Dose-Time Response Modeling of Rat Brain AChE Activity: Oxamyl Gavage Dosing

June 24, 2005

1 Preamble

Here is some code to set up the analysis: loading required libraries and datasets, and defining some functions.

First, `CarbamateData` loads the full dataset for this risk assessment, and causes the library `DRUtils` to be loaded.

```
> library(CarbamateData)

Loading required package: DRUtils
Loading required package: nlme
Loading required package: tcltk
```

Set up lattice to use B&W instead of color:

```
> library(lattice)
> ltheme <- canonical.theme(color = FALSE)
> ltheme$strip.background$col <- "transparent"
> lattice.options(default.theme = ltheme)
```

Use package `Hmisc` for some formatting support.

```
> library(Hmisc)

Hmisc library by Frank E Harrell Jr

Type library(help='Hmisc'), ?Overview, or ?Hmisc.Overview')
to see overall documentation.

NOTE:Hmisc no longer redefines [.factor to drop unused levels when
subsetting.  To get the old behavior of Hmisc type dropUnusedLevels().

Attaching package 'Hmisc':


        The following object(s) are masked from package:stats :

         ecdf
```

All the rat gavage data for this analysis are in `AggData`. The following code prints out documentation for the datasets in use:

```
> printDataDoc(AggData)
```

```
----------------------------------------
Data set: AggData

Dataset creation date: Wed Jun 22 12:07:24 2005
Script name: /home/setzer/tasks/CarbamateCRA/EmpiricalDoseResponsesFinal/Data/getdata.R
Script last modified: 2005-06-22 12:05:47
sysname: Linux
release: 2.4.24-openmosix2
version: #1 Wed Jul 28 14:33:52 CEST 2004
nodename: node24.cluster2.org
machine: i686
login: unknown
user: setzer
----------------------------------------

> printDataDoc(PadillaData)

----------------------------------------
Data set: PadillaData

Dataset creation date: Wed Jun 22 12:07:28 2005
Script name: /home/setzer/tasks/CarbamateCRA/EmpiricalDoseResponsesFinal/Data/getdata.R
Script last modified: 2005-06-22 12:05:47
sysname: Linux
release: 2.4.24-openmosix2
version: #1 Wed Jul 28 14:33:52 CEST 2004
nodename: node24.cluster2.org
machine: i686
login: unknown
user: setzer
----------------------------------------
```

The following function turns out to be quite useful on subsetted dataframes. It just eliminates unused levels of all factors in the data frame:

```
> CleanUp <- function(x) {
+     for (nm in names(x)) {
+         if (is.factor(x[, nm]))
+             x[, nm] <- factor(x[, nm])
+     }
+     x
+ }
```

To get starting values, we often have to extract values from a previously fit model. The following function simplifies that. The argument `what` is a regular expression:

```
> getParms <- function(what, Par) {
+     Par[grep(what, names(Par))]
+ }
```

This script is for modeling the dose-time response for rat brain. via gavage dosing. It includes acute, subchronic, and chronic studies.

All the data used for this DR model are in `AggData` and in `PadillaData`. The carbaryl data need to be extracted from both data sets, then several variables (n = 1, sd = 0, tmonstdy = 1, mrid = "Padilla", cheact = Brain.R) added to the Padilla dataset. To keep the response scale similar across studies, Padilla's values for cheact need to be divided by 500. Finally the two datasets are combined, and all activity levels and their standard deviation rescaled by ten (this seems to make it easier for

These are all the names used for the brain sections we want from `AggData`:

```
> BrainSections <- levels(AggData$sctn)[grep("(^BRAIN)|(^WHOLEBRAIN)|(LEFT HEMISPHERE)|(HALFBRAIN)",
+     levels(AggData$sctn))]
```

