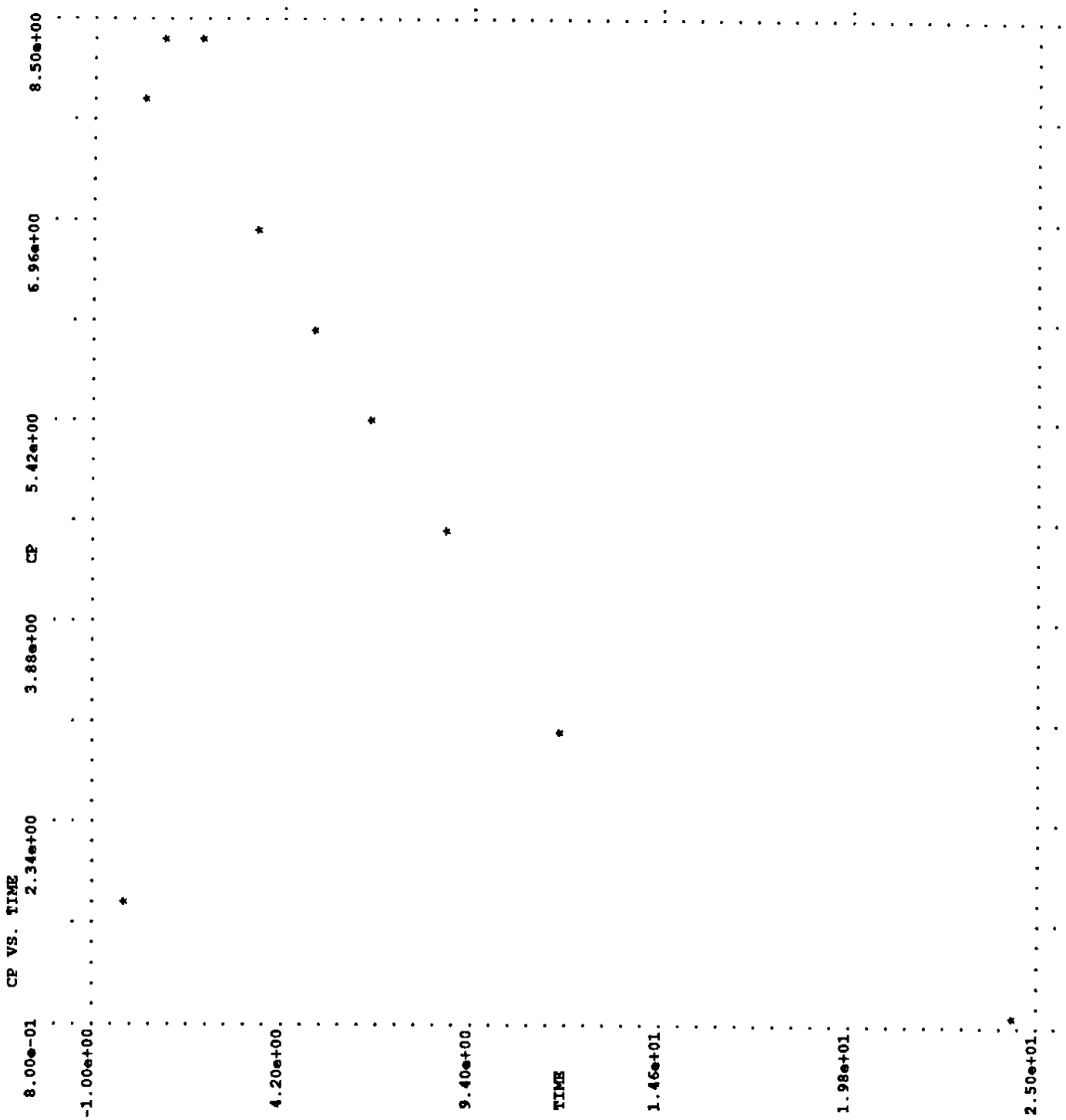

CP VS. TIME
8.50e+00
6.96e+00
5.42e+00
3.88e+00
2.34e+00
8.00e-01
CP
-1.00e+00
4.20e+00
9.40e+00
1.46e+01
1.98e+01
2.50e+01
TIME

Fig. 16

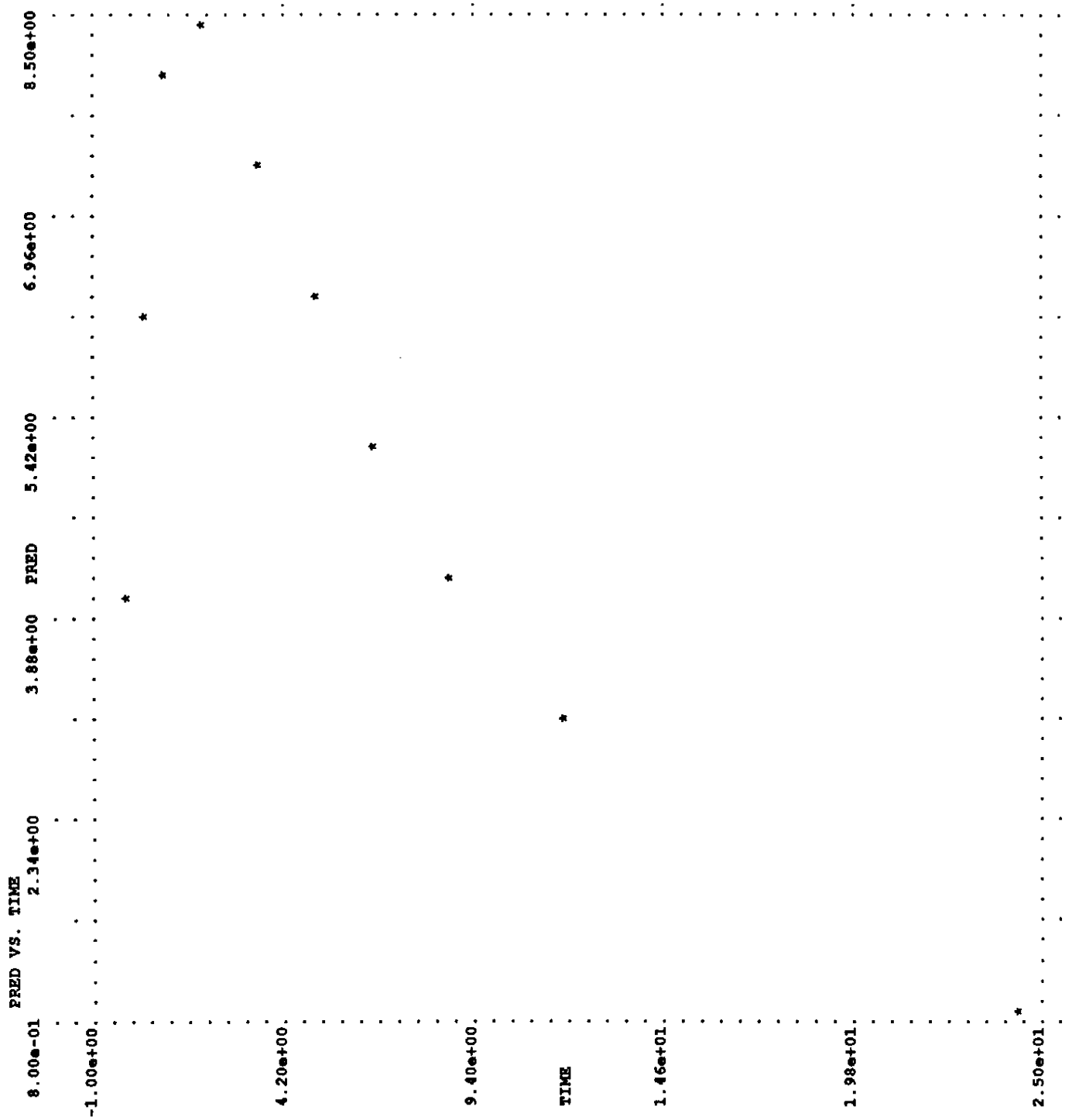

PRED VS. TIME
8.00e-01
2.34e+00
3.88e+00
PRED
5.42e+00
6.96e+00
8.50e+00
-1.00e+00
4.20e+00
9.40e+00
TIME
1.46e+01
1.98e+01
2.50e+01

Fig. 17

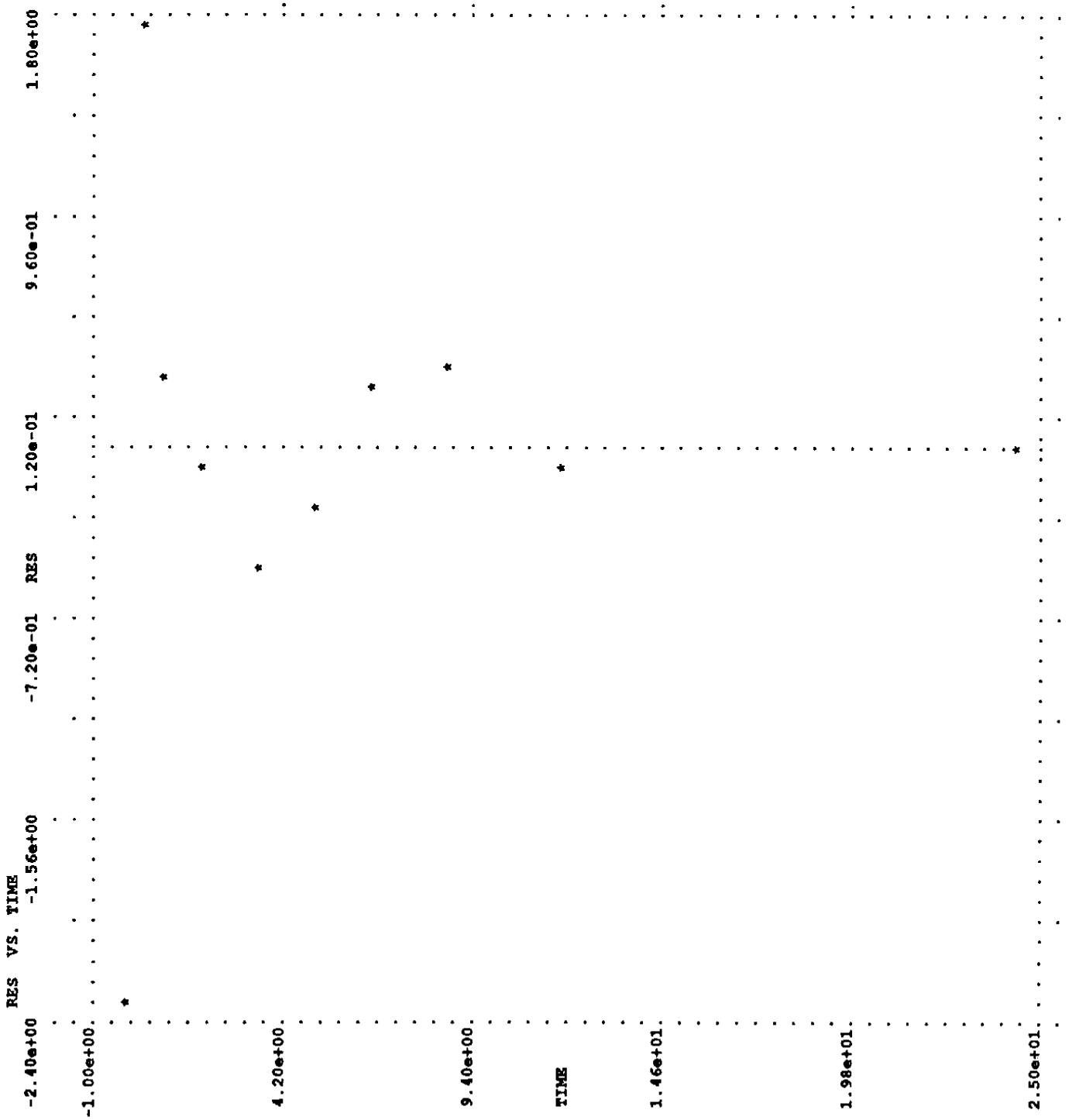
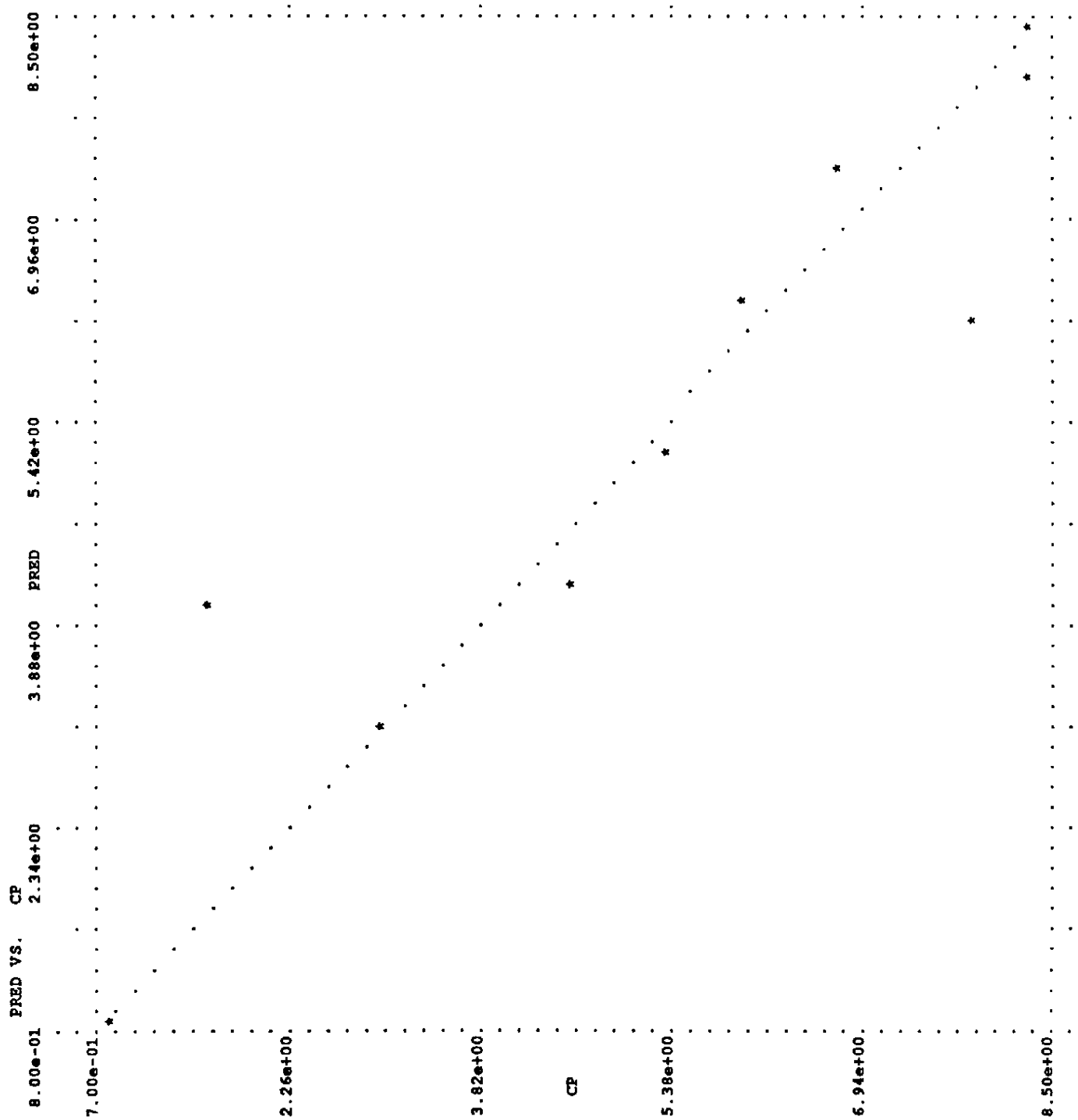

RES VS. TIME
-2.40e+00
-1.56e+00
-7.20e-01
1.20e-01
9.60e-01
1.80e+00
RES
-1.00e+00
4.20e+00
9.40e+00
1.46e+01
1.98e+01
2.50e+01
TIME

Fig. 18


PRED VS. CP
8.00e-01
2.34e+00
3.88e+00
5.42e+00
6.96e+00
8.50e+00
PRED
7.00e-01
2.26e+00
3.82e+00
5.38e+00
6.94e+00
8.50e+00
CP

```
      SUBROUTINE PRED (ICALL,NEWIND,THETA,DATREC,INDXS,F,G,H)
C
C     THETA(1)=ABSORPTION RATE CONSTANT (1/HR)
C     THETA(2)=ELIMINATION RATE CONSTANT (1/HR)
C     THETA(3)=VOLUME OF DISTRIBUTION (LITERS)
C     DATREC(1)=DOSE (MG)
C     DATREC(2)=TIME (HR)
C
C                                          COMPUTED VALUES
C
C     C=CONCENTRATION IN PLASMA AT CURRENT TIME (MG/L)
C     DO=DOSE IN DEPOT AT CURRENT TIME (MG)
C     DELTA=INCREMENTAL DIFFERENCE IN TIME FROM PREVIOUS TIME
C
      DIMENSION THETA(*),DATREC(*),INDXS(*),G(*),H(*)
      DOUBLE PRECISION THETA,F,G,H,DO,A,B,BA,C
C
      IF (NEWIND.NE.0) GO TO 10
C                                          INITIALIZE RECURSION
      C=0.
      TIME=0.
      DO=DATREC(1)
C                                          COMPUTE TIME INCREMENT
   10 DELTA=DATREC(2)-TIME
C                                          COMPUTE EXPONENTIALS
      A=EXP(-THETA(2)*DELTA)
      B=EXP(-THETA(1)*DELTA)
C                                          GET BATEMAN VALUE
      CALL BATE (DO,DELTA,THETA(1),THETA(2),THETA(3),A,B,BA)
C                                          UPDATE C AND DO
      C=BA+C*A
      DO=DO*B
C                                          UPDATE TIME
      TIME=DATREC(2)
C                                          SET OUTPUTS
      F=C
      G(1)=1.
      RETURN
      END
```

```
      SUBROUTINE BATE (DO,DELTA,KA,KD,VL,A,B,BA)
C
C                                          INPUTS
C     DO=DOSE
C     DELTA=TIME
C     KA=MEAN ABSORPTION RATE
C     KD=MEAN ELIMINATION RATE
C     VL=VOLUME OF DISTRIBUTION
C     A=EXP(-KD*DELTA)
C     B=EXP(-KA*DELTA)
C                                          OUTPUTS
C     BA=BATEMAN VALUE
C
      DOUBLE PRECISION DO,KA,KD,VL,A,B,BA,C,D
C
      C=KA-KD
      D=A-B
      BA=DO*KA/(VL*C)*D
      RETURN
      END
```

```
      SUBROUTINE PRED (ICALL,NEWIND,THETA,DATREC,INDXS,F,G,H)
C
C     THETA(1)=ABSORPTION RATE CONSTANT (1/HR)
C     THETA(2)=ELIMINATION RATE CONSTANT (1/HR)
C     THETA(3)=VOLUME OF DISTRIBUTION (LITERS)
C     INDXS(1)=DOSE (MG)
C     INDXS(2)=TIME (HR)
C
      DIMENSION THETA(*),DATREC(*),INDXS(*),G(*),H(*)
      DOUBLE PRECISION THETA,F,G,H,A,B,C,D
C
      DO=DATREC(INDXS(1))
      TIME=DATREC(INDXS(2))
      A=EXP(-THETA(2)*TIME)
      B=EXP(-THETA(1)*TIME)
      C=THETA(1)-THETA(2)
      D=A-B
      F=((DO*THETA(1))/(THETA(3)*C))*D
      G(1)=1.
      RETURN
      END
```

```
FILE     NULL
PROB     SIMPLE NONLINEAR REGRESSION OF CP VS TIME DATA FROM ONE SUBJECT
DATA        0    0  10    3
ITEM        0    3   0    2    1
INDX        1    2
LABL     DOSE     TIME        CP
FORM
(3F10.0)
        320         .27        1.71
        320         .52        7.91
        320        1.0         8.31
        320        1.92        8.33
        320        3.5         6.85
        320        5.02        6.08
        320        7.03        5.4
        320        9.0         4.55
        320       12.0         3.01
        320       24.3          .90
STRC        3    1                    1
THCN        1
THTA          1.7      .102       29.
LOWR           .4      .025       10.
UPPR          7.        .4        80.
DIAG    2
ESTM        0 240    4    2
COVR        0
TABL        0    1
TABL        1    2
SCAT        0    4
SCAT        2    3
SCAT        2    4
SCAT        2    5
SCAT        3    4                    1
```

