

The following bugs have been detected in NONMEM 7.4.3

- 1) The \$PRIOR TNPRI method may not work correctly when there are fixed thetas and the prior information is brought in from an MSF file by a \$MSFI record. This bug has been present since NONMEM VI. A work-around is to convert fixed thetas to fixed scalar parameters in the \$PK record so they are not defined in the theta vector, in the control stream generating the MSF file, and in the control stream using it via the \$PRIOR TNPRI record.
- 2) The CWRES and CPRED are incorrectly calculated as CIWRES and CIPRED when INTERACTION is not specified in the \$EST record. This error has been present since NONMEM 7.4.0. As a work-around, always set INTERACTION (this is default for EM and Bayes methods) for the \$EST record. Setting INTERACTION does not impact the analysis when the residual error is homoscedastic, and INTERACTION should always be used when residual error is heteroscedastic.
- 3) When \$ABBR PROTECT is used and EXP(), PEXP() or X**Y expressions are used, the protect routines may occasionally not accurately evaluate eta derivatives due to a low threshold (100.0) placed on the argument to avoid floating overflow upon exponentiation. If this occurs, you will likely see poor objective function values when implementing \$ABBR PROTECT, or PEXP(), or observe 0 gradients. A modified protect.f90 file is available with a higher threshold (350.0), can be downloaded from <https://nonmem.iconplc.com/nonmem743> and can be used as a plug-in with the control stream statement \$ABBR SUBROUTINES ... other=protect.f90.

In general, the protect.f90 file is available for the user to modify the behavior of protection functions and their derivatives, if necessary. See the section **Stable Routines for Estimation Methods and Automated Protection Against Floating Point Exceptions** in intro7.pdf for further information.

- 4) Negative valued Lower bounds with an upper bound on thetas can result in an NaN valued theta for EM algorithms. Work-around is to remove the upper or lower bound, or scale theta so bounds are in positive region. This bug has been present since version NONMEM 7.1.0
- 5) When using VARCALC=1 in a \$TABLE record, if a label exceeds 5 characters, an internal Fortran write error will occur while writing variance labels in the .vpd table. To prevent this from occurring, either enter a FORMAT statement in the \$EST record that will define at least S=2X+2 characters, where X=largest label length in the \$TABLE records and S is the character length that FORMAT is describing, or shorten the labels used in the \$TABLE record.

For example, the largest label is 10 characters long. The format could be set to \$EST ... FORMAT=s1PE23.16

This format defines a 24 character length, which is more than $2*10+2=22$.

Or, shorten the labels in the \$TABLE record to less than 6 characters:
\$TABLE ... SHORT=LONGNAME...

- 6) During parallelization, the THIN setting is not transferred to workers during \$EST METHOD=BAYES THIN=... method, and the BAYES_EXTRA setting is not transferred to workers during the \$EST METHOD=NUTS method. When a user desires to control printing of additional individual parameters to a file using the BAYES_EXTRA switch, such as is shown in example8.ctl:

```
IF (BAYES_EXTRA==1 .AND. ITER_REPORT>=0 .AND. TIME==0.0) THEN  
"  WRITE(51,98) ITER_REPORT,ID,CL,V1,Q,V2  
" 98 FORMAT(I12,1X,F14.0,4(1X,1PG12.5))  
ENDIF
```

The BAYES_EXTRA is never set to 1 for workers during METHOD=NUTS, so no records are placed in the file. When METHOD=BAYES THIN=..., the BAYES_EXTRA is 1 for every iteration, instead of every THIN iteration, so worker's files contain too many records.

As a work-around, incorporate the source code file extrasend.f90 (located in <https://nonmem.iconplc.com/nonmem743>) into your control stream as an OTHER routine:

```
$SUBROUTINES ... other=extrasend.f90
```

In \$PK, place the following line, after the last MU_ referencing declaration (or just before the first IF (BAYES_EXTRA==1... statement):

```
" CALL EXTRASEND()
```

The extrasend.f90 will transfer the appropriate BAYES_EXTRA and THINPRINT variables from manager to worker. The extrasend.f90 will transfer the appropriate BAYES_EXTRA and THINPRINT variables from manager to worker.

- 7) For data sets with many items (columns), and when =DROP requests are made on several of these items, the FDATA file may not be correctly constructed. As a work-around, add the option WIDE to the \$DATA record.
- 8) When using ADVAN13 or ADVAN14 with the -2LL options, such as:
\$EST METHOD=1 LAPLACE -2LL
NMTRAN fails to create second derivatives in the \$ERROR segment. The problem will fail immediately with an error message. As a work-around, add the option NUMERICAL. This bug affects only version NONMEM 7.4.x
- 9) In the Windows environment, when -tprdefault is used, and NMTRAN reports that certain predpp routines need to be recompiled so that some arrays are resized

for the problem, the nmfe74.bat script should force a predpp recompile. However, this does not occur, due to the ordering of certain lines in nmfe74.bat. The problem is likely to fail with access violations or some other error. As a remedy, download the updated nmfe74.bat located at <https://nonmem.iconplc.com/nonmem743>, and replace the values of dir, f, and op defined in the first several lines of the script with the appropriate values for your NONMEM installation. This bug does not occur in versions of NONMEM earlier than 7.4.0.

- 10) In Windows and linux, if LVR is set to a value higher than 93 with \$SIZES record, such as
\$SIZES LVR=95
then diagnostic items such as CPRED, CWRES, will be incorrectly selected from what the user requested, due to NMTRAN not inserting the correct table ID's in the FCON file for NONMEM to use. As a remedy, download the updated nmfe74.bat (windows) or nmfe74 (Linux, MAC) file, located at <https://nonmem.iconplc.com/nonmem743>, and replace the values of dir, f, and op defined in the first several lines of the script with the appropriate values for your NONMEM installation. Furthermore, download also the tabindex_correct.* files, and place them in the ..\util directory of your nonmem installation. The tabindex_correct utility will be called by the updated nmfe74 scripts and correct the FCON table item ID's. This bug does not occur in versions of NONMEM earlier than 7.4.0.
- 11) With table step parallelization, sometimes the first record of the last individual is placed at the beginning of the table. To avoid this, add the command line option -maxlim=3