Now, set up the analysis dataset.

```
> dta <- CleanUp(subset(AggData, chemical %in% "OXAMYL" & species %in%
+     "RAT" & dsmtd %in% "GAVAGE" & sctn %in% BrainSections & !is.na(cheact) &
+     (n == 1 | !is.na(sd)), select = c("cheact", "sd", "n", "dose",
+     "tmonstdy", "tmpstds", "sex", "mrid")))
> Pdta <- subset(PadillaData, chemical %in% "oxamyl", select = c("dose",
+     "brain.R", "TMPSTDS"))
> names(Pdta) <- c("dose", "cheact", "tmpstds")
> Pdta$tmonstdy <- rep(1, nrow(Pdta))
> Pdta$n <- rep(1, nrow(Pdta))
> Pdta$sd <- rep(0, nrow(Pdta))
> Pdta$sex <- factor(rep("M", nrow(Pdta)))
> Pdta$mrid <- factor(rep("Padilla", nrow(Pdta)))
> Pdta$cheact <- Pdta$cheact/500
> dta <- rbind(dta, Pdta[, names(dta)])
> dta$cheact <- dta$cheact/10
> dta$sd <- dta$sd/10
```

Summary of the relevant variables in this dataset:

```
> by(dta, dta$mrid, summary)

dta$mrid: 44254401
     cheact            sd                n                dose          tmonstdy
 Min.   :0.376   Min.   :0.02800   Min.   : 9.000   Min.   :0.000   Min.   :1
 1st Qu.:1.089   1st Qu.:0.06000   1st Qu.:10.000   1st Qu.:0.075   1st Qu.:1
 Median :1.133   Median :0.06700   Median :10.000   Median :0.550   Median :1
 Mean   :1.048   Mean   :0.07633   Mean   : 9.958   Mean   :0.775   Mean   :1
 3rd Qu.:1.196   3rd Qu.:0.07750   3rd Qu.:10.000   3rd Qu.:1.250   3rd Qu.:1
 Max.   :1.235   Max.   :0.21900   Max.   :10.000   Max.   :2.000   Max.   :1
    tmpstds      sex          mrid
 Min.   :  1.0   F:12   44254401:24
 1st Qu.:  1.0   M:12   44420301: 0
 Median : 24.0          44472001: 0
 Mean   :128.3          Padilla : 0
 3rd Qu.:360.0
 Max.   :360.0
------------------------------------------------------------
dta$mrid: 44420301
     cheact             sd                n           dose           tmonstdy
 Min.   :0.3760   Min.   :0.02800   Min.   :60   Min.   :0.0000   Min.   :1
 1st Qu.:0.5403   1st Qu.:0.06150   1st Qu.:60   1st Qu.:0.0750   1st Qu.:1
 Median :0.8695   Median :0.06750   Median :60   Median :0.4250   Median :1
 Mean   :0.8246   Mean   :0.08737   Mean   :60   Mean   :0.6813   Mean   :1
 3rd Qu.:1.1320   3rd Qu.:0.08575   3rd Qu.:60   3rd Qu.:1.1250   3rd Qu.:1
 Max.   :1.1970   Max.   :0.21900   Max.   :60   Max.   :2.0000   Max.   :1
    tmpstds    sex         mrid
 Min.   :0.5   F:4   44254401:0
 1st Qu.:0.5   M:4   44420301:8
 Median :0.5         44472001:0
 Mean   :0.5         Padilla :0
```

```
 3rd Qu.:0.5
 Max.   :0.5
------------------------------------------------------------
dta$mrid: 44472001
     cheact            sd                n           dose        tmonstdy
 Min.   :0.622   Min.   :0.02900   Min.   :10   Min.   :0.0   Min.   :1
 1st Qu.:1.122   1st Qu.:0.05025   1st Qu.:10   1st Qu.:0.0   1st Qu.:1
 Median :1.190   Median :0.05950   Median :10   Median :0.5   Median :1
 Mean   :1.115   Mean   :0.06546   Mean   :10   Mean   :0.5   Mean   :1
 3rd Qu.:1.217   3rd Qu.:0.07472   3rd Qu.:10   3rd Qu.:1.0   3rd Qu.:1
 Max.   :1.258   Max.   :0.11700   Max.   :10   Max.   :1.0   Max.   :1
    tmpstds      sex         mrid
 Min.   :0.500   F:8   44254401: 0
 1st Qu.:1.625   M:8   44420301: 0
 Median :2.500         44472001:16
 Mean   :2.375         Padilla : 0
 3rd Qu.:3.250
 Max.   :4.000
------------------------------------------------------------
dta$mrid: Padilla
     cheact             sd          n          dose           tmonstdy
 Min.   :0.3879   Min.   :0   Min.   :1   Min.   :0.0000   Min.   :1
 1st Qu.:0.7307   1st Qu.:0   1st Qu.:1   1st Qu.:0.0833   1st Qu.:1
 Median :1.0142   Median :0   Median :1   Median :1.0000   Median :1
 Mean   :0.9660   Mean   :0   Mean   :1   Mean   :0.6751   Mean   :1
 3rd Qu.:1.2363   3rd Qu.:0   3rd Qu.:1   3rd Qu.:1.0000   3rd Qu.:1
 Max.   :1.4670   Max.   :0   Max.   :1   Max.   :1.5000   Max.   :1
    tmpstds        sex          mrid
 Min.   : 0.5000   F: 0   44254401: 0
 1st Qu.: 0.6667   M:59   44420301: 0
 Median : 0.6667          44472001: 0
 Mean   : 3.0847          Padilla :59
 3rd Qu.: 1.5000
 Max.   :24.0000

> unique(subset(dta, select = c("mrid", "tmonstdy", "tmpstds")))

         mrid tmonstdy     tmpstds
1021 44420301        1   0.5000000
1115 44254401        1   1.0000000
1119 44254401        1  24.0000000
1123 44254401        1 360.0000000
1147 44472001        1   0.5000000
1148 44472001        1   2.0000000
1149 44472001        1   3.0000000
1150 44472001        1   4.0000000
32    Padilla        1   0.6666667
371   Padilla        1   0.5000000
381   Padilla        1   1.0000000
391   Padilla        1   1.5000000
401   Padilla        1   4.0000000
411   Padilla        1  24.0000000

> by(dta, dta$mrid, function(x) with(x, table(dose, tmpstds)))
```

```
dta$mrid: 44254401
     tmpstds
dose  1 24 360
  0   2 2  2
  0.1 2 2  2
  1   2 2  2
  2   2 2  2
------------------------------------------------------------
dta$mrid: 44420301
      tmpstds
dose   0.5
  0    2
  0.1  2
  0.75 1
  1    1
  1.5  1
  2    1
------------------------------------------------------------
dta$mrid: 44472001
    tmpstds
dose 0.5 2 3 4
   0 2   2 2 2
   1 2   2 2 2
------------------------------------------------------------
dta$mrid: Padilla
        tmpstds
dose     0.5 0.666666666666667 1 1.5 4 24
  0      1   5                 1 1   1 1
  0.0666 0   5                 0 0   0 0
  0.1    0   5                 0 0   0 0
  0.5    0   5                 0 0   0 0
  1      5   5                 5 5   5 4
  1.5    0   5                 0 0   0 0
```