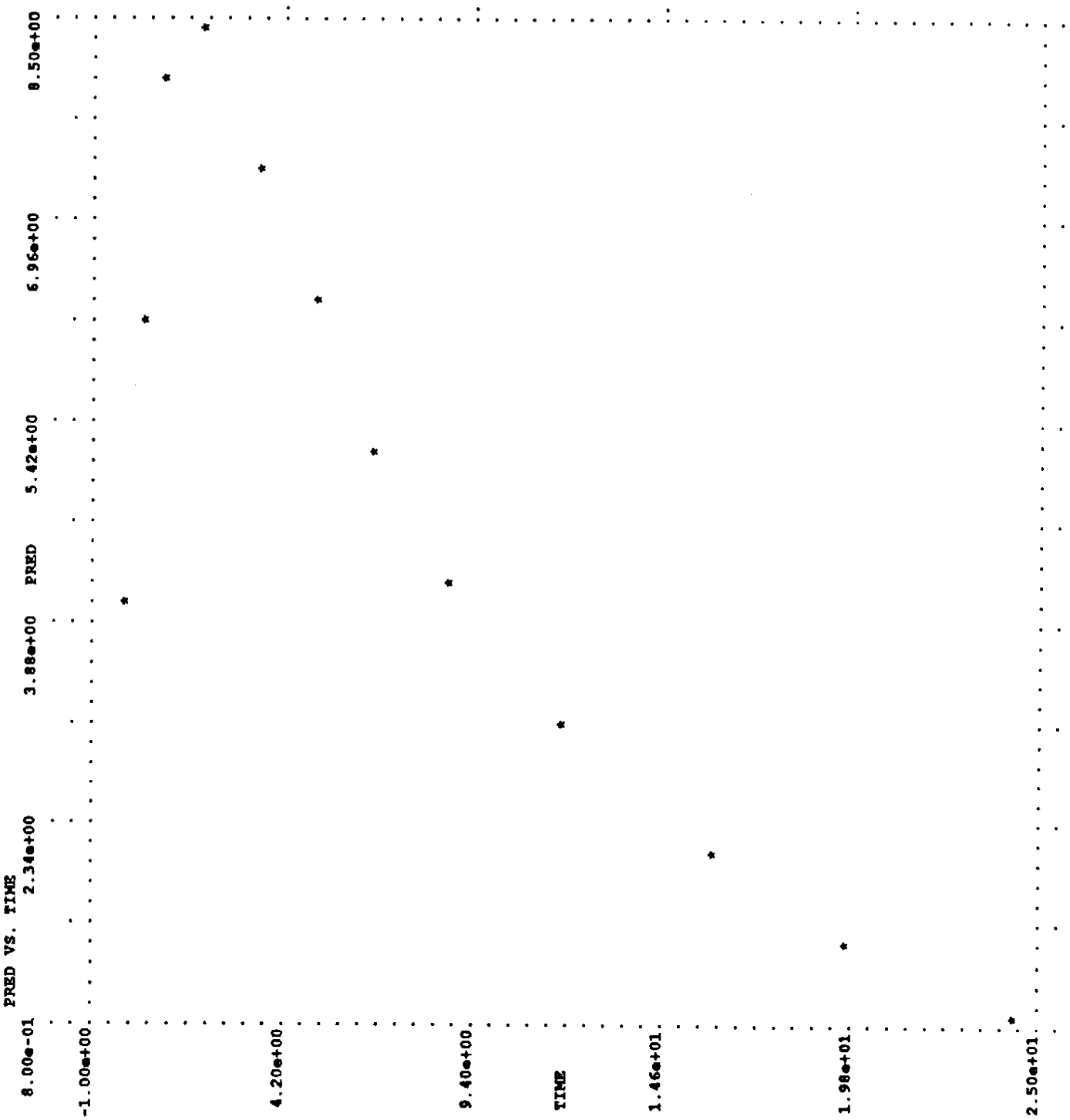
```
FILE     NULL
PROB     SIMPLE NONLINEAR REGRESSION OF CP VS TIME DATA FROM ONE SUBJECT
DATA        0    0  10    3
ITEM        0    3   0    2    1
INDX        2    1
LABL     TIME      DOSE        CP
FORM
(3F10.0)
        .27          320        1.71
        .52          320        7.91
       1.0           320        8.31
       1.92          320        8.33
       3.5           320        6.85
       5.02          320        6.08
       7.03          320        5.4
       9.0           320        4.55
      12.0           320        3.01
      24.3           320         .90
STRC         3    1                    1
THCN         1
THTA           1.7      .102       29.
LOWR            .4      .025       10.
UPPR           7.        .4        80.
DIAG    2
ESTM         0 240    4    2
COVR         0
TABL         0    1
TABL         1    1
SCAT         0    4
SCAT         1    3
SCAT         1    4
SCAT         1    5
SCAT         3    4                    1
```

```
      SUBROUTINE PRED (ICALL,NEWIND,THETA,DATREC,INDXS,F,G,H)
C
C     THETA(1)=ABSORPTION RATE CONSTANT (1/HR)
C     THETA(2)=ELIMINATION RATE CONSTANT (1/HR)
C     THETA(3)=VOLUME OF DISTRIBUTION (LITERS)
C     DATREC(1)=TIME (HR)
C
      DIMENSION THETA(*),DATREC(*),INDXS(*),G(*),H(*)
      DOUBLE PRECISION THETA,F,G,H,A,B,C,D
C
      IF (ICALL.EQ.0) RETURN
      IF (ICALL.EQ.1) THEN
C                              INPUT DOSE
      READ (5,5) DOSE
    5 FORMAT (F10.0)
      RETURN
C
      ELSEIF (ICALL.EQ.2) THEN
C                                COMPUTE F AND G
      A=EXP(-THETA(2)*DATREC(1))
      B=EXP(-THETA(1)*DATREC(1))
      C=THETA(1)-THETA(2)
      D=A-B
      F=((DOSE*THETA(1))/(THETA(3)*C))*D
      G(1)=1.
      RETURN
C
      ENDIF
      END
```

```
FILE     NULL
PROB     SIMPLE NONLINEAR REGRESSION OF CP VS TIME DATA FROM ONE SUBJECT
DATA        0    0  10    2
ITEM        0    2   0    0    1
LABL     TIME       CP
FORM
(2F10.0)
        .27        1.71
        .52        7.91
       1.0         8.31
       1.92        8.33
       3.5         6.85
       5.02        6.08
       7.03        5.4
       9.0         4.55
      12.0         3.01
      24.3          .90
STRC         3    1                    1
THCN         1
THTA           1.7      .102       29.
LOWR            .4      .025       10.
UPPR           7.        .4        80.
DIAG    2
ESTM         0 240    4    2
COVR         0
TABL         0    1
TABL         1    1
SCAT         0    4
SCAT         1    2
SCAT         1    3
SCAT         1    4
SCAT         2    3                    1
       320.
```

```
FILE     NULL
PROB     SIMPLE NONLINEAR REGRESSION OF CP VS TIME DATA FROM ONE SUBJECT
DATA        0    0  12    5
ITEM        5    3   4    0   1
LABL     DOSE     TIME        CP      MDV       ID
FORM
(5F10.0)
        320         .27        1.71          0          1
        320         .52        7.91          0          2
        320        1.0         8.31          0          3
        320        1.92        8.33          0          4
        320        3.5         6.85          0          5
        320        5.02        6.08          0          6
        320        7.03        5.4           0          7
        320        9.0         4.55          0          8
        320       12.0         3.01          0          9
        320       16.0                       1          9
        320       20.0                       1          9
        320       24.3          .90          0         10
STRC        3    1                    1
THCN        1
THTA          1.7      .102      29.
LOWR           .4      .025      10.
UPPR          7.        .4        80.
DIAG    2
ESTM        0 240    4    2
COVR        0
TABL        0    1
TABL        1    2
SCAT        0    4
SCAT        2    3
SCAT        2    6
SCAT        2    7
SCAT        3    6                    1
```

Fig. 27


PRED VS. TIME
8.00e-01
2.34e+00
3.88e+00
PRED
5.42e+00
6.96e+00
8.50e+00
-1.00e+00
4.20e+00
9.40e+00
TIME
1.46e+01
1.98e+01
2.50e+01

```
FILE    FILESTREAM
PROB    SIMPLE NONLINEAR REGRESSION OF CP VS TIME DATA FROM ONE SUBJECT
DATA       0    0  10    3
ITEM       0    3   0    0   1
LABL    DOSE     TIME        CP
FORM
(3F10.0)
        320         .27        1.71
        320         .52        7.91
        320        1.0         8.31
        320        1.92        8.33
        320        3.5         6.85
        320        5.02        6.08
        320        7.03        5.4
        320        9.0         4.55
        320       12.0         3.01
        320       24.3          .90
STRC        3    1                   1
THCN        1
THTA          1.7      .102       29.
LOWR           .4      .025       10.
UPPR          7.        .4        80.
DIAG    2
ESTM        0   50    4    2         1
COVR        0
TABL        0    1
TABL        1    2
SCAT        0    4
SCAT        2    3
SCAT        2    4
SCAT        2    5
SCAT        3    4                   1
```

Fig. 29

MSFO MSF1
****

```
MONITORING OF SEARCH:


ITERATION NO.:    0     OBJECTIVE VALUE:  0.1157e+02     NO. OF FUNC. EVALS.: 5
PARAMETER:  0.1000e+00  0.1000e+00  0.1000e+00  0.1000e+00
GRADIENT:   0.2395e+02 -0.2631e+03 -0.6027e+03  0.3695e-04

ITERATION NO.:    2     OBJECTIVE VALUE:  0.9807e+01     NO. OF FUNC. EVALS.: 6
PARAMETER:  0.1102e+00  0.1059e+00  0.1031e+00  0.9106e-01
GRADIENT:   0.1051e+03 -0.3883e+02 -0.3453e+03 -0.2402e+01

ITERATION NO.:    4     OBJECTIVE VALUE:  0.9577e+01     NO. OF FUNC. EVALS.: 7
PARAMETER:  0.1153e+00  0.9850e-01  0.1079e+00  0.7942e-01
GRADIENT:   0.9697e+02 -0.6965e+02 -0.2652e+03 -0.6587e+02

ITERATION NO.:    6     OBJECTIVE VALUE:  0.8943e+01     NO. OF FUNC. EVALS.: 6
PARAMETER:  0.1098e+00  0.9997e-01  0.1085e+00  0.8684e-01
GRADIENT:   0.4124e+01 -0.5664e+00 -0.1038e+02 -0.4515e+01

MINIMIZATION ROUTINE TERMINATED
DUE TO MAX. NO. OF FUNCTION EVALUATIONS EXCEEDED
NO. OF FUNCTION EVALUATIONS USED:   51
NO. OF SIG. DIGITS IN FINAL EST.:  1.7
```

Fig. 30

```
FILE     FILESTREAM
PROB     SIMPLE NONLINEAR REGRESSION OF CP VS TIME DATA FROM ONE SUBJECT
DATA        0    0  10    3
ITEM        0    3   0    0    1
LABL     DOSE     TIME        CP
FORM
(3F10.0)
        320         .27        1.71
        320         .52        7.91
        320        1.0         8.31
        320        1.92        8.33
        320        3.5         6.85
        320        5.02        6.08
        320        7.03        5.4
        320        9.0         4.55
        320       12.0         3.01
        320       24.3          .90
FIND
ESTM        0 150    4    2         1
COVR        0
TABL        0    1
TABL        1    2
SCAT        0    4
SCAT        2    3
SCAT        2    4
SCAT        2    5
SCAT        3    4                   1
```

```
MSFO     MSF2
MSFI     MSF1
****
```

```
MONITORING OF SEARCH:


ITERATION NO.:     0      OBJECTIVE VALUE:  0.8943e+01      NO. OF FUNC. EVALS.: 5
PARAMETER:   0.1098e+00  0.9997e-01  0.1085e+00  0.8684e-01
GRADIENT:    0.4124e+01 -0.5664e+00 -0.1038e+02 -0.4515e+01

ITERATION NO.:     2      OBJECTIVE VALUE:  0.8940e+01      NO. OF FUNC. EVALS.: 6
PARAMETER:   0.1097e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:    0.5923e-01  0.4162e-01 -0.5070e-01  0.1247e-01

ITERATION NO.:     4      OBJECTIVE VALUE:  0.8940e+01      NO. OF FUNC. EVALS.: 6
PARAMETER:   0.1096e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:   -0.2348e-03  0.4554e-03  0.5354e-03  0.3576e-04

ITERATION NO.:     6      OBJECTIVE VALUE:  0.8940e+01      NO. OF FUNC. EVALS.: 6
PARAMETER:   0.1096e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:   -0.5436e-05  0.0000e+00 -0.2194e-05  0.0000e+00

ITERATION NO.:     8      OBJECTIVE VALUE:  0.8940e+01      NO. OF FUNC. EVALS.: 9
PARAMETER:   0.1096e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:    0.1359e-04 -0.2861e-04 -0.6857e-04 -0.6557e-05

ITERATION NO.:    10      OBJECTIVE VALUE:  0.8940e+01      NO. OF FUNC. EVALS.: 1
PARAMETER:   0.1096e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:   -0.1087e-05  0.2384e-05 -0.2194e-05  0.0000e+00

MINIMIZATION ROUTINE SUCCESSFULLY TERMINATED
NO. OF FUNCTION EVALUATIONS USED:    68
NO. OF SIG. DIGITS IN FINAL EST.:  8.5
```

Fig. 33

```
FILE     NULL
PROB     SIMPLE NONLINEAR REGRESSION OF CP VS TIME DATA FROM ONE SUBJECT
DATA        0    0  10    3
ITEM        0    3   0    0   1
LABL     DOSE     TIME       CP
FORM
(3F10.0)
        320         .27       1.71
        320         .52       7.91
        320        1.0        8.31
        320        1.92       8.33
        320        3.5        6.85
        320        5.02       6.08
        320        7.03       5.4
        320        9.0        4.55
        320       12.0        3.01
        320       24.3         .90
STRC        3    1                   1
THCN        1
THTA                    .102      29.
LOWR             .4     .025      10.
UPPR           7.       .4        80.
DIAG    2
ESTM        0  240    4    2
COVR        0
TABL        0    1
TABL        1    2
SCAT        0    4
SCAT        2    3
SCAT        2    4
SCAT        2    5
SCAT        3    4                   1
```

****
****
****
****

INITIAL PARAMETER ESTIMATE

****
****
****
****

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

TH 1	TH 2	TH 3
1.50e+00	1.02e-01	2.90e+01

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

	ETA1
ETA1	1.20e+00

Fig. 35

```
      SUBROUTINE PRED (ICALL,NEWIND,THETA,DATREC,INDXS,F,G,H)
C
C     THETA(1)=ABSORPTION RATE CONSTANT (1/HR)
C     THETA(2)=ELIMINATION RATE CONSTANT (1/HR)
C     THETA(3)=VOLUME OF DISTRIBUTION (LITERS)
C     THETA(4)=POWER PARAMETER
C     DATREC(1)=DOSE (MG)
C     DATREC(2)=TIME (HR)
C
      DIMENSION THETA(*),DATREC(*),INDXS(*),G(*),H(*)
      DOUBLE PRECISION THETA,F,G,H,A,B,C,D
C
      A=EXP(-THETA(2)*DATREC(2))
      B=EXP(-THETA(1)*DATREC(2))
      C=THETA(1)-THETA(2)
      D=A-B
      F=((DATREC(1)*THETA(1))/(THETA(3)*C))*D
      G(1)=F**THETA(4)
      RETURN
      END
```

```
FILE     NULL
PROB     NONLINEAR REGRESSION WITH POWER FUNCTION VARIANCE MODEL
DATA        0    0  10    3
ITEM        0    3   0    0   1
LABL     DOSE     TIME       CP
FORM
(3F10.0)
        320         .27       1.71
        320         .52       7.91
        320        1.0        8.31
        320        1.92       8.33
        320        3.5        6.85
        320        5.02       6.08
        320        7.03       5.4
        320        9.0        4.55
        320       12.0        3.01
        320       24.3         .90
STRC         4    1                    1
THCN         1         10
THTA           1.7      .102      29.
LOWR            .4      .025      10.       0.
UPPR           7.       .4        80.       3.
DIAG    2
ESTM         0 240    4    2
COVR         0
TABL         0    1
TABL         1    2
SCAT         0    4
SCAT         2    3
SCAT         2    4
SCAT         2    6
SCAT         3    4                    1
```

```
      SUBROUTINE PRED (ICALL,NEWIND,THETA,DATREC,INDXS,F,G,H)
C
C     THETA(1)=PROPORTIONALITY CONSTANT
C     THETA(2)=ELIMINATION RATE CONSTANT (1/HR)
C     THETA(3)=VOLUME OF DISTRIBUTION (LITERS)
C     DATREC(1)=DOSE (MG)
C     DATREC(2)=TIME (HR)
C
      DIMENSION THETA(*),DATREC(*),INDXS(*),G(*),H(*)
      DOUBLE PRECISION THETA,F,G,H,B,C
C
      B=EXP(-THETA(2)*DATREC(2))
      C=DATREC(1)/THETA(3)*B
      F=C
      IF (DATREC(4).EQ.1.) F=THETA(1)*C
      G(1)=1.-DATREC(4)
      G(2)=DATREC(4)
      RETURN
      END
```

```
FILE     NULL
PROB     NONLINEAR REGRESSION WITH TWO TYPES OF OBSERVATIONS
DATA        0    0  23    4
ITEM        2    3   0    0   1
LABL     DOSE     TIME      CONC      P/S
FORM
(4F10.0)
        160        1.          5.32          0
        160        2.          4.88          0
        160        3.          4.1           0
        160        4.          4.21          0
        160        4.          2.24          1
        160        5.          3.96          0
        160        5.          2.31          1
        160        6.          3.76          0
        160        6.          2.05          1
        160        7.17        3.61          0
        160        7.17        1.91          1
        160        8.          3.40          0
        160        8.          1.90          1
        160        8.78        3.14          0
        160        8.78        1.84          1
        160        9.95        1.67          1
        160       12.00        1.47          1
        160       14.50        1.31          1
        160       15.92        1.17          1
        160       24.33        1.03          0
        160       26.           .89          0
        160       28.           .78          0
        160       32.           .56          0
STRC        3    2                      1
STRC        1    2
THCN        1
THTA          .60       .07     28.1
LOWR          .12       .01      6.0
UPPR         3.0        .40    140.0
BLST    2
ESTM        0 450    4    5
COVR        0
TABL        0    1
TABL        2    2    2    4    1
SCAT        0    8
SCAT        2    3
SCAT        2    3    1    4
SCAT        2    5
SCAT        2    5    1    4
SCAT        2    6
SCAT        2    6    1    4
SCAT        3    5                   1
SCAT        3    5    1    4         1
```

TABLE NO. 1

LINE NO.	P/S	TIME	CONC	PRED	RES	WRES
1	0.00e+00	1.00e+00	5.32e+00	5.09e+00	2.31e-01	1.36e+00
2	0.00e+00	2.00e+00	4.88e+00	4.78e+00	9.79e-02	5.77e-01
3	0.00e+00	3.00e+00	4.10e+00	4.49e+00	-3.94e-01	-2.32e+00
4	0.00e+00	4.00e+00	4.21e+00	4.22e+00	-1.31e-02	-1.19e-01
5	0.00e+00	5.00e+00	3.96e+00	3.97e+00	-8.65e-03	-3.13e-02
6	0.00e+00	6.00e+00	3.76e+00	3.73e+00	3.05e-02	1.64e-01
7	0.00e+00	7.17e+00	3.61e+00	3.47e+00	1.42e-01	8.25e-01
8	0.00e+00	8.00e+00	3.40e+00	3.29e+00	1.06e-01	6.40e-01
9	0.00e+00	8.78e+00	3.14e+00	3.14e+00	2.28e-03	3.30e-02
10	0.00e+00	2.43e+01	1.03e+00	1.19e+00	-1.64e-01	-9.65e-01
11	0.00e+00	2.60e+01	8.90e-01	1.08e+00	-1.86e-01	-1.10e+00
12	0.00e+00	2.80e+01	7.80e-01	9.50e-01	-1.70e-01	-1.00e+00
13	0.00e+00	3.20e+01	5.60e-01	7.41e-01	-1.81e-01	-1.07e+00
14	1.00e+00	4.00e+00	2.24e+00	2.38e+00	-1.44e-01	-2.18e+00
15	1.00e+00	5.00e+00	2.31e+00	2.24e+00	6.95e-02	1.05e+00
16	1.00e+00	6.00e+00	2.05e+00	2.11e+00	-5.55e-02	-8.28e-01
17	1.00e+00	7.17e+00	1.91e+00	1.96e+00	-4.78e-02	-6.81e-01
18	1.00e+00	8.00e+00	1.90e+00	1.86e+00	4.06e-02	6.42e-01
19	1.00e+00	8.78e+00	1.84e+00	1.77e+00	6.86e-02	1.03e+00
20	1.00e+00	9.95e+00	1.67e+00	1.65e+00	2.28e-02	3.43e-01
21	1.00e+00	1.20e+01	1.47e+00	1.45e+00	1.99e-02	2.99e-01
22	1.00e+00	1.45e+01	1.31e+00	1.24e+00	6.86e-02	1.03e+00
23	1.00e+00	1.59e+01	1.17e+00	1.14e+00	3.34e-02	5.03e-01

Fig. 40

Fig. 41

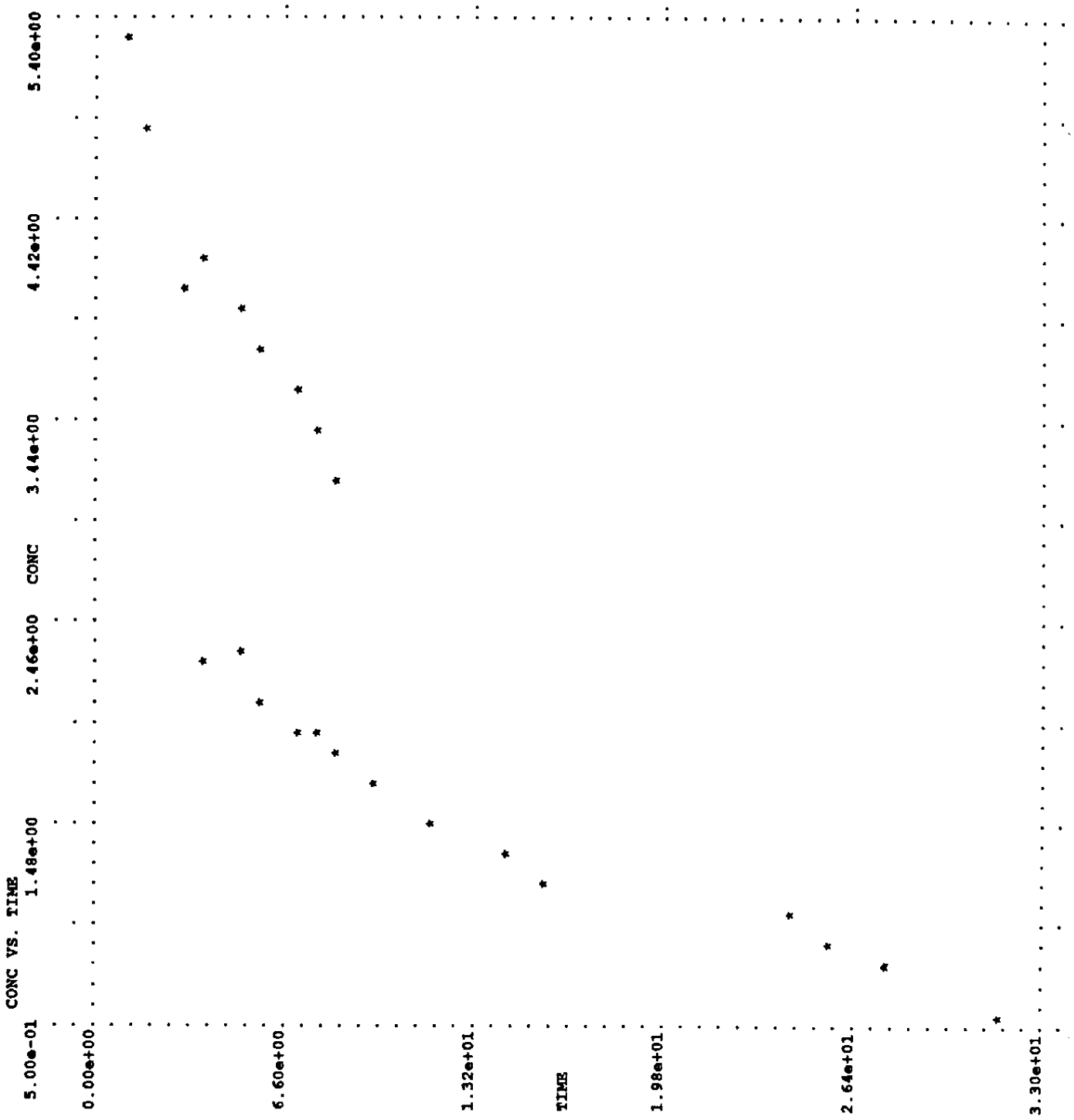

CONC VS. TIME
CONC
TIME
5.00e-01
1.48e+00
2.46e+00
3.44e+00
4.42e+00
5.40e+00
0.00e+00
6.60e+00
1.32e+01
1.98e+01
2.64e+01
3.30e+01

Fig. 42

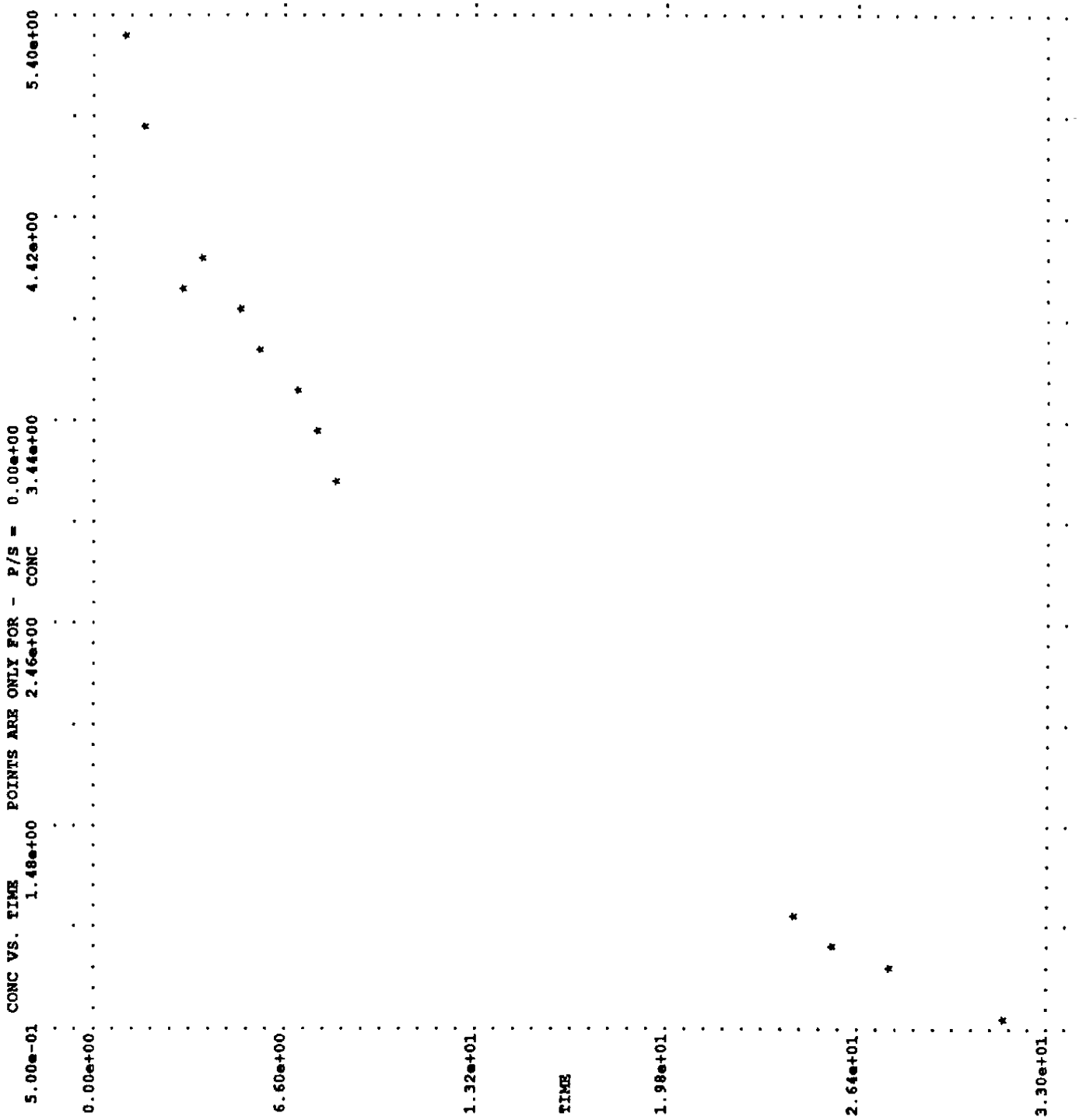

CONC VS. TIME POINTS ARE ONLY FOR - P/S = 0.00e+00
5.00e-01 1.48e+00 2.46e+00 CONC 3.44e+00 4.42e+00 5.40e+00
0.00e+00
6.60e+00
1.32e+01
TIME
1.98e+01
2.64e+01
3.30e+01

Fig. 43

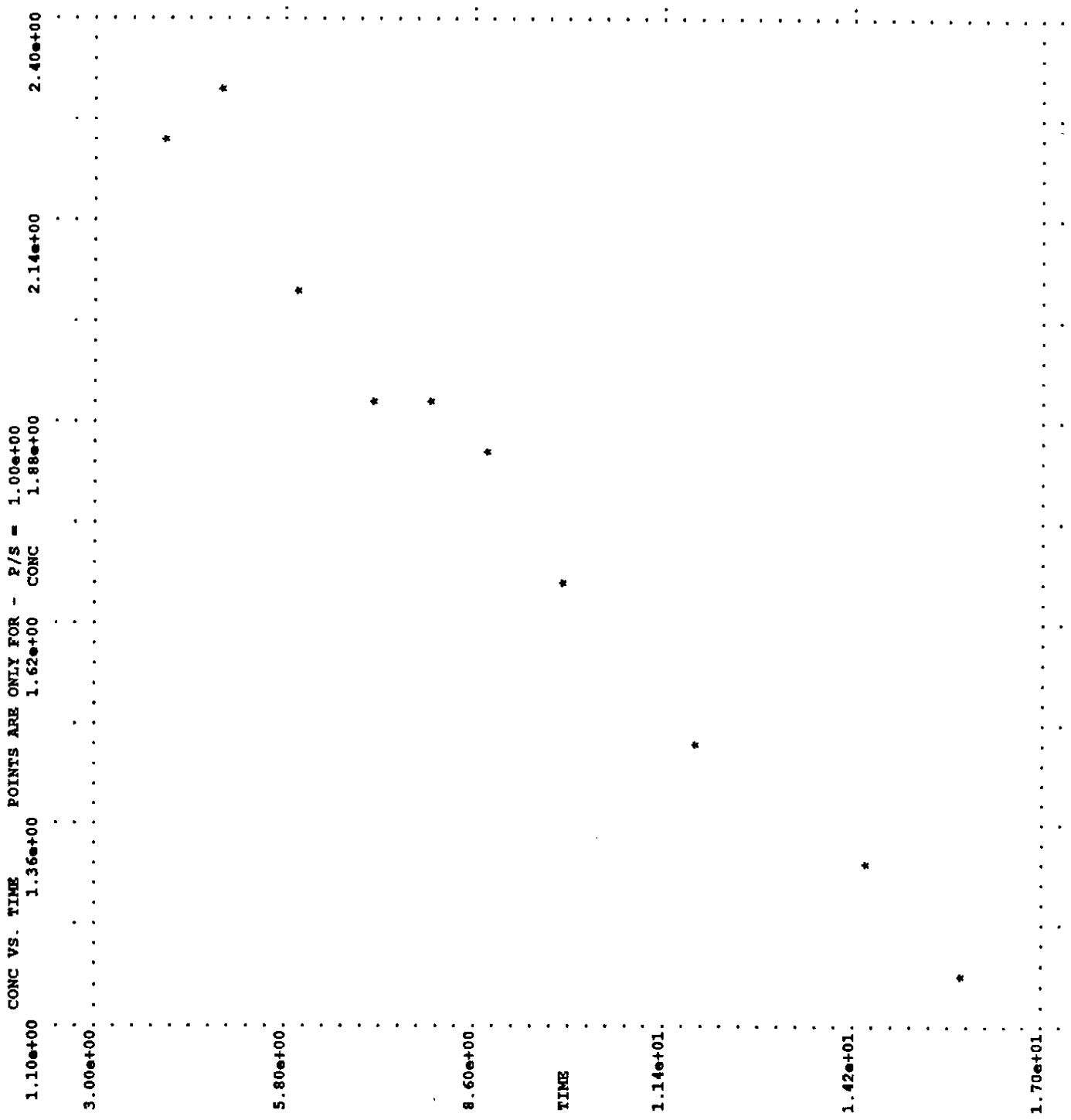

CONC VS. TIME POINTS ARE ONLY FOR - P/S = 1.00e+00
1.10e+00
1.36e+00
1.62e+00
CONC
1.88e+00
2.14e+00
2.40e+00
3.00e+00.
5.80e+00.
8.60e+00.
TIME
1.14e+01.
1.42e+01.
1.70e+01.

Fig. 44

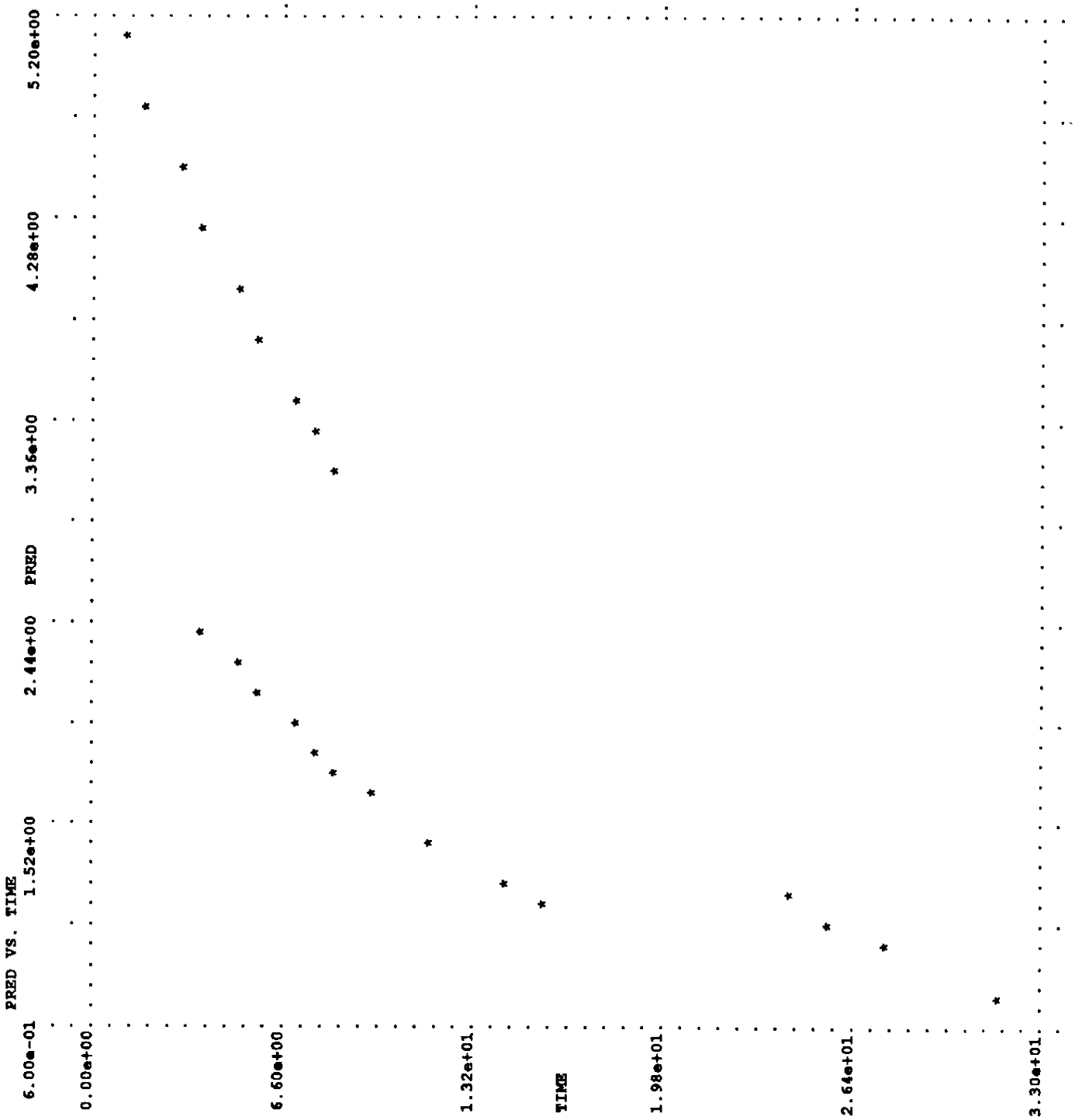

PRED VS. TIME
6.00e-01
1.52e+00
2.44e+00
PRED
3.36e+00
4.28e+00
5.20e+00
0.00e+00
6.60e+00
1.32e+01
TIME
1.98e+01
2.64e+01
3.30e+01

Fig. 45

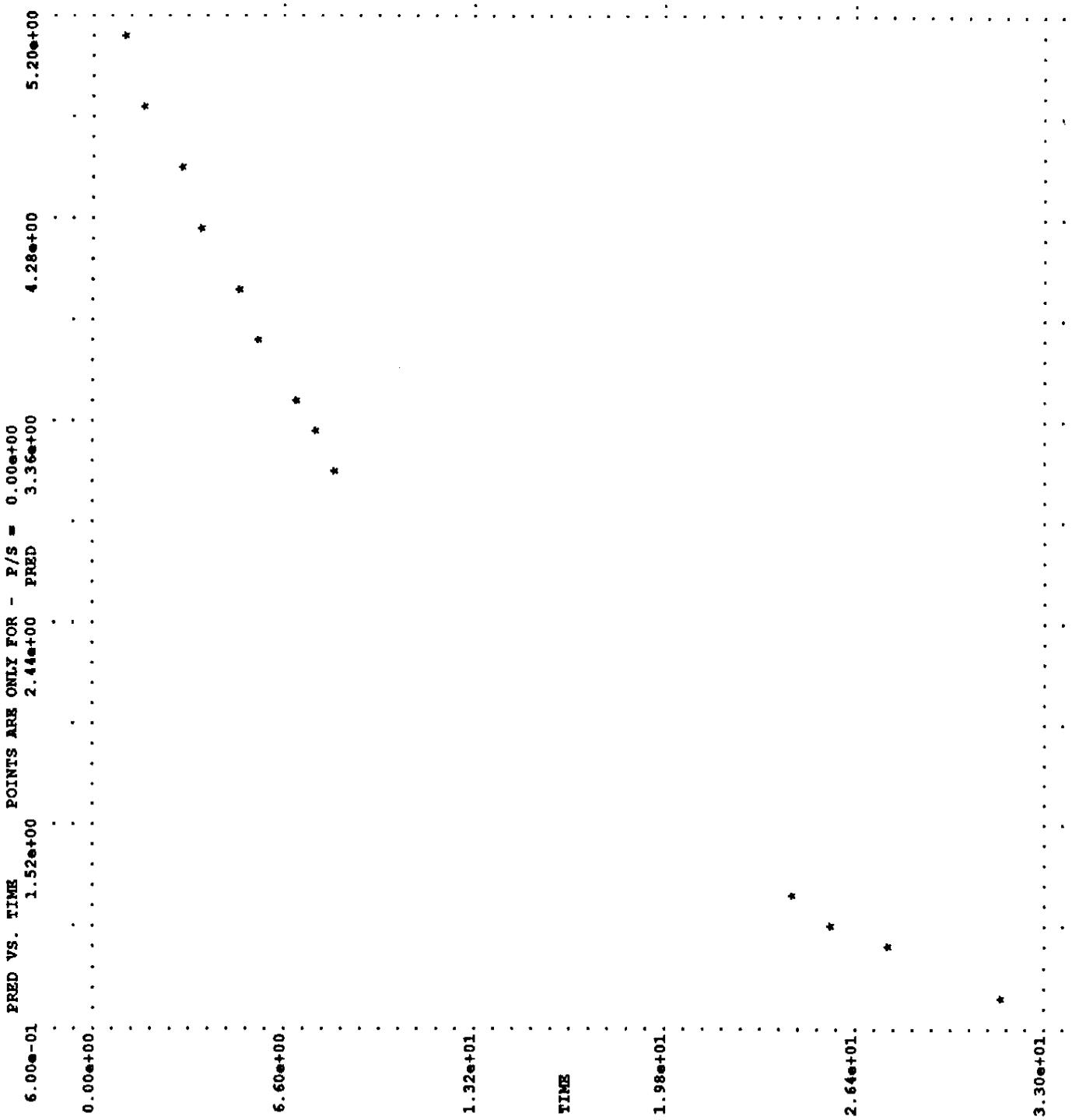

PRED VS. TIME POINTS ARE ONLY FOR - P/S = 0.00e+00
6.00e-01
1.52e+00
2.44e+00
PRED
3.36e+00
4.28e+00
5.20e+00
0.00e+00
6.60e+00
1.32e+01
TIME
1.98e+01
2.64e+01
3.30e+01