Padilla's data are from an acute study, with multiple doses at one time point, and multiple timepoints for 1 mg/kg. Mrids 44254401, 44420301, and 44472001 are acute studies. The only dose at which there is a useful time course is at 1 mg/kg, in both the Padilla study and 44472001.

Create some new factors, for splitting up the background parameters and allowing groups to have different variances.

```
> dta$mridXsex <- with(dta, interaction(mrid, sex, drop = TRUE,
+     sep = ":"))
> dta$mridXsexXtmpstds <- with(dta, interaction(mrid, sex, tmpstds,
+     drop = TRUE, sep = ":"))
```

2 Dose-Response Modeling

2.1 strategy

Use the model with simple exponential recovery (`tcmfn4()`), first. It looks as if the time to peak effect for all these chemicals is likely to be less than a half-hour (the earliest time point in this dataset), so the exponential recovery model is probably indistinguishable from the one with the more complex time course.

Fitting the model will follow these steps:

1. First, use `GetInitialValues()` to get starting values for the model against these data, and determine how finely we can estimate `lg` and `tz` of the dose-response parameters, and `lTr`, the log of the recovery half-life.

2. Next, fit `tcmfn4()` using the parameterizations determined in the previous step, and a constant variance model, allowing `lD` to vary among mrids.

   Try fitting with other variance models the same model for fixed and random effects, using AIC to identify the best variance model.

3. Can we simplify the model for `lD`, that is, does `lD` differ among `tmonstdy` and among sexes? Use contrasts in the best model identified in the previous section.