Fig. 46

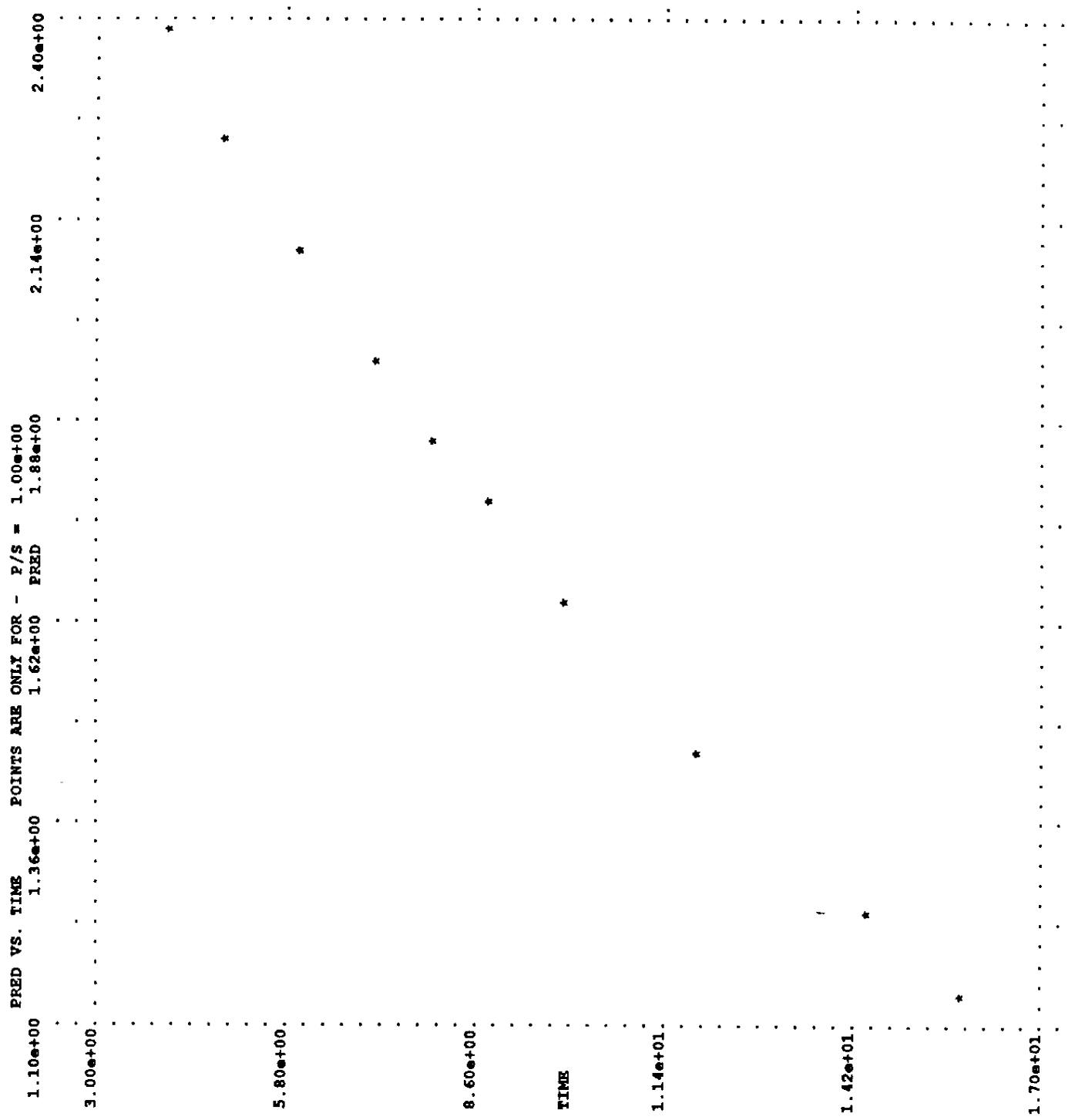

PRED VS. TIME POINTS ARE ONLY FOR - P/S = 1.00e+00
1.10e+00
1.36e+00
1.62e+00
PRED
1.88e+00
2.14e+00
2.40e+00
3.00e+00
5.80e+00
8.60e+00
TIME
1.14e+01
1.42e+01
1.70e+01

Fig. 47

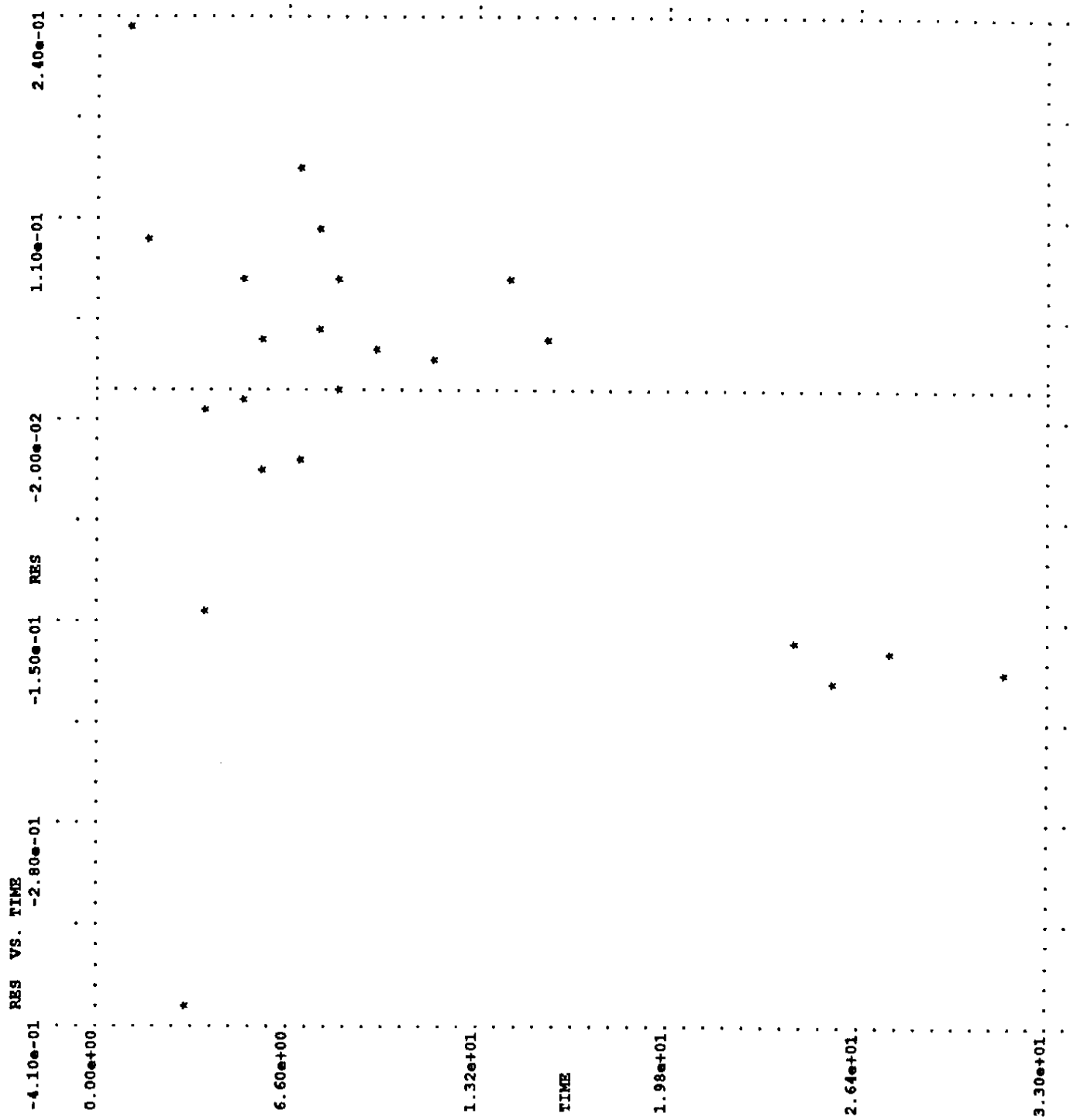

RES VS. TIME
RES
TIME
-4.10e-01
-2.80e-01
-1.50e-01
-2.00e-02
1.10e-01
2.40e-01
0.00e+00
6.60e+00
1.32e+01
1.98e+01
2.64e+01
3.30e+01

Fig. 48

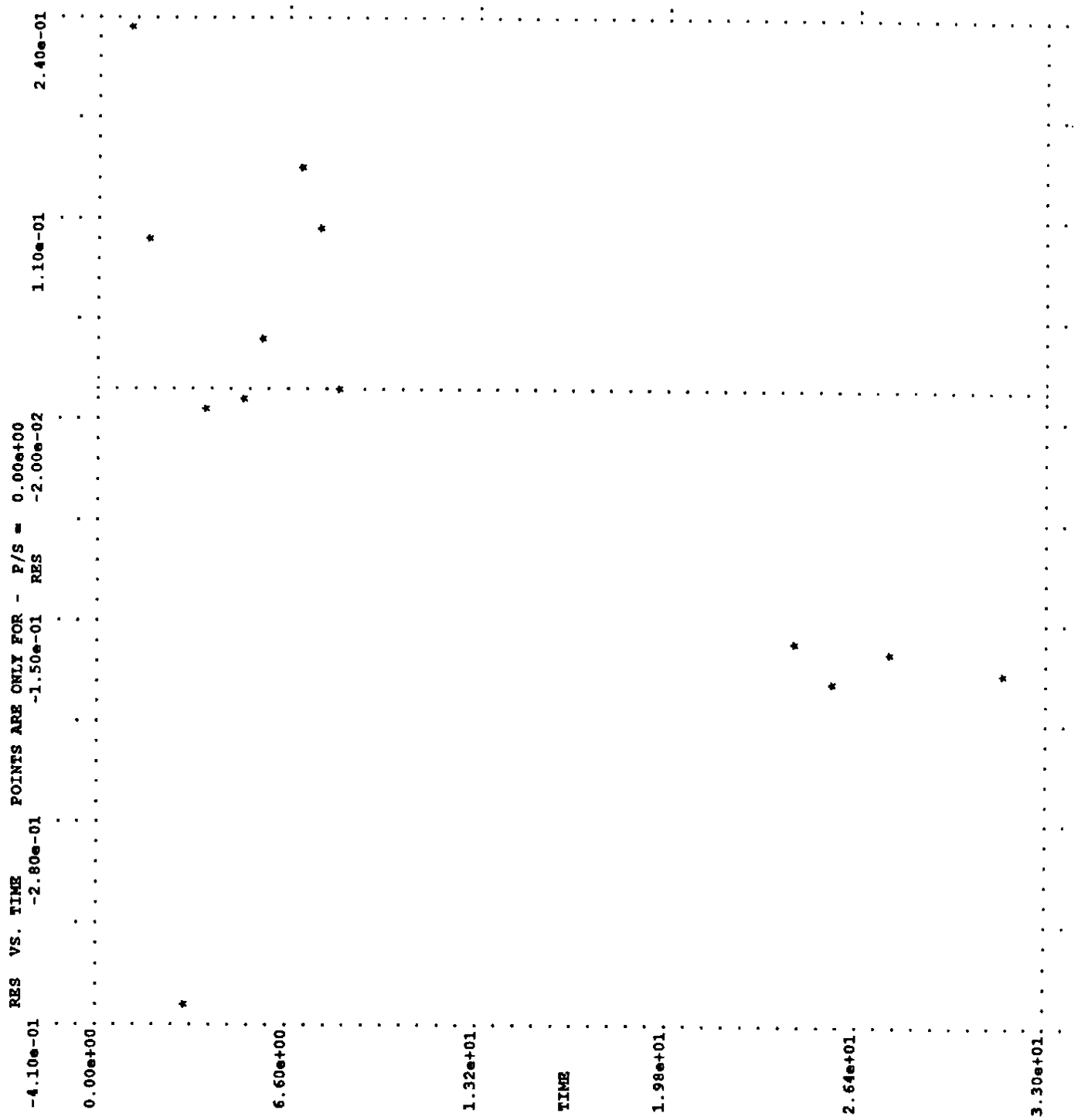

RES VS. TIME POINTS ARE ONLY FOR - P/S = 0.00e+00
-4.10e-01
-2.80e-01
-1.50e-01
RES
-2.00e-02
1.10e-01
2.40e-01
0.00e+00
6.60e+00
1.32e+01
TIME
1.98e+01
2.64e+01
3.30e+01

Fig. 49

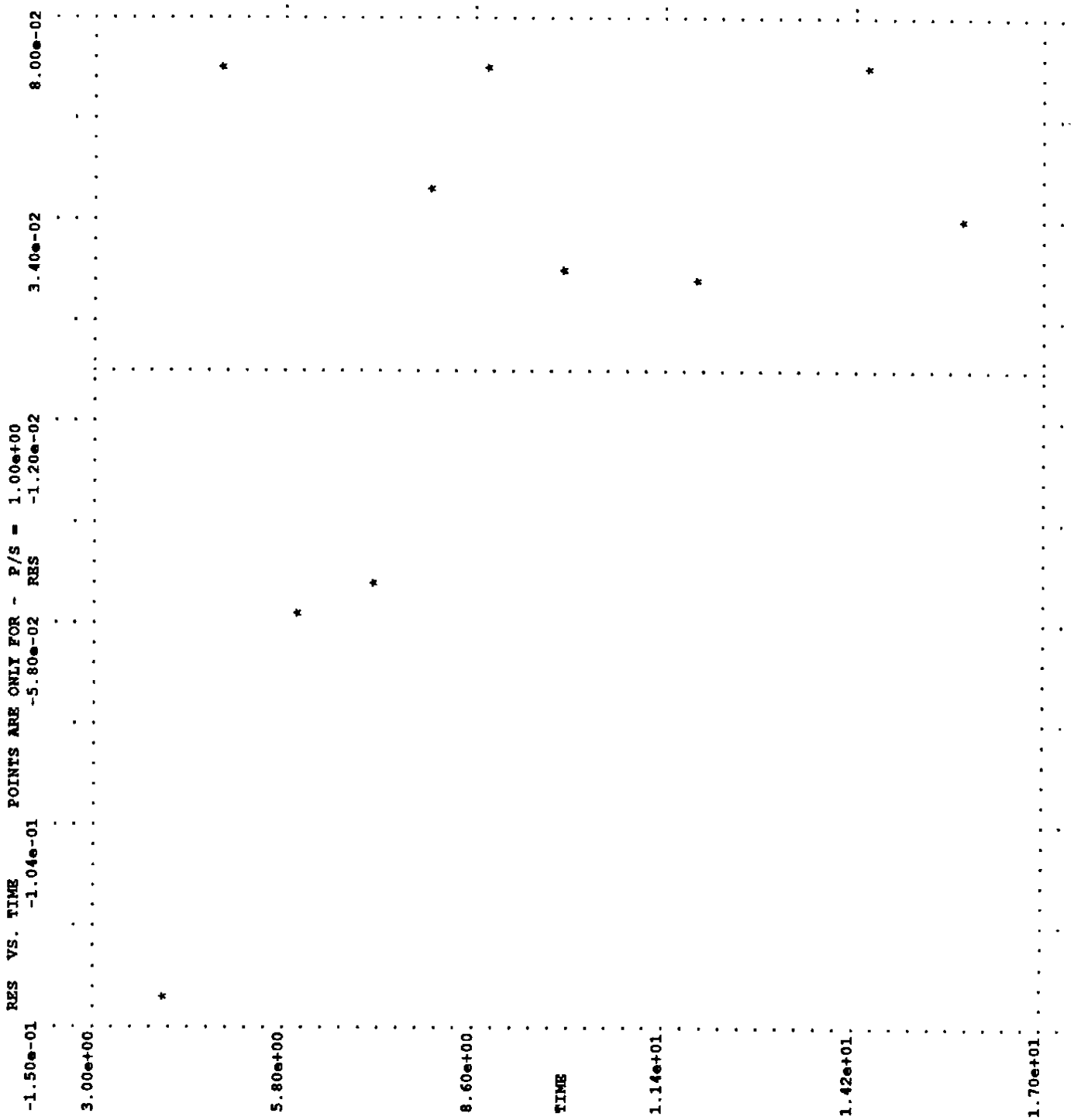

RES VS. TIME POINTS ARE ONLY FOR - P/S = 1.00e+00
-1.50e-01
-1.04e-01
-5.80e-02
RES
-1.20e-02
3.40e-02
8.00e-02
3.00e+00
5.80e+00
8.60e+00
TIME
1.14e+01
1.42e+01
1.70e+01

Fig. 50

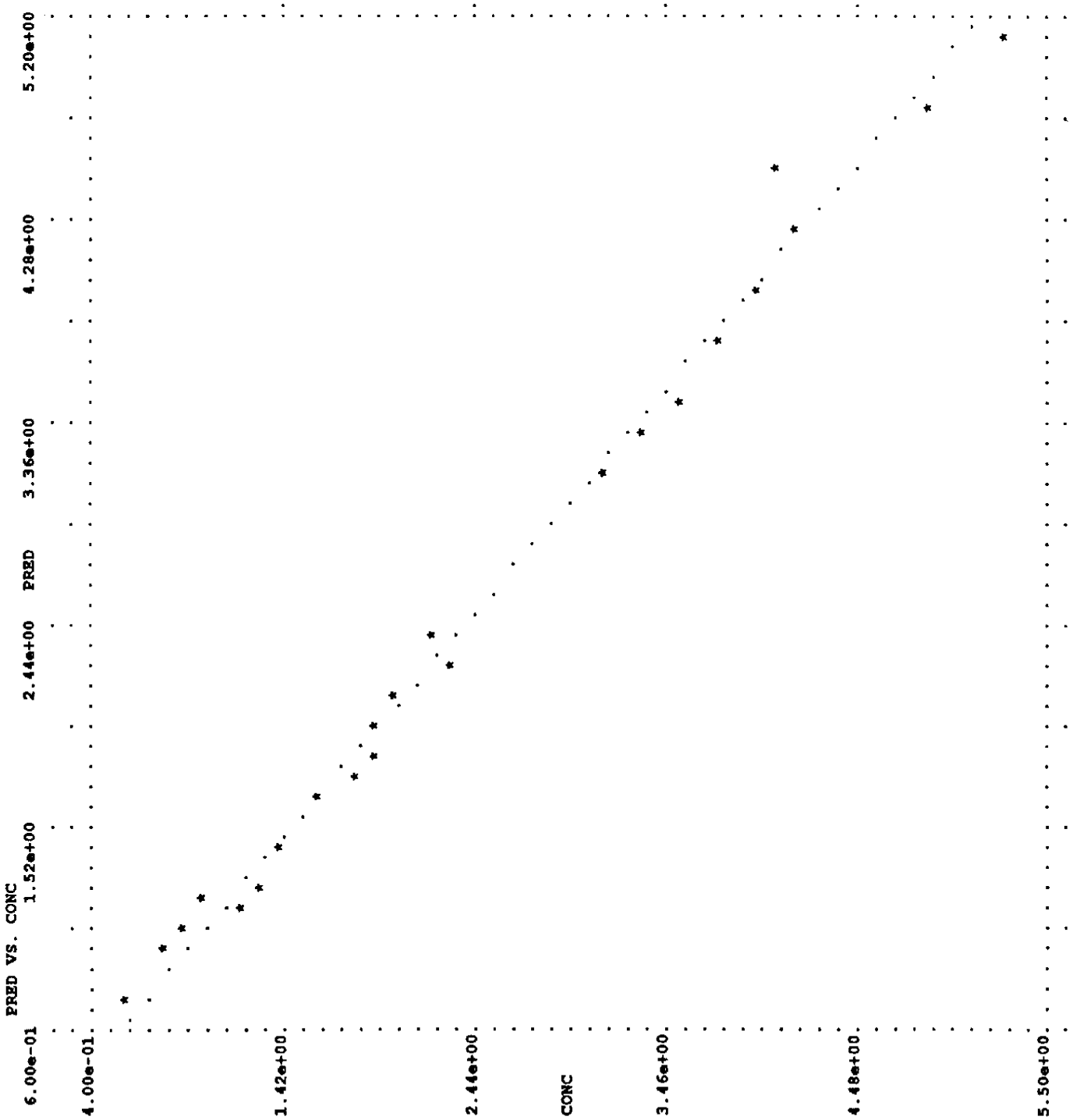

PRED VS. CONC
6.00e-01
4.00e-01
1.52e+00
2.44e+00
PRED
3.36e+00
4.28e+00
5.20e+00
1.42e+00
2.44e+00
CONC
3.46e+00
4.48e+00
5.50e+00

Fig. 51

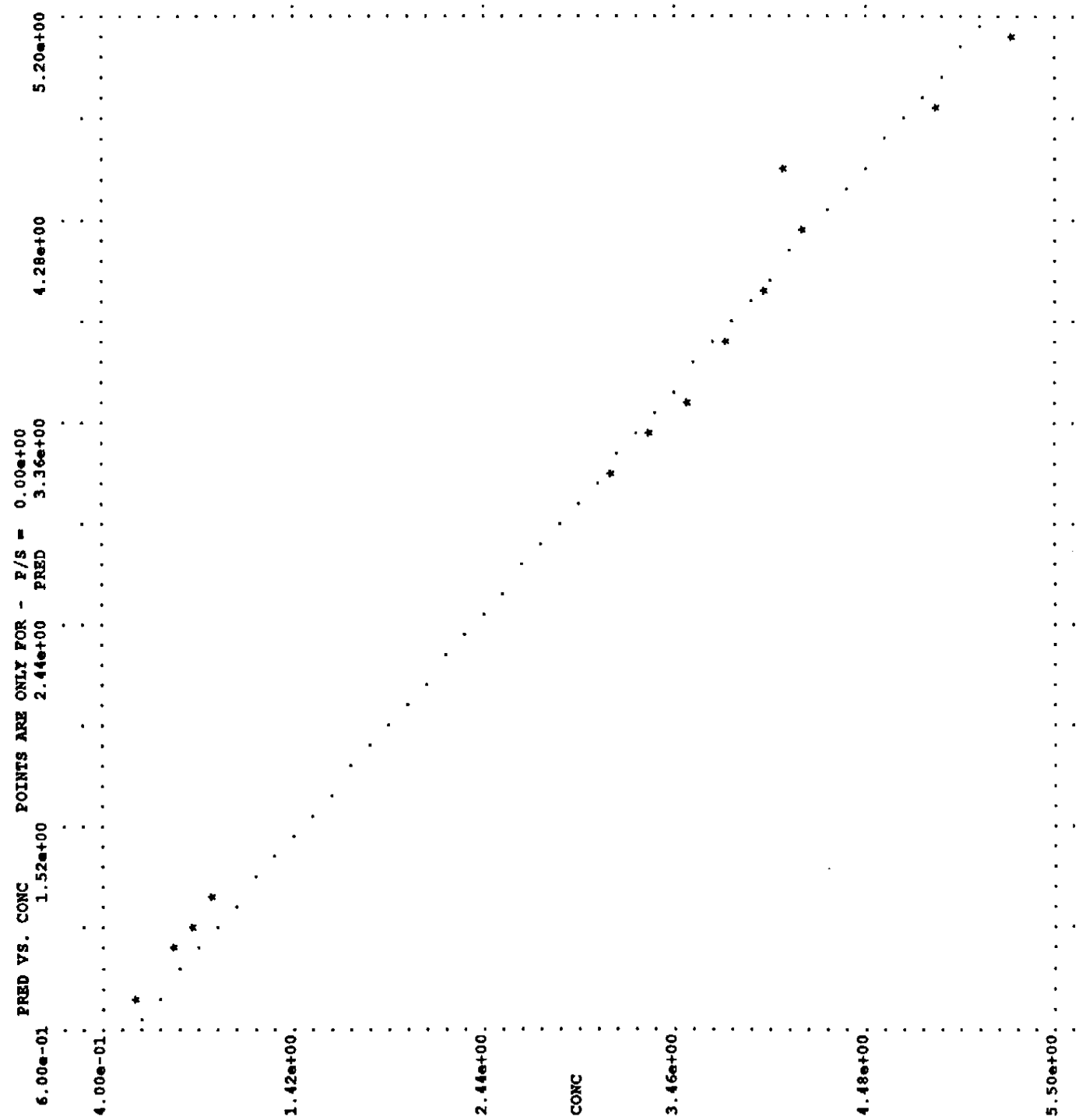
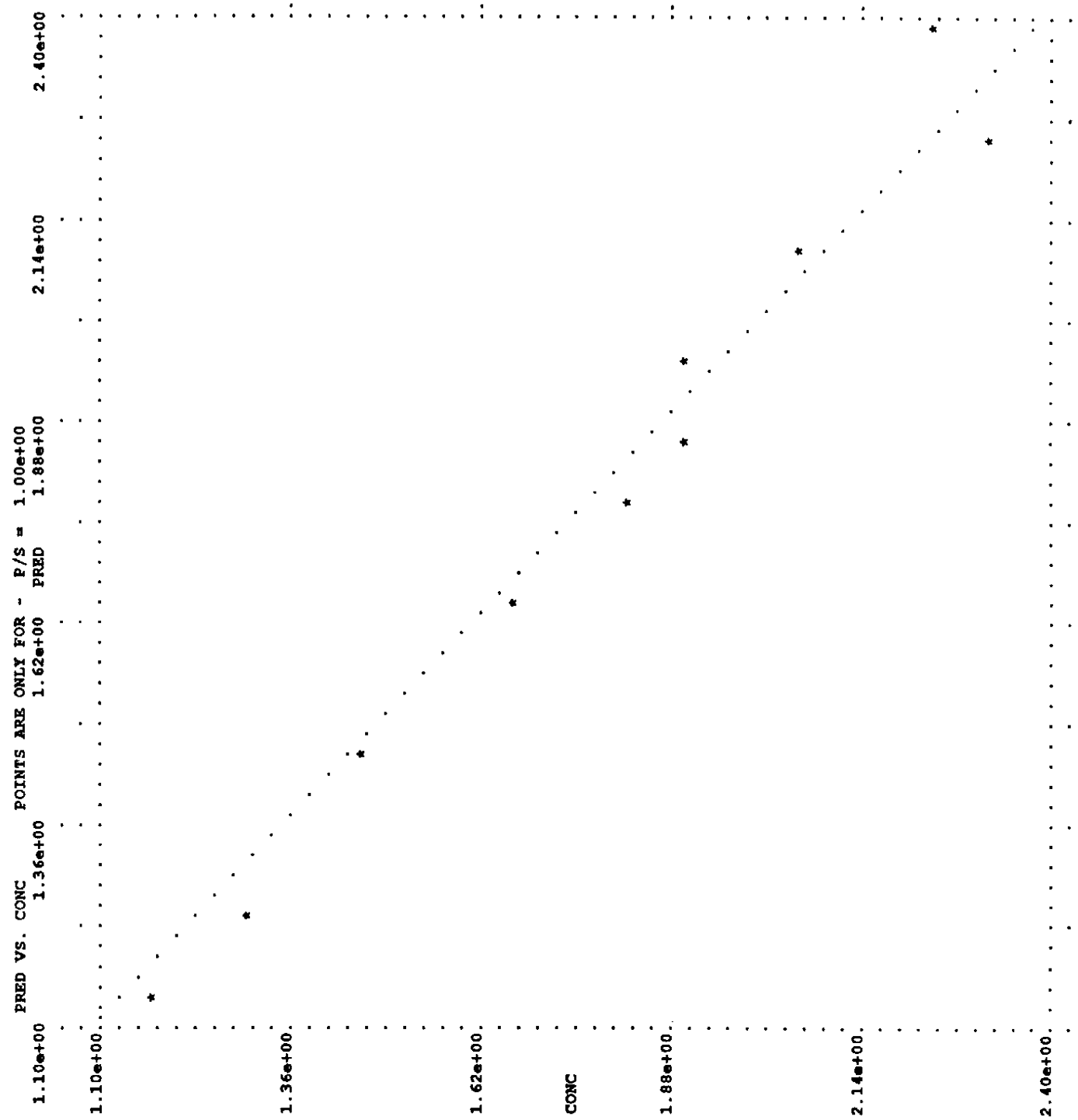

PRED VS. CONC POINTS ARE ONLY FOR - P/S = 0.00e+00
6.00e-01 1.52e+00 2.44e+00 PRED 3.36e+00 4.28e+00 5.20e+00
4.00e-01
1.42e+00
2.44e+00
CONC
3.46e+00
4.48e+00
5.50e+00

Fig. 52


PRED VS. CONC POINTS ARE ONLY FOR - P/S = 1.00e+00
1.10e+00 1.36e+00 1.62e+00 PRED 1.88e+00 2.14e+00 2.40e+00
1.10e+00
1.36e+00
1.62e+00
CONC
1.88e+00
2.14e+00
2.40e+00

```
NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM)    DOUBLE PRECISION NONMEM    VERSION III LEVEL 1.0
DEVELOPED AND PROGRAMMED BY STUART BEAL AND LEWIS SHEINER

PROBLEM NO.  1
NONLINEAR REGRESSION WITH TWO TYPES OF OBSERVATIONS

NO. OF DATA RECS IN DATA SET:   23
NO. OF DATA ITEMS IN DATA SET:   4
ID DATA ITEM IS DATA ITEM NO.:   2
DEP VARIABLE IS DATA ITEM NO.:   3

LABELS TO BE USED FOR ITEMS APPEARING
       IN TABLES AND SCATTERPLOTS ARE:
DOSE    TIME    CONC     P/S    PRED    RES     WRES

FORMAT FOR DATA IS:
(4F10.0)

TOT. NO. OF OBS RECS:      23
TOT. NO. OF INDIVIDUALS:   17

LENGTH OF THETA:  3

OMEGA HAS BLOCK FORM:
 1
 1  1

INITIAL ESTIMATE OF THETA:
LOWER BOUND    INITIAL EST    UPPER BOUND
 0.1200e+00     0.6000e+00     0.3000e+01
 0.1000e-01     0.7000e-01     0.4000e+00
 0.6000e+01     0.2810e+02     0.1400e+03

ESTIMATION STEP OMITTED:    NO
NO. OF FUNCT. EVALS. ALLOWED:  450
NO. OF SIG. FIGURES REQUIRED:    4
INTERMEDIATE PRINTOUT:   YES
CONVERGENCE REPEATED:     NO
MSF OUTPUT:               NO

COVARIANCE STEP OMITTED:    NO
EIGENVLS. PRINTED:    NO
SPECIAL COMPUTATION:  NO

TABLES STEP OMITTED:    NO
NO. OF TABLES:       1
TABLES PRINTED:    YES
TABLES FILE USED:   NO

USER CHOSEN DATA ITEMS FOR TABLE  1,
IN THE ORDER THEY WILL APPEAR IN THE TABLE, ARE:
 P/S    TIME
     THE FIRST 2 OF THESE WILL BE SORTED IN THE ORDER IN WHICH THEY APPEAR
```

Fig. 53a

```
SCATTERPLOT STEP OMITTED:    NO
NO. OF PAIRS OF ITEMS GENERATING
        FAMILIES OF SCATTERPLOTS:  9

ITEMS TO BE SCATTERED ARE:    TIME    CONC
ITEMS TO BE SCATTERED ARE:    TIME    CONC
    FOR FIXED VALUES OF ITEMS:     P/S
ITEMS TO BE SCATTERED ARE:    TIME    PRED
ITEMS TO BE SCATTERED ARE:    TIME    PRED
    FOR FIXED VALUES OF ITEMS:     P/S
ITEMS TO BE SCATTERED ARE:    TIME    RES
ITEMS TO BE SCATTERED ARE:    TIME    RES
    FOR FIXED VALUES OF ITEMS:     P/S
ITEMS TO BE SCATTERED ARE:    TIME    WRES
    FOR FIXED VALUES OF ITEMS:     P/S
ITEMS TO BE SCATTERED ARE:    CONC    PRED
    UNIT SLOPE LINE INCLUDED
ITEMS TO BE SCATTERED ARE:    CONC    PRED
    FOR FIXED VALUES OF ITEMS:     P/S
    UNIT SLOPE LINE INCLUDED
```

Fig. 53b

****
****
****
****
****

FINAL PARAMETER ESTIMATE

****
****
****
****
****

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

TH 1	TH 2	TH 3
5.65e-01	6.22e-02	2.95e+01

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

	ETA1	ETA2
ETA1	2.88e-02	
ETA2	-7.55e-04	4.42e-03

Fig. 54

Fig. 55

```
************************************************************************************************************************
********************                                                                             **********************
********************                       STANDARD ERROR OF ESTIMATE                            **********************
********************                                                                             **********************
************************************************************************************************************************
```

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

TH 1	TH 2	TH 3
1.21e-02	5.65e-03	1.12e+00

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

	ETA1	ETA2
ETA1	2.13e-02	
ETA2	7.11e-04	3.34e-03

****
****
****
****

CORRELATION MATRIX OF ESTIMATE

****
****
****
****

	TH 1	TH 2	TH 3	OM11	OM12	OM22
TH 1	1.00e+00					
TH 2	3.76e-01	1.00e+00				
TH 3	-1.13e-01	-9.37e-01	1.00e+00			
OM11	-1.42e-01	-8.94e-01	9.25e-01	1.00e+00		
OM12	-1.54e-01	7.98e-01	-9.03e-01	-9.01e-01	1.00e+00	
OM22	1.07e-01	8.42e-01	-7.70e-01	-7.83e-01	8.00e-01	1.00e+00

Fig. 56

```
      SUBROUTINE PRED (ICALL,NEWIND,THETA,DATREC,INDXS,F,G,H)
C
C     THETA(1)=SLOPE (LITERS/HR/KG)
C     THETA(2)=INTERCEPT (LITERS/HR)
C     DATREC(2)=WEIGHT (KG)
C
      DIMENSION THETA(*),DATREC(*),INDXS(*),G(*),H(*)
      DOUBLE PRECISION THETA,F,G,H
C
      F=THETA(1)*DATREC(2)+THETA(2)
      G(1)=1.
      H(1)=1.
      RETURN
      END
```

```
FILE     NULL
PROB     LIN REGRESSION OF CLEARANCE VS WT; REPEATED MEASURES
DATA        0    0  72    3
ITEM        1    3   0    0    1
LABL       ID       WT       CL
FORM
(F2.0,3X,F4.0,1X,F6.0)
 1    79.6 1.850
 1    79.6 2.642
 1    79.6 1.963
 1    79.6 2.415
 1    79.6 1.905
 1    79.6 2.120
 2    72.4 3.270
 2    72.4 3.600
 2    72.4 3.530
 2    72.4 3.689
 2    72.4 3.940
 2    72.4 4.526
 3    70.5 2.977
 3    70.5 3.143
 3    70.5 3.497
 3    70.5 3.264
 3    70.5 3.447
 3    70.5 3.652
 4    72.7 2.768
 4    72.7 3.183
 4    72.7 3.119
 4    72.7 3.435
 4    72.7 3.520
 4    72.7 3.603
 5    54.6 2.335
 5    54.6 2.241
 5    54.6 2.149
 5    54.6 2.381
 5    54.6 2.184
 5    54.6 1.805
 6    80.0 3.885
 6    80.0 3.079
 6    80.0 3.600
 6    80.0 3.963
 6    80.0 3.598
 6    80.0 3.415
 7    64.6 3.175
 7    64.6 3.260
 7    64.6 3.590
 7    64.6 3.154
 7    64.6 3.616
 7    64.6 3.027
 8    70.5 3.140
 8    70.5 3.310
 8    70.5 3.426
 8    70.5 3.445
 8    70.5 3.237
 8    70.5 3.279
 9    86.4 3.247
 9    86.4 2.628
 9    86.4 3.296
 9    86.4 3.380
 9    86.4 3.621
 9    86.4 3.240
```

```
10    58.2 1.889
10    58.2 2.800
10    58.2 1.865
10    58.2 1.828
10    58.2 3.106
10    58.2 2.386
11    65.0 3.674
11    65.0 4.151
11    65.0 3.670
11    65.0 3.324
11    65.0 4.941
11    65.0 4.129
12    60.5 2.331
12    60.5 2.521
12    60.5 3.194
12    60.5 2.928
12    60.5 2.868
12    60.5 2.406
STRC        2   1   1            1        1
THCN        1
THTA          .04        0
LOWR    -1000000         0
UPPR     1000000         0
DIAG           .4
DIAG           .1
ESTM        0 150   4
COVR        0
TABL        0   1
TABL        2   1        2
SCAT        0   2
SCAT        2   5
SCAT        2   6
```

```
********************************************************************************************************************************
**********                                                                                                          **********
**********                                    FINAL PARAMETER ESTIMATE                                              **********
**********                                                                                                          **********
********************************************************************************************************************************

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

           TH 1      TH 2

        4.41e-02  0.00e+00


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

           ETA1

ETA1     3.26e-01


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

           EPS1

EPS1     1.25e-01
```

Fig. 59

```
********************************************************************************************************************************
**********                                                                                                          **********
**********                                    STANDARD ERROR OF ESTIMATE                                            **********
**********                                                                                                          **********
********************************************************************************************************************************


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

           TH 1      TH 2

        2.56e-03 .........


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

           ETA1

ETA1    1.61e-01


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

           EPS1

EPS1    2.65e-02
```

Fig. 60

****
****
****
****

CORRELATION MATRIX OF ESTIMATE

****
****
****
****

	TH 1	TH 2	OM11	SG11
TH 1	1.00e+00			
TH 2	.....	.....		
OM11	-3.75e-01	.....	1.00e+00	
SG11	2.90e-01	.....	2.87e-01	1.00e+00

Fig. 61

Fig. 62

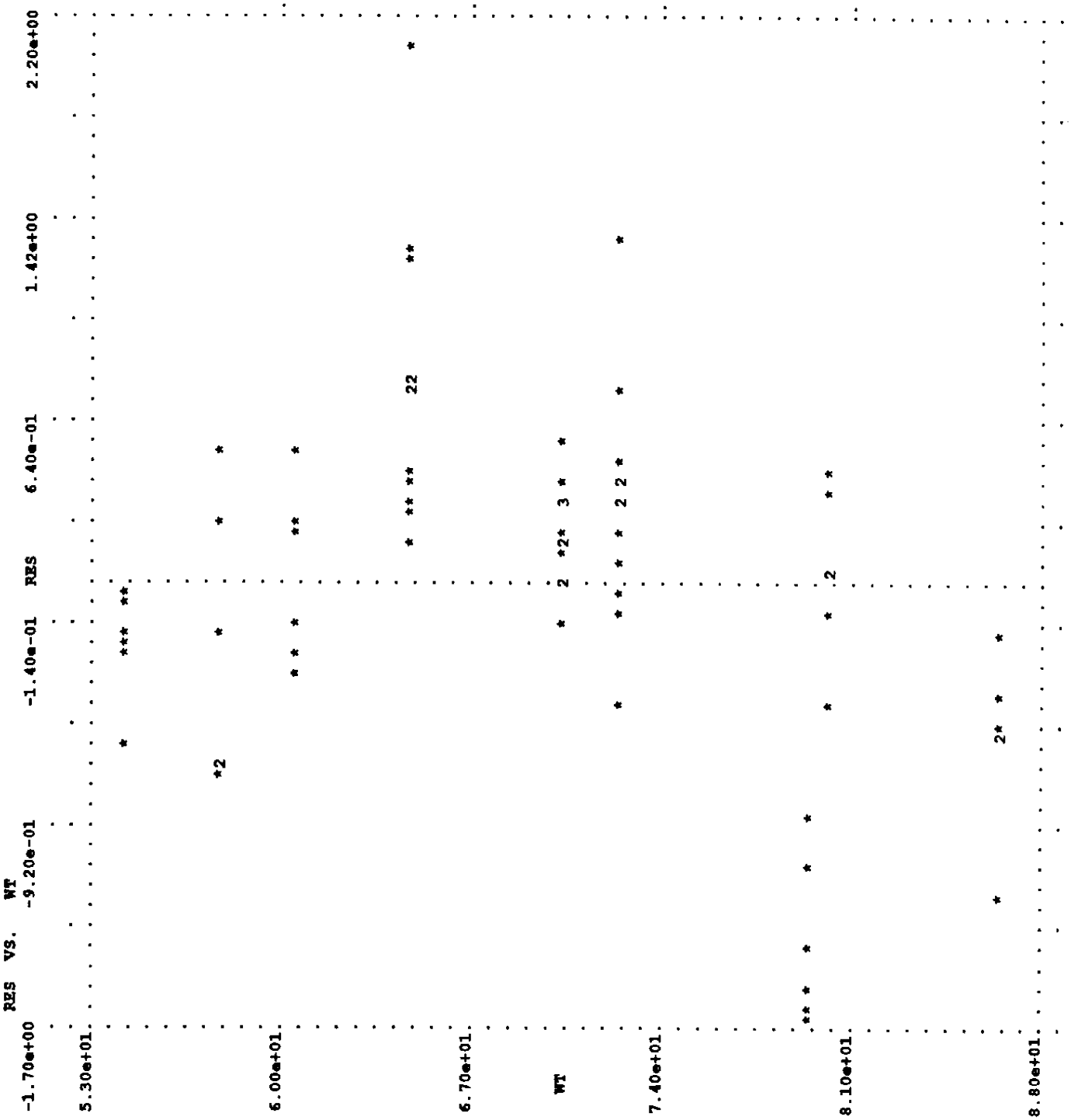
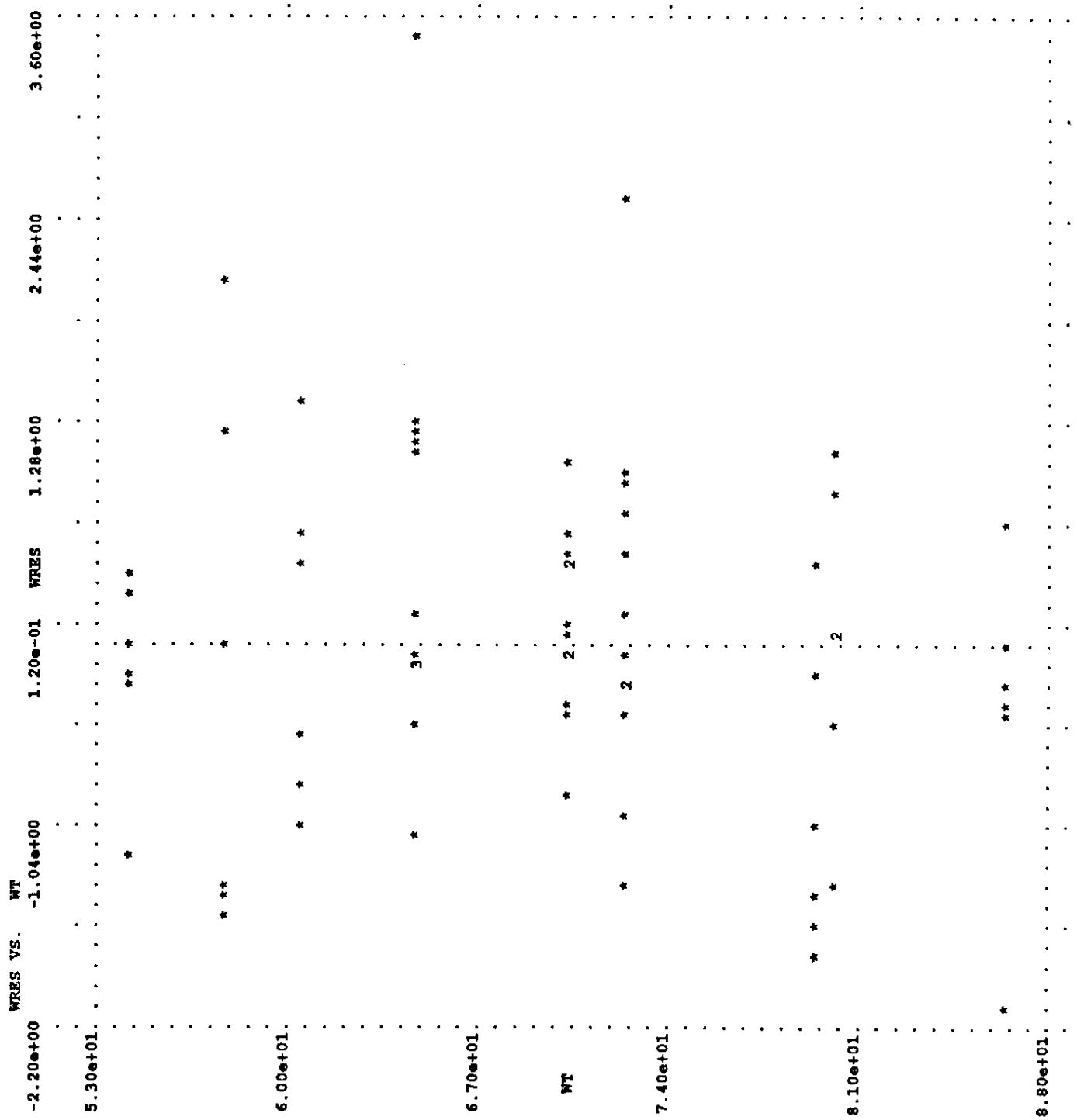