4. Can we simplify the model for `lTr`, first between sexes, then among doses.?

2.2 Initial Values

Save the initial values so that we do not need to go through all this to re-run the analysis. Also, set the argument `delta` to 0.5, the earliest non-zero time point.

```
> formals(tcmfn4)$delta <- min(dta$tmpstds[dta$tmpstds > 0])
> initfile <- paste("initvals-brain-DR-1.RData", sep = "")
> if (!file.exists(initfile)) {
+     lA.start <- lm(I(log(cheact)) ~ mridXsexXtmpstds - 1, data = CleanUp(subset(dta,
+         dose %in% 0)))
+     Start <- c(coef(lA.start), rep(log(0.2), nlevels(dta$mrid)),
+         0, -2, 0, log(1), 0, log(1.5))
+     init1 <- GetInitialValues(cbind(resp = cheact, sd = sd, n = n) ~
+         tcmfn4(dose, tmpstds, lA = lA, tz = tz, lD = lD, lg = lg,
+             lTr = lTr), data = dta, params = list(lA ~ mridXsexXtmpstds -
+         1, lD ~ mrid + sex - 1, tz ~ sex, lg ~ sex, lTr ~ 1),
+         start = Start, weights = varComb(varIdent(form = ~1 |
+             mrid), varPower(value = 1)))
+     save(init1, file = initfile)
+ } else load(initfile)
> tmp <- t(init1$Redundancy[[1]]$Eigens)
> tmp <- tmp[-grep("^lA", rownames(tmp)), ]
> round(tmp[, 1:5], digits = 2)
```

```
                 [,1]  [,2] [,3] [,4] [,5]
CondIndex       54.44 29.36 9.29 8.42 6.15
mu               0.04  0.07 0.24 0.26 0.36
lD.mrid44254401  0.47  0.17 0.00 0.00 0.31
lD.mrid44420301  0.69  0.27 0.03 0.01 0.00
lD.mrid44472001  0.58  0.20 0.00 0.00 0.01
lD.mridPadilla   0.51  0.25 0.02 0.00 0.03
lD.sexM          0.85  0.11 0.02 0.02 0.00
tz.(Intercept)   0.26  0.23 0.36 0.08 0.02
tz.sexM          0.13  0.61 0.02 0.23 0.01
lg.(Intercept)   0.68  0.31 0.01 0.00 0.00
lg.sexM          0.85  0.14 0.01 0.00 0.00
lTr              0.02  0.10 0.24 0.21 0.35
```

The above shows the results of a redundancy analysis. The largest condition index is about 54, with strong loadings with all levels of `lD` and `lg`. More important, perhaps, is that after an initial optimization, the estimated values for `tz` are quite small, with very large standard errors:

```
> cbind(est = getParms("^tz", init1$start$beta), se = getParms("^tz",
+     init1$Redundancy[[1]]$SE))

                 est          se
tz.(Intercept) -4.80    85.29033
tz.sexM        -5.46 33007.21343
```

Optimization of the above model did not go to completion, and already the value of `tz` has become quite small (even smaller for males). Set `tz` to -10, and do not estimate it. Rerun `GetInitialValues()` with this reduced model:

```
> formals(tcmfn4)$delta <- min(dta$tmpstds[dta$tmpstds > 0])
> formals(tcmfn4)$tz <- -10
> initfile <- paste("initvals-brain-DR-2.RData", sep = "")
> if (!file.exists(initfile)) {
+     lA.start <- lm(I(log(cheact)) ~ mridXsexXtmpstds - 1, data = CleanUp(subset(dta,
+         dose %in% 0)))
+     Start <- init1$start$beta
+     Start <- Start[-grep("^tz", names(Start))]
+     init2 <- GetInitialValues(cbind(resp = cheact, sd = sd, n = n) ~
+         tcmfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr),
+         data = dta, params = list(lA ~ mridXsexXtmpstds - 1,
+             lD ~ mrid + sex - 1, lg ~ sex, lTr ~ 1), start = Start,
+         weights = varComb(varIdent(form = ~1 | mrid), varPower(value = 1)))
+     save(init2, file = initfile)
+ } else load(initfile)
> tmp <- t(init2$Redundancy[[1]]$Eigens)
> tmp <- tmp[-grep("^lA", rownames(tmp)), ]
> round(tmp[, 1:5], digits = 2)

                 [,1]  [,2] [,3] [,4] [,5]
CondIndex       33.84 15.40 5.93 3.96 3.39
mu               0.06  0.13 0.33 0.50 0.58
lD.mrid44254401  0.44  0.12 0.39 0.01 0.00
lD.mrid44420301  0.83  0.16 0.00 0.00 0.01
lD.mrid44472001  0.63  0.04 0.02 0.00 0.00
lD.mridPadilla   0.61  0.08 0.03 0.24 0.02
lD.sexM          0.80  0.19 0.00 0.00 0.00
lg.(Intercept)   0.83  0.15 0.00 0.00 0.00
lg.sexM          0.81  0.18 0.00 0.00 0.01
lTr              0.02  0.01 0.84 0.00 0.00
```