RES VS. WT
-1.70e+00
-9.20e-01
-1.40e-01
1.42e+00
2.20e+00
6.40e-01
RES
5.30e+01
6.00e+01
6.70e+01
7.40e+01
8.10e+01
8.80e+01
WT

Fig. 63


WRES VS. WT
-2.20e+00
-1.04e+00
1.20e-01
1.28e+00
2.44e+00
3.60e+00
WRES
5.30e+01
6.00e+01
6.70e+01
7.40e+01
8.10e+01
8.80e+01
WT

```
      SUBROUTINE PRED (ICALL,NEWIND,THETA,DATREC,INDXS,F,G,H)
C
C     THETA(1)=SLOPE (LITERS/HR/KG)
C     THETA(2)=INTERCEPT (LITERS/HR)
C     THETA(3)=MEAN KE (1/HR)
C     DATREC(2)=WEIGHT (KG)
C     DATREC(4)=TYPE DATA ITEM
C
      DIMENSION THETA(*),DATREC(*),INDXS(*),G(*),H(*)
      DOUBLE PRECISION THETA,F,G,H
C
      IF (DATREC(4).EQ.0.) THEN
         F=THETA(1)*DATREC(2)+THETA(2)
         G(1)=1.
         G(2)=0.
         H(1)=1.
         H(2)=0.
      ELSE
         F=THETA(3)
         G(1)=0.
         G(2)=1.
         H(1)=0.
         H(2)=1.
      ENDIF
      RETURN
      END
```

```
FILE     NULL
PROB     MULTIV LIN REG OF CLEARANCE AND RATE CONSTANT VS WT; REPEATED MEASURES
DATA        0    0 144    5
ITEM        1    3    0    0    1        5
LABL       L1        WT        CL     TYPE       L2
FORM
(F2.0,3X,F4.0,1X,F6.0,2(1X,F1.0))
 1    79.6 1.850
 1    79.6  .0475 1
 1    79.6 2.642    1
 1    79.6  .0558 1 1
 1    79.6 1.963
 1    79.6  .0440 1
 1    79.6 2.415    1
 1    79.6  .0560 1 1
 1    79.6 1.905
 1    79.6  .0442 1
 1    79.6 2.120    1
 1    79.6  .0513 1 1
 2    72.4 3.270
 2    72.4  .0996 1
 2    72.4 3.600    1
 2    72.4  .0919 1 1
 2    72.4 3.530
 2    72.4  .0961 1
 2    72.4 3.689    1
 2    72.4  .0940 1 1
 2    72.4 3.940
 2    72.4  .0996 1
 2    72.4 4.526    1
 2    72.4  .0996 1 1
 3    70.5 2.977
 3    70.5  .0942 1
 3    70.5 3.143    1
 3    70.5  .0731 1 1
 3    70.5 3.497
 3    70.5  .1000 1
 3    70.5 3.264    1
 3    70.5  .0843 1 1
 3    70.5 3.447
 3    70.5  .0818 1
 3    70.5 3.652    1
 3    70.5  .0986 1 1
 4    72.7 2.768
 4    72.7  .0922 1
 4    72.7 3.183    1
 4    72.7  .0885 1 1
 4    72.7 3.119
 4    72.7  .0859 1
 4    72.7 3.435    1
 4    72.7  .0926 1 1
 4    72.7 3.520
 4    72.7  .0968 1
 4    72.7 3.603    1
 4    72.7  .0880 1 1
```

```
5    54.6 2.335
5    54.6  .0840 1
5    54.6 2.241    1
5    54.6  .0907 1 1
5    54.6 2.149
5    54.6  .0910 1
5    54.6 2.381    1
5    54.6  .0866 1 1
5    54.6 2.184
5    54.6  .0842 1
5    54.6 1.805    1
5    54.6  .0651 1 1
6    80.0 3.885
6    80.0  .0881 1
6    80.0 3.079    1
6    80.0  .0758 1 1
6    80.0 3.600
6    80.0  .0739 1
6    80.0 3.963    1
6    80.0  .0982 1 1
6    80.0 3.598
6    80.0  .0751 1
6    80.0 3.415    1
6    80.0  .0947 1 1
7    64.6 3.175
7    64.6  .0897 1
7    64.6 3.260    1
7    64.6  .0997 1 1
7    64.6 3.590
7    64.6  .1033 1
7    64.6 3.154    1
7    64.6  .0890 1 1
7    64.6 3.616
7    64.6  .0951 1
7    64.6 3.027    1
7    64.6  .0871 1 1
8    70.5 3.140
8    70.5  .0814 1
8    70.5 3.310    1
8    70.5  .0859 1 1
8    70.5 3.426
8    70.5  .0875 1
8    70.5 3.445    1
8    70.5  .0732 1 1
8    70.5 3.237
8    70.5  .0767 1
8    70.5 3.279    1
8    70.5  .0834 1 1
9    86.4 3.247
9    86.4  .0784 1
9    86.4 2.628    1
9    86.4  .0550 1 1
9    86.4 3.296
9    86.4  .0878 1
9    86.4 3.380    1
9    86.4  .0663 1 1
9    86.4 3.621
9    86.4  .0761 1
9    86.4 3.240    1
9    86.4  .0741 1 1
```

```
10    58.2 1.889
10    58.2  .0722 1
10    58.2 2.800    1
10    58.2  .0900 1 1
10    58.2 1.865
10    58.2  .0578 1
10    58.2 1.828    1
10    58.2  .0575 1 1
10    58.2 3.106
10    58.2  .0957 1
10    58.2 2.386    1
10    58.2  .0730 1 1
11    65.0 3.674
11    65.0  .0945 1
11    65.0 4.151    1
11    65.0  .1026 1 1
11    65.0 3.670
11    65.0  .1092 1
11    65.0 3.324    1
11    65.0  .0911 1 1
11    65.0 4.941
11    65.0  .0939 1
11    65.0 4.129    1
11    65.0  .0947 1 1
12    60.5 2.331
12    60.5  .1039 1
12    60.5 2.521    1
12    60.5  .0807 1 1
12    60.5 3.194
12    60.5  .1006 1
12    60.5 2.928    1
12    60.5  .1131 1 1
12    60.5 2.868
12    60.5  .1000 1
12    60.5 2.406    1
12    60.5  .0730 1 1
STRC        3   2   2                1       1
STRC        1   2
STRC        1   2
THCN        1
THTA          .04       0     .08
LOWR    -1000000       0-1000000
UPPR     1000000       0 1000000
BLST          .4    .006   .0002
BLST          .1    .002  .00008
ESTM        0 500   4   5
COVR        0
TABL        0   1
TABL        3   1   2   2   0   4   1
SCAT        0   2
SCAT        2   7   1   4
SCAT        2   8   1   4
```

```
********************************************************************************************************************************
**********                                                                                                          **********
**********                                      FINAL PARAMETER ESTIMATE                                            **********
**********                                                                                                          **********
********************************************************************************************************************************
```

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

TH 1	TH 2	TH 3
4.46e-02	0.00e+00	8.43e-02

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

	ETA1	ETA2
ETA1	3.27e-01	
ETA2	6.72e-03	1.54e-04

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

	EPS1	EPS2
EPS1	1.25e-01	
EPS2	1.73e-03	9.21e-05

Fig. 66

```
********************************************************************************************************************************
**********                                                                                                          **********
**********                                    STANDARD ERROR OF ESTIMATE                                            **********
**********                                                                                                          **********
********************************************************************************************************************************


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

           TH 1      TH 2      TH 3

        2.30e-03 .........  3.68e-03


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

           ETA1      ETA2

ETA1    1.62e-01

ETA2    3.71e-03  9.05e-05


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

           EPS1      EPS2

EPS1    2.65e-02

EPS2    6.18e-04  2.23e-05
```

Fig. 67

Fig. 68

CORRELATION MATRIX OF ESTIMATE

	TH 1	TH 2	TH 3	OM11	OM12	OM22	SG11	SG12	SG22
TH 1	1.00e+00								
TH 2	....	....							
TH 3	9.08e-01	....	1.00e+00						
OM11	-3.16e-01	....	-5.17e-01	1.00e+00					
OM12	-5.05e-01	....	-6.43e-01	9.61e-01	1.00e+00				
OM22	-6.10e-01	....	-6.87e-01	8.86e-01	9.77e-01	1.00e+00			
SG11	2.22e-01	....	3.92e-02	2.78e-01	1.42e-01	4.07e-02	1.00e+00		
SG12	-4.02e-01	....	-3.50e-01	-2.14e-01	-1.25e-01	-5.05e-02	4.03e-01	1.00e+00	
SG22	-1.67e-01	....	-3.13e-02	-3.71e-01	-3.39e-01	-2.71e-01	2.83e-01	8.25e-01	1.00e+00

TABLE NO. 1

LINE NO.	TYPE	L1	WT	CL	PRED	RES	WRES
1	0.00e+00	1.00e+00	7.96e+01	1.85e+00	3.55e+00	-1.70e+00	-1.80e+00
2	0.00e+00	1.00e+00	7.96e+01	2.41e+00	3.55e+00	-1.13e+00	-2.11e-01
3	0.00e+00	1.00e+00	7.96e+01	2.64e+00	3.55e+00	-9.05e-01	4.35e-01
4	0.00e+00	1.00e+00	7.96e+01	1.96e+00	3.55e+00	-1.58e+00	-1.48e+00
5	0.00e+00	1.00e+00	7.96e+01	2.12e+00	3.55e+00	-1.43e+00	-1.04e+00
6	0.00e+00	1.00e+00	7.96e+01	1.90e+00	3.55e+00	-1.64e+00	-1.64e+00
7	0.00e+00	2.00e+00	7.24e+01	3.27e+00	3.23e+00	4.35e-02	-1.03e+00
8	0.00e+00	2.00e+00	7.24e+01	3.94e+00	3.23e+00	7.13e-01	8.76e-01
9	0.00e+00	2.00e+00	7.24e+01	3.69e+00	3.23e+00	4.62e-01	1.70e-01
10	0.00e+00	2.00e+00	7.24e+01	3.60e+00	3.23e+00	3.73e-01	-7.94e-02
11	0.00e+00	2.00e+00	7.24e+01	3.53e+00	3.23e+00	3.03e-01	-2.85e-01
12	0.00e+00	2.00e+00	7.24e+01	4.53e+00	3.23e+00	1.30e+00	2.54e+00
13	0.00e+00	3.00e+00	7.05e+01	2.98e+00	3.14e+00	-1.65e-01	-8.84e-01
14	0.00e+00	3.00e+00	7.05e+01	3.14e+00	3.14e+00	1.14e-03	-3.77e-01
15	0.00e+00	3.00e+00	7.05e+01	3.45e+00	3.14e+00	3.05e-01	4.73e-01
16	0.00e+00	3.00e+00	7.05e+01	3.65e+00	3.14e+00	5.10e-01	1.03e+00
17	0.00e+00	3.00e+00	7.05e+01	3.26e+00	3.14e+00	1.22e-01	-5.15e-02
18	0.00e+00	3.00e+00	7.05e+01	3.50e+00	3.14e+00	3.55e-01	5.86e-01
19	0.00e+00	4.00e+00	7.27e+01	3.52e+00	3.24e+00	2.80e-01	7.10e-01
20	0.00e+00	4.00e+00	7.27e+01	3.18e+00	3.24e+00	-5.69e-02	-2.35e-01
21	0.00e+00	4.00e+00	7.27e+01	3.60e+00	3.24e+00	3.63e-01	9.61e-01
22	0.00e+00	4.00e+00	7.27e+01	3.43e+00	3.24e+00	1.95e-01	4.75e-01
23	0.00e+00	4.00e+00	7.27e+01	2.77e+00	3.24e+00	-4.72e-01	-1.42e+00
24	0.00e+00	4.00e+00	7.27e+01	3.12e+00	3.24e+00	-1.21e-01	-4.13e-01
25	0.00e+00	5.00e+00	5.46e+01	2.18e+00	2.43e+00	-2.49e-01	-1.77e-01

Fig. 69a

LINE NO.	TYPE	L1	WT	CL	PRED	RES	WRES
130	1.00e+00	1.00e+01	5.82e+01	5.78e-02	8.43e-02	-2.65e-02	-1.60e+00
131	1.00e+00	1.00e+01	5.82e+01	9.00e-02	8.43e-02	5.75e-03	7.69e-01
132	1.00e+00	1.00e+01	5.82e+01	7.22e-02	8.43e-02	-1.21e-02	1.03e-01
133	1.00e+00	1.10e+01	6.50e+01	9.45e-02	8.43e-02	1.02e-02	-5.09e-01
134	1.00e+00	1.10e+01	6.50e+01	9.47e-02	8.43e-02	1.04e-02	-1.23e+00
135	1.00e+00	1.10e+01	6.50e+01	1.03e-01	8.43e-02	1.83e-02	-3.09e-01
136	1.00e+00	1.10e+01	6.50e+01	9.39e-02	8.43e-02	9.65e-03	-2.66e+00
137	1.00e+00	1.10e+01	6.50e+01	1.09e-01	8.43e-02	2.49e-02	1.28e+00
138	1.00e+00	1.10e+01	6.50e+01	9.11e-02	8.43e-02	6.85e-03	-3.48e-01
139	1.00e+00	1.20e+01	6.05e+01	1.13e-01	8.43e-02	2.88e-02	2.63e+00
140	1.00e+00	1.20e+01	6.05e+01	1.00e-01	8.43e-02	1.57e-02	1.14e+00
141	1.00e+00	1.20e+01	6.05e+01	8.07e-02	8.43e-02	-3.55e-03	-6.32e-01
142	1.00e+00	1.20e+01	6.05e+01	1.01e-01	8.43e-02	1.63e-02	6.78e-01
143	1.00e+00	1.20e+01	6.05e+01	1.04e-01	8.43e-02	1.96e-02	2.49e+00
144	1.00e+00	1.20e+01	6.05e+01	7.30e-02	8.43e-02	-1.13e-02	-1.38e+00

Fig. 69b

Fig. 70

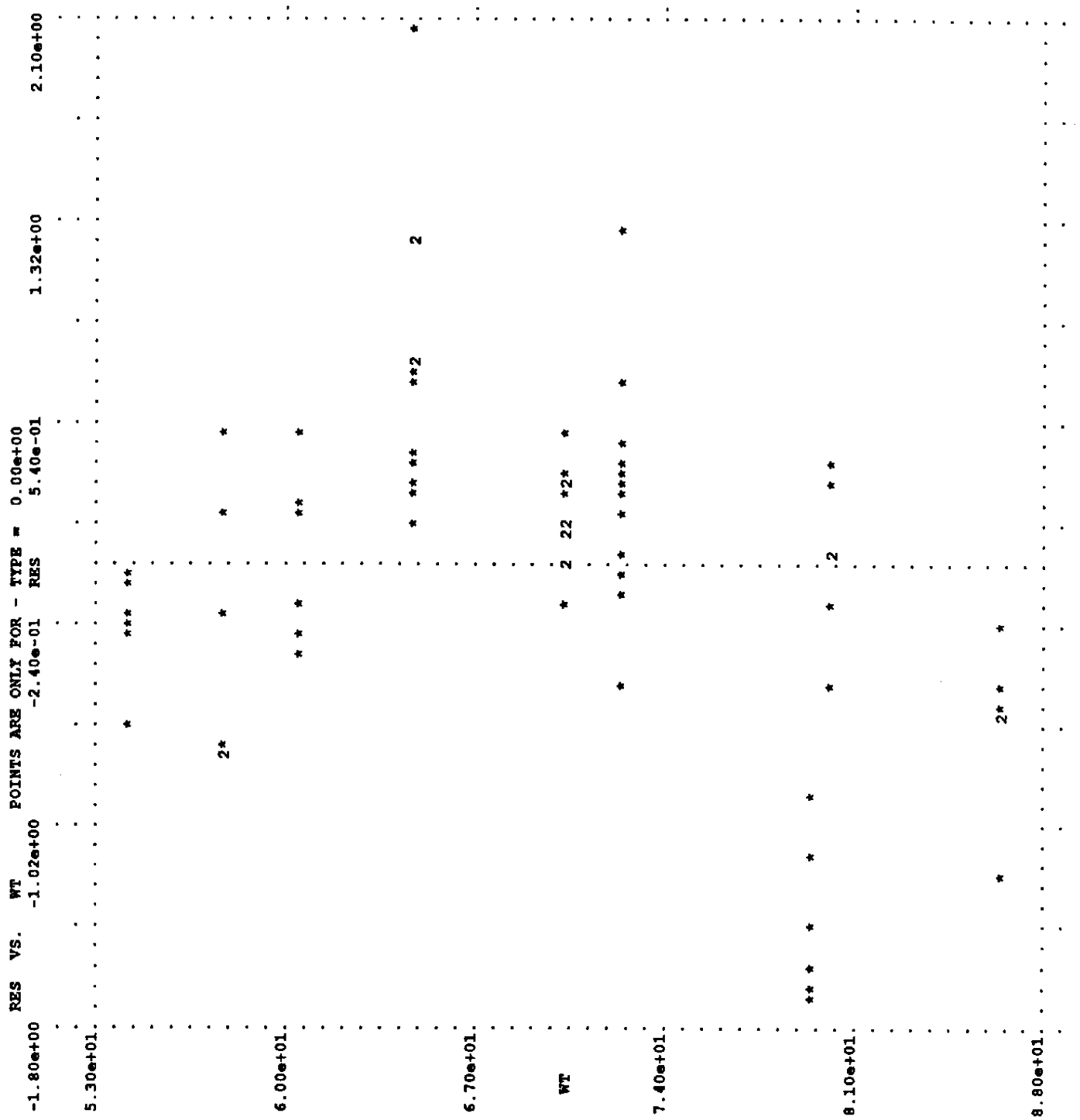

RES VS. WT POINTS ARE ONLY FOR - TYPE = 0.00e+00
-1.80e+00
-1.02e+00
-2.40e-01
1.32e+00
2.10e+00
RES
5.40e-01
5.30e+01
6.00e+01
6.70e+01
7.40e+01
8.10e+01
8.80e+01
WT

Fig. 71

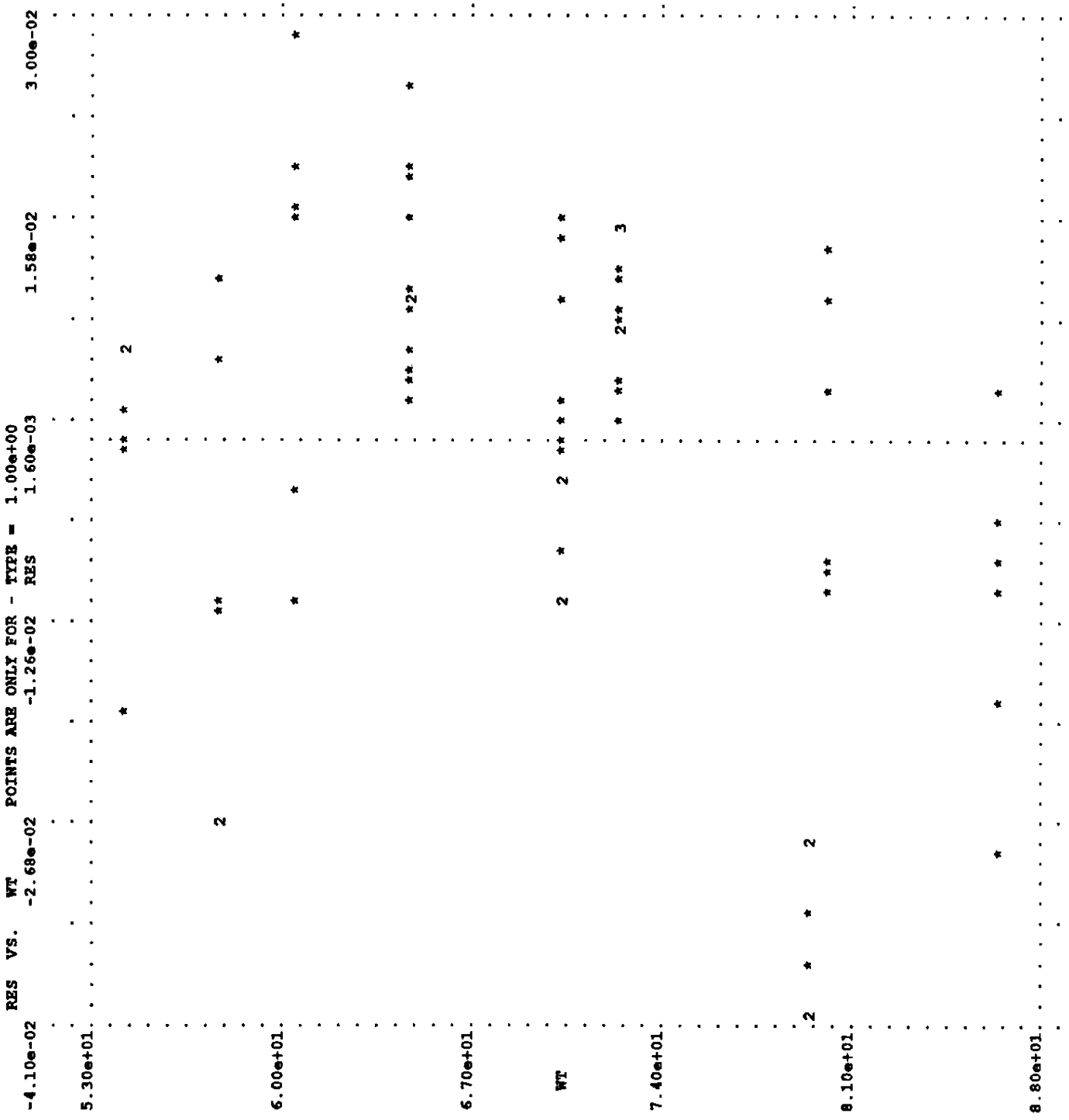

RES VS. WT POINTS ARE ONLY FOR - TYPE = 1.00e+00
-4.10e-02
-2.68e-02
-1.26e-02
1.60e-03
1.58e-02
3.00e-02
RES
5.30e+01
6.00e+01
6.70e+01
7.40e+01
8.10e+01
8.80e+01
WT

Fig. 72

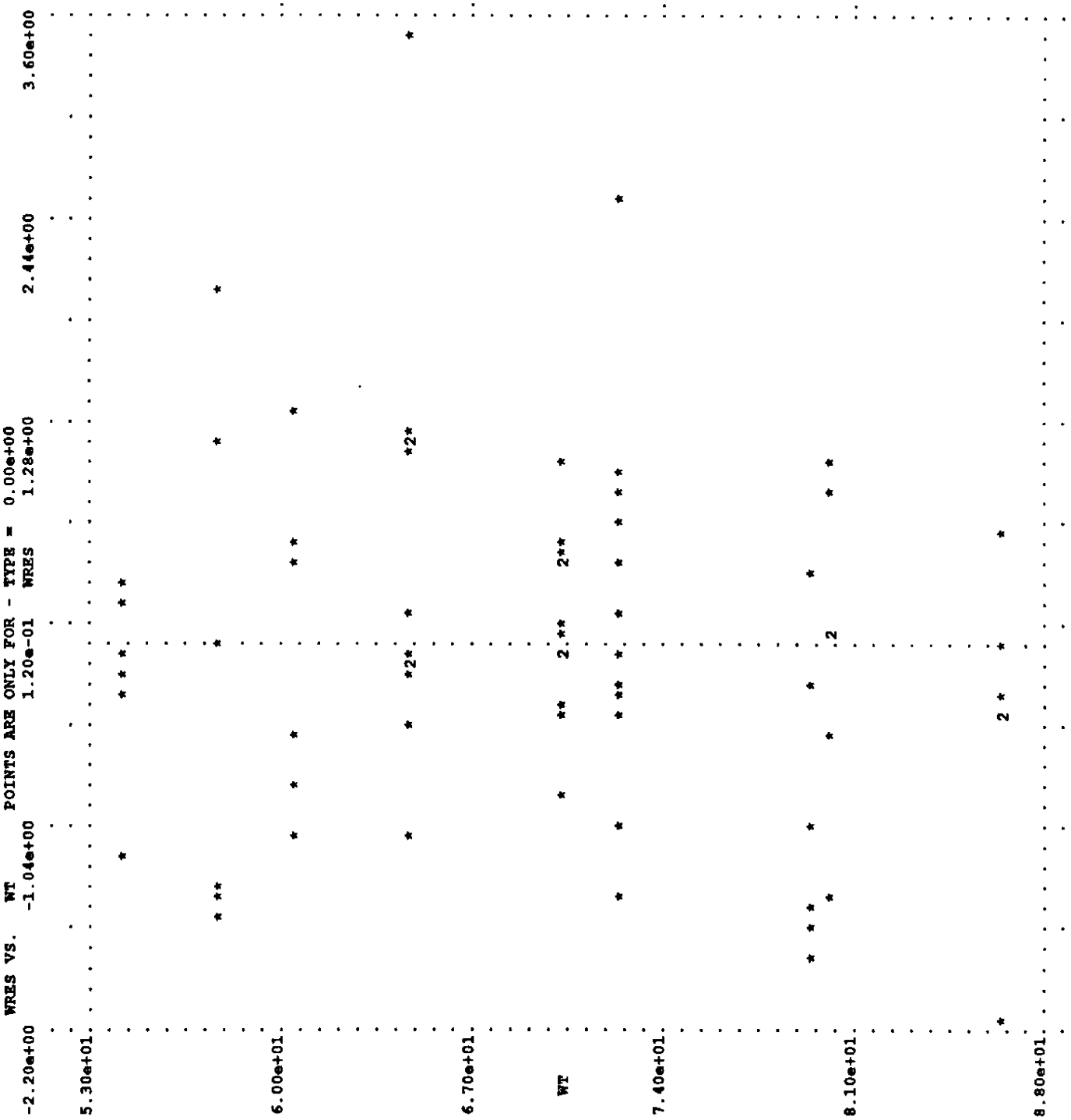
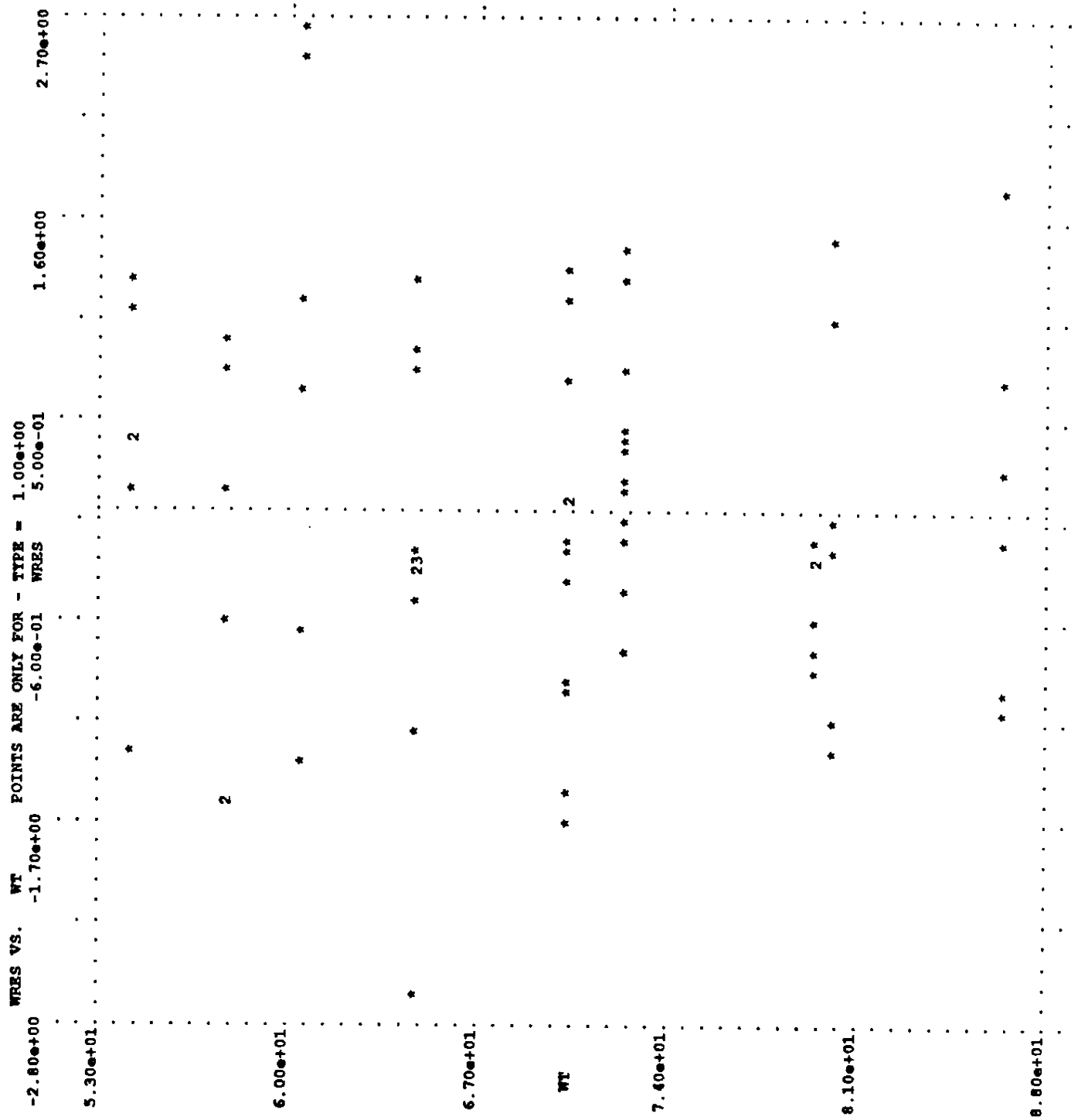

WRES VS. WT POINTS ARE ONLY FOR - TYPE = 0.00e+00
-2.20e+00
-1.04e+00
1.20e-01
1.28e+00
2.44e+00
3.60e+00
5.30e+01
6.00e+01
6.70e+01
7.40e+01
8.10e+01
8.80e+01
WT
WRES

Fig. 73


WRES VS. WT POINTS ARE ONLY FOR - TYPE = 1.00e+00
-2.80e+00
-1.70e+00
-6.00e-01
5.00e-01
1.60e+00
2.70e+00
5.30e+01
6.00e+01
6.70e+01
7.40e+01
8.10e+01
8.80e+01
WT
WRES

```
      SUBROUTINE PRED (ICALL,NEWIND,THETA,DATREC,INDXS,F,G,H)
C
C     THETA(1)=MEAN ABSORPTION RATE CONSTANT (1/HR)
C     THETA(2)=MEAN ELIMINATION RATE CONSTANT (1/HR)
C     THETA(3)=SLOPE OF CLEARANCE VS WEIGHT RELATIONSHIP (LITERS/HR/KG)
C     DATREC(2)=WEIGHT-ADJUSTED DOSE (MG/KG)
C     DATREC(3)=TIME (HR)
C     DATREC(5)=WEIGHT (KG)
C
      DIMENSION THETA(*),DATREC(*),INDXS(*),G(*),H(*)
      DOUBLE PRECISION THETA,F,G,H,A,B,C,D,E
      DOUBLE PRECISION DAD2,DBD1,DFD1,DFD2,DFDD,DFDE
C
      IF (NEWIND.NE.2) THEN
         DOSE=DATREC(2)
         WT=DATREC(5)
      ENDIF
      A=EXP(-THETA(2)*DATREC(3))
              DAD2=-DATREC(3)*A
      B=EXP(-THETA(1)*DATREC(3))
              DBD1=-DATREC(3)*B
      C=THETA(1)-THETA(2)
      D=A-B
      E=THETA(3)*C
      F=((DOSE*THETA(1)*THETA(2))/E)*D
              DFD1=((DOSE*THETA(2))/E)*D
              DFD2=((DOSE*THETA(1))/E)*D
              DFDD=(DOSE*THETA(1)*THETA(2))/E
              DFDE=-((DOSE*THETA(1)*THETA(2))/E**2)*D
      G(1)=DFD1-DFDD*DBD1+DFDE*THETA(3)
      G(2)=DFD2+DFDD*DAD2-DFDE*THETA(3)
      G(3)=DFDE*C/WT
      H(1)=1.
      RETURN
      END
```

```
FILE    NULL
PROB    NONLINEAR REGRESSION OF CP VS TIME DATA FROM 12 SUBJECTS
DATA       0    0 132    5
ITEM       1    4    0    0    1
LABL    ID       DOSE     TIME     CP       WT
FORM
(5F10.0)
          1       4.02       0.        .74      79.6
          1                  0.25     2.84
          1                  0.57     6.57
          1                  1.12    10.5
          1                  2.02     9.66
          1                  3.82     8.58
          1                  5.1      8.36
          1                  9.05     6.89
          1                  7.03     7.47
          1                 12.12     5.94
          1                 24.37     3.28
          2       4.4        0.       0.       72.4
          2                   .27     1.72
          2                   .52     7.91
          2                  1.       8.31
          2                  1.92     8.33
          2                  3.5      6.85
          2                  5.02     6.08
          2                  7.03     5.4
          2                  9.       4.55
          2                 12.       3.01
          2                 24.3       .90
          3       4.53       0.       0.       70.5
          3                   .27     4.4
          3                   .58     6.9
          3                  1.02     8.2
          3                  2.02     7.8
          3                  3.62     7.5
          3                  5.08     6.2
          3                  7.07     5.3
          3                  9.       4.9
          3                 12.15     3.7
          3                 24.17     1.05
          4       4.4        0.       0.       72.7
          4                   .35     1.89
          4                   .6      4.6
          4                  1.07     8.6
          4                  2.13     8.38
          4                  3.5      7.54
          4                  5.02     6.88
          4                  7.02     5.78
          4                  9.02     5.33
          4                 11.98     4.19
          4                 24.65     1.15
          5       5.86       0.       0.       54.6
          5                   .3      2.02
          5                   .52     5.63
          5                  1.       11.4
          5                  2.02     9.33
          5                  3.5      8.74
          5                  5.02     7.56
          5                  7.02     7.09
          5                  9.1      5.9
          5                 12.       4.37
          5                 24.35     1.57
```

6	4.	0.	0.	80.
6		.27	1.29	
6		.58	3.08	
6		1.15	6.44	
6		2.03	6.32	
6		3.57	5.53	
6		5.	4.94	
6		7.	4.02	
6		9.22	3.46	
6		12.1	2.78	
6		23.85	.92	
7	4.95	0.	.15	64.6
7		.25	.85	
7		.5	2.35	
7		1.02	5.02	
7		2.02	6.58	
7		3.48	7.09	
7		5.	6.66	
7		6.98	5.25	
7		9.	4.39	
7		12.05	3.53	
7		24.22	1.15	
8	4.53	0.	0.	70.5
8		.25	3.05	
8		0.52	3.05	
8		.98	7.31	
8		2.02	7.56	
8		3.53	6.59	
8		5.05	5.88	
8		7.15	4.73	
8		9.07	4.57	
8		12.1	3.	
8		24.12	1.25	
9	3.1	.0	.0	86.4
9		.3	7.37	
9		.63	9.03	
9		1.05	7.14	
9		2.02	6.33	
9		3.53	5.66	
9		5.02	5.67	
9		7.17	4.24	
9		8.8	4.11	
9		11.6	3.16	
9		24.43	1.12	
10	5.5	0.	.24	58.2
10		.37	2.89	
10		.77	5.22	
10		1.02	6.41	
10		2.05	7.83	
10		3.55	10.21	
10		5.05	9.18	
10		7.08	8.02	
10		9.38	7.14	
10		12.1	5.68	
10		23.7	2.42	

```
11       4.92        0.          0.        65.
11                    .25        4.86
11                     .5        7.24
11                     .98       8.
11                    1.98       6.81
11                    3.6        5.87
11                    5.02       5.22
11                    7.03       4.45
11                    9.03       3.62
11                   12.12       2.69
11                   24.08        .86
12       5.3         0.          0.        60.5
12                    .25        1.25
12                     .5        3.96
12                    1.         7.82
12                    2.         9.72
12                    3.52       9.75
12                    5.07       8.57
12                    7.07       6.59
12                    9.03       6.11
12                   12.05       4.57
12                   24.15       1.17
STRC      3   3   1                  1   1
STRC      1   3
THCN      1
THTA          3.      .08      .04
LOWR          .1     .008     .004
UPPR          5.       .5       .9
BLST          6.     .005       .3   .0002     .006       .4
DIAG        .4
ESTM      0 450   3   5
COVR      0
TABL      0   1
TABL      4   1       2        5        3
SCAT      0   2
SCAT      3   7   1   1
SCAT      3   8   1   1
```

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FINAL PARAMETER ESTIMATE

****
****
****
****
****

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

TH 1	TH 2	TH 3
2.77e+00	7.81e-02	3.63e-02

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

	ETA1	ETA2	ETA3
ETA1	5.55e+00		
ETA2	5.24e-03	2.40e-04	
ETA3	-1.28e-01	9.11e-03	5.15e-01

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

	EPS1
EPS1	3.88e-01

Fig. 76

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****
****
****
****

STANDARD ERROR OF ESTIMATE

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

TH 1	TH 2	TH 3
7.01e-01	7.36e-03	4.66e-03

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

	ETA1	ETA2	ETA3
ETA1	4.78e+00		
ETA2	1.24e-02	1.18e-04	
ETA3	4.25e-01	3.62e-03	2.08e-01

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

	EPS1
EPS1	1.06e-01

****
****
****
****

CORRELATION MATRIX OF ESTIMATE

****
****
****
****

	TH 1	TH 2	TH 3	OM11	OM12	OM13	OM22	OM23	OM33	SG11
TH 1	1.00e+00									
TH 2	1.83e-01	1.00e+00								
TH 3	-1.61e-02	9.52e-01	1.00e+00							
OM11	9.70e-01	1.48e-01	-3.71e-02	1.00e+00						
OM12	3.80e-01	7.48e-01	6.54e-01	2.82e-01	1.00e+00					
OM13	-9.82e-02	4.62e-01	5.17e-01	-2.30e-01	6.93e-01	1.00e+00				
OM22	3.43e-02	4.55e-01	3.90e-01	-4.95e-02	7.99e-01	6.61e-01	1.00e+00			
OM23	-3.25e-02	-9.02e-02	-5.88e-02	-1.64e-01	3.57e-01	6.19e-01	6.69e-01	1.00e+00		
OM33	1.56e-02	-2.64e-01	-1.75e-01	-1.08e-01	1.13e-01	4.75e-01	3.04e-01	8.93e-01	1.00e+00	
SG11	-1.70e-01	2.57e-01	1.32e-01	-2.64e-01	4.84e-01	3.66e-01	6.11e-01	2.65e-01	-4.85e-02	1.00e+00