Although not shown above, dropping the male term for `lg` drops the largest condition index to about 18. Fit the above model with `gnls()` to determine the best error variance model:

```
> Start <- Start0 <- init2$start$beta
> idta <- init2$data
> idta$mridXsex <- with(idta, interaction(mrid, sex, drop = TRUE,
+     sep = ":"))
> icnt <- 1
> Maxcnt <- 20
> repeat {
+     drmod1 <- try(gnls(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, lg = lg, lTr = lTr), data = idta, params = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ mrid + sex - 1, lg ~ sex,
+         lTr ~ 1), start = Start), silent = TRUE)
```

```
+     if (!inherits(drmod1, "try-error") || icnt > Maxcnt) {
+         if (icnt <= Maxcnt)
+             writeLines(paste("Successful in ", icnt, if (icnt >
+                 1)
+                 "tries"
+             else "try"))
+         else writeLines("Maxcnt exceeded")
+         break
+     }
+     icnt <- icnt + 1
+     Start <- Start0 * (1 + rnorm(length(Start0), sd = 0.2))
+ }
```

```
Successful in  1 try
```

Now, a separate standard deviation for each mrid X sex:

```
> Start <- Start0 <- coef(drmod1)
> idta <- init2$data
> idta$mridXsex <- with(idta, interaction(mrid, sex, drop = TRUE,
+     sep = ":"))
> icnt <- 1
> Maxcnt <- 20
> repeat {
+     drmod2 <- try(gnls(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, lg = lg, lTr = lTr), data = idta, params = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ mrid + sex - 1, lg ~ sex,
+         lTr ~ 1), weights = varIdent(form = ~1 | mridXsex), start = Start),
+         silent = TRUE)
+     if (!inherits(drmod2, "try-error") || icnt > Maxcnt) {
+         if (icnt <= Maxcnt)
+             writeLines(paste("Successful in ", icnt, if (icnt >
+                 1)
+                 "tries"
+             else "try"))
+         else writeLines("Maxcnt exceeded")
+         break
+     }
+     icnt <- icnt + 1
+     Start <- Start0 * (1 + rnorm(length(Start0), sd = 0.2))
+ }
```

```
Successful in  1 try
```

Now, include a power term in the variance model:

```
> Start <- Start0 <- coef(drmod2)
> idta <- init2$data
> idta$mridXsex <- with(idta, interaction(mrid, sex, drop = TRUE,
+     sep = ":"))
> icnt <- 1
> Maxcnt <- 20
> repeat {
+     drmod3 <- try(gnls(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, lg = lg, lTr = lTr), data = idta, params = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ mrid + sex - 1, lg ~ sex,
```

```
+         lTr ~ 1), weights = varComb(varIdent(form = ~1 | mridXsex),
+         varPower()), start = Start), silent = TRUE)
+     if (!inherits(drmod3, "try-error") || icnt > Maxcnt) {
+         if (icnt <= Maxcnt)
+             writeLines(paste("Successful in ", icnt, if (icnt >
+                 1)
+                 "tries"
+             else "try"))
+         else writeLines("Maxcnt exceeded")
+         break
+     }
+     icnt <- icnt + 1
+     Start <- Start0 * (1 + rnorm(length(Start0), sd = 0.2))
+ }
```

```
Successful in  1 try
```