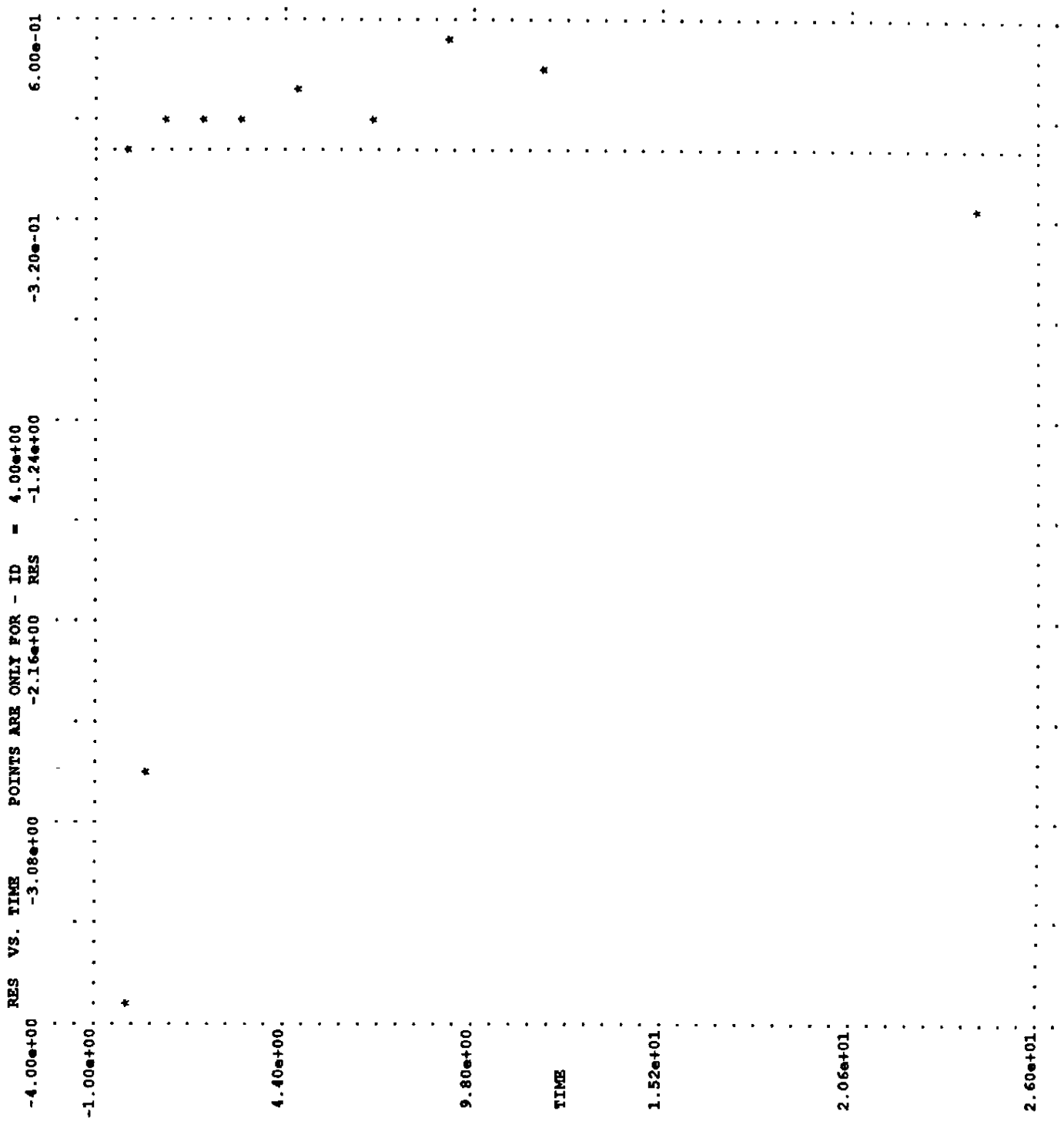
Fig. 78

TABLE NO. 1

LINE NO.	ID	DOSE	WT	TIME	CP	PRED	RES	WRES
1	1.00e+00	4.02e+00	7.96e+01	0.00e+00	7.40e-01	0.00e+00	7.40e-01	1.19e+00
2	1.00e+00	0.00e+00	0.00e+00	2.50e-01	2.84e+00	4.28e+00	-1.44e+00	-1.35e+00
3	1.00e+00	0.00e+00	0.00e+00	5.70e-01	6.57e+00	6.68e+00	-1.12e-01	-2.59e-01
4	1.00e+00	0.00e+00	0.00e+00	1.12e+00	1.05e+01	7.76e+00	2.74e+00	2.50e+00
5	1.00e+00	0.00e+00	0.00e+00	2.02e+00	9.66e+00	7.57e+00	2.09e+00	4.50e-01
6	1.00e+00	0.00e+00	0.00e+00	3.82e+00	8.58e+00	6.60e+00	1.98e+00	9.26e-02
7	1.00e+00	0.00e+00	0.00e+00	5.10e+00	8.36e+00	5.98e+00	2.38e+00	7.70e-01
8	1.00e+00	0.00e+00	0.00e+00	9.05e+00	6.89e+00	4.39e+00	2.50e+00	1.16e+00
9	1.00e+00	0.00e+00	0.00e+00	7.03e+00	7.47e+00	5.14e+00	2.33e+00	7.63e-01
10	1.00e+00	0.00e+00	0.00e+00	1.21e+01	5.94e+00	3.45e+00	2.49e+00	1.37e+00
11	1.00e+00	0.00e+00	0.00e+00	2.44e+01	3.28e+00	1.33e+00	1.95e+00	1.56e+00
12	2.00e+00	4.40e+00	7.24e+01	0.00e+00	0.00e+00	0.00e+00	0.00e+00	0.00e+00
13	2.00e+00	0.00e+00	0.00e+00	2.70e-01	1.72e+00	4.93e+00	-3.21e+00	-3.63e+00
14	2.00e+00	0.00e+00	0.00e+00	5.20e-01	7.91e+00	7.05e+00	8.58e-01	2.85e+00
15	2.00e+00	0.00e+00	0.00e+00	1.00e+00	8.31e+00	8.40e+00	-9.23e-02	6.28e-01
16	2.00e+00	0.00e+00	0.00e+00	1.92e+00	8.33e+00	8.34e+00	-8.12e-03	2.06e-01
17	2.00e+00	0.00e+00	0.00e+00	3.50e+00	6.85e+00	7.41e+00	-5.61e-01	-6.63e-01
18	2.00e+00	0.00e+00	0.00e+00	5.02e+00	6.08e+00	6.58e+00	-5.02e-01	-4.75e-01
19	2.00e+00	0.00e+00	0.00e+00	7.03e+00	5.40e+00	5.63e+00	-2.25e-01	5.94e-02
20	2.00e+00	0.00e+00	0.00e+00	9.00e+00	4.55e+00	4.82e+00	-2.73e-01	3.90e-02
21	2.00e+00	0.00e+00	0.00e+00	1.20e+01	3.01e+00	3.82e+00	-8.05e-01	-7.76e-01
22	2.00e+00	0.00e+00	0.00e+00	2.43e+01	9.00e-01	1.46e+00	-5.59e-01	-4.81e-01
23	3.00e+00	4.53e+00	7.05e+01	0.00e+00	0.00e+00	0.00e+00	0.00e+00	0.00e+00
24	3.00e+00	0.00e+00	0.00e+00	2.70e-01	4.40e+00	5.08e+00	-6.78e-01	-1.80e-01
25	3.00e+00	0.00e+00	0.00e+00	5.80e-01	6.90e+00	7.58e+00	-6.79e-01	-8.43e-02

Fig. 79

Fig. 80


RES VS. TIME POINTS ARE ONLY FOR - ID = 4.00e+00
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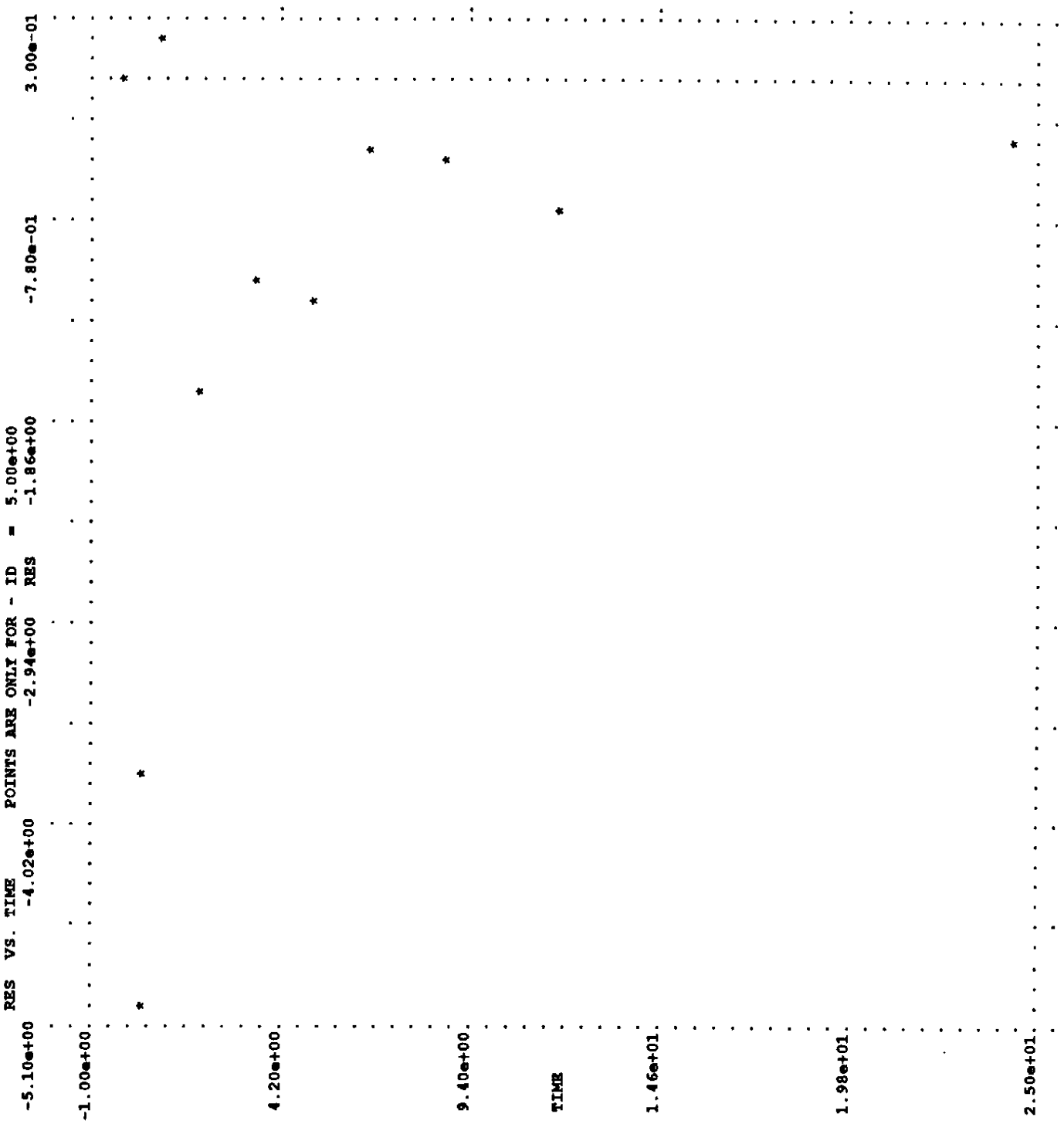
-3.08e+00
-2.16e+00
RES
-1.24e+00
-3.20e-01
6.00e-01
-1.00e+00
4.40e+00
9.80e+00
TIME
1.52e+01
2.06e+01
2.60e+01

Fig. 81


RES VS. TIME POINTS ARE ONLY FOR - ID = 5.00e+00
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-4.02e+00
-2.94e+00
RES
-1.86e+00
-7.80e-01
3.00e-01
-1.00e+00
4.20e+00
9.40e+00
TIME
1.46e+01
1.98e+01
2.50e+01

Fig. 82

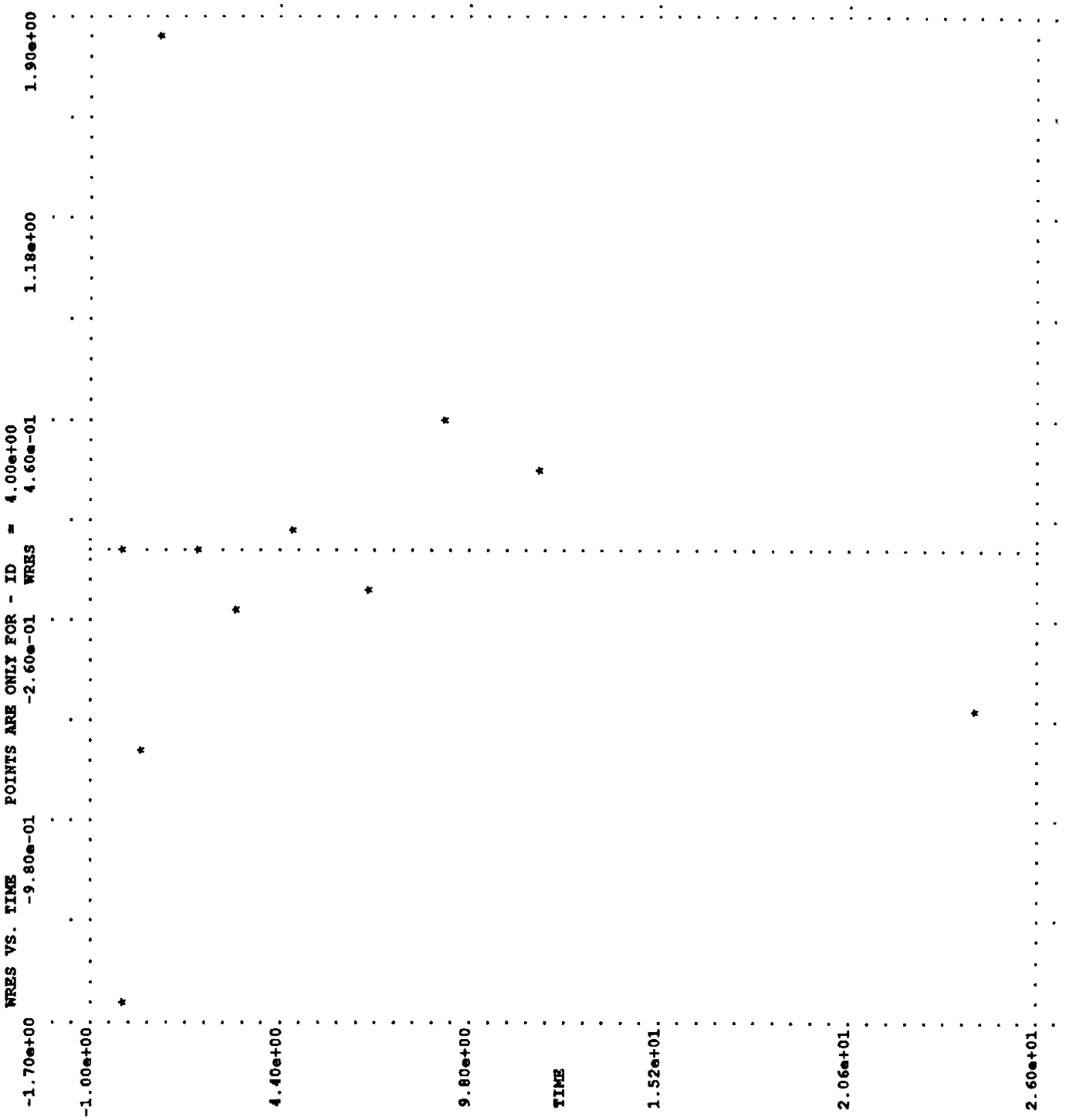
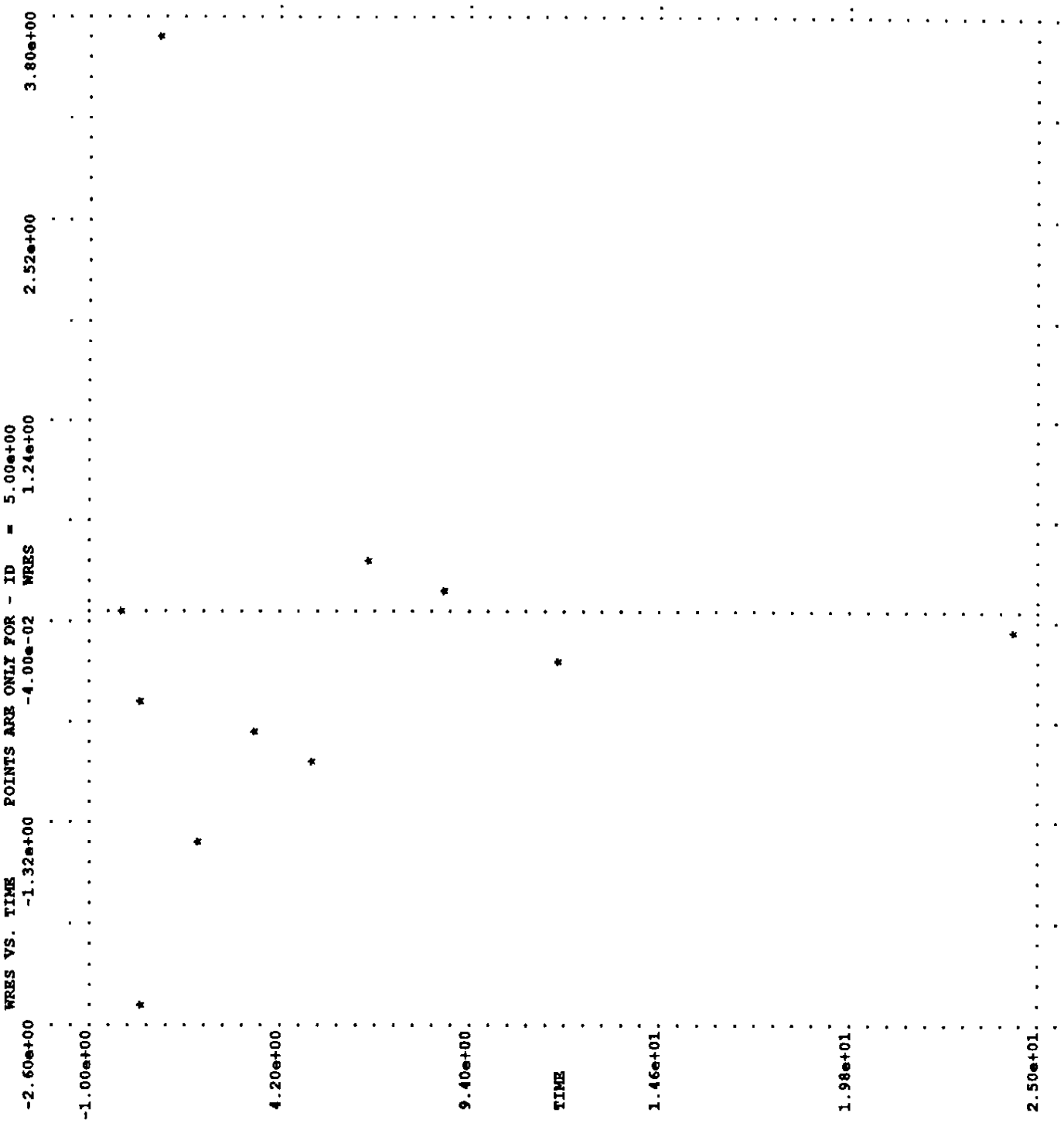

WRES VS. TIME POINTS ARE ONLY FOR - ID = 4.00e+00
-9.80e-01 -2.60e-01 WRES 4.60e-01
-1.70e+00
-1.00e+00
4.40e+00
9.80e+00
1.18e+00
1.90e+00
TIME
1.52e+01
2.06e+01
2.60e+01

Fig. 83


WRES VS. TIME POINTS ARE ONLY FOR - ID = 5.00e+00
-2.60e+00
-1.32e+00
-4.00e-02
1.24e+00
2.52e+00
3.80e+00
WRES
-1.00e+00
4.20e+00
9.40e+00
1.46e+01
1.98e+01
2.50e+01
TIME