Compare the three:

```
> anova(drmod1, drmod2, drmod3)
```

```
       Model df       AIC       BIC   logLik   Test  L.Ratio p-value
drmod1     1 31 -1631.991 -1481.835 846.9955
drmod2     2 37 -1700.323 -1521.104 887.1615 1 vs 2 80.33209  <.0001
drmod3     3 38 -1722.219 -1538.156 899.1093 2 vs 3 23.89552  <.0001
```

Adding the `varPower()` component to the weights improves the fit. Use the variance model in `drmod3` for the following mixed effects model:

```
> Par <- coef(drmod3)
> lDpar <- getParms("^lD", Par)
> lD.sexF <- mean(lDpar[grep("mrid", names(lDpar))])
> Start0 <- c(getParms("^lA", Par), lD.sexF, getParms("lD\\.sexM",
+     Par), getParms("^lg", Par), getParms("^lTr", Par))
> RE <- matrix(lDpar[grep("mrid", names(lDpar))] - mean(lDpar[grep("mrid",
+     names(lDpar))]), ncol = 1, dimnames = list(levels(idta$mrid),
+     NULL))
> Start <- list(fixed = Start0, random = RE)
> icnt <- 1
> Maxcnt <- 30
> repeat {
+     drmod4 <- try(nlme(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, lg = lg, lTr = lTr), data = idta, fixed = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ sex, lg ~ sex, lTr ~ 1), random = lD ~
+         1 | mrid, weights = varComb(varIdent(form = ~1 | mridXsex),
+         varPower(value = 0.5)), start = Start), silent = TRUE)
+     if (!inherits(drmod4, "try-error") || icnt > Maxcnt) {
+         if (icnt <= Maxcnt)
+             writeLines(paste("Success after", icnt, "trie(s)."))
+         else writeLines(paste("Maxcnt,", Maxcnt, "exceeded"))
+         break
+     }
+     Start <- list(fixed = Start0 * (1 + rnorm(length(Start0),
+         sd = 0.2)), random = RE)
+     icnt <- icnt + 1
+ }
```

```
Success after 1 trie(s).
```

The interesting fitted values:

```
> nms <- names(fixed.effects(drmod4))
> summary(drmod4)$tTable[-grep("^lA", nms), ]
```

```
                    Value  Std.Error  DF     t-value      p-value
lD.(Intercept) -1.9031415 0.16783474 908 -11.3393780 5.750312e-28
lD.sexM         0.1634431 0.14824833 908   1.1024952 2.705386e-01
lg.(Intercept)  0.1496498 0.04708270 908   3.1784458 1.530771e-03
lg.sexM        -0.0477314 0.07814944 908  -0.6107708 5.415041e-01
lTr            -0.2868298 0.06957433 908  -4.1226387 4.088657e-05
```

Note that sex differences in `lD` and `lg` are not significant individually. Are they, jointly? If not, refit a simpler model.

```
> L <- diag(2)
> colnames(L) <- c("lD.sexM", "lg.sexM")
> anova(drmod4, L = L)
```

```
F-test for linear combination(s)
  lD.sexM lg.sexM
1       1       0
2       0       1
  numDF denDF  F-value p-value
1     2   908 22.82644  <.0001
```

Cute! P-value is < 0.0001. This is due to the redundancy between the two parameters: we do not need them both, but certainly need one of them. Their correlation is 0.97

Refit with a single value for `lg`.

```
> Par <- fixed.effects(drmod4)
> Start0 <- c(getParms("^lA", Par), getParms("^lD", Par), Par["lg.(Intercept)"],
+     getParms("^lTr", Par))
> RE <- data.matrix(random.effects(drmod4))
> Start <- list(fixed = Start0, random = RE)
> icnt <- 1
> Maxcnt <- 30
> repeat {
+     drmod5 <- try(nlme(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, lg = lg, lTr = lTr), data = idta, fixed = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ sex, lg ~ 1, lTr ~ 1), random = lD ~
+         1 | mrid, weights = varComb(varIdent(form = ~1 | mridXsex),
+         varPower(value = 0.5)), start = Start), silent = TRUE)
+     if (!inherits(drmod5, "try-error") || icnt > Maxcnt) {
+         if (icnt <= Maxcnt)
+             writeLines(paste("Success after", icnt, "trie(s)."))
+         else writeLines(paste("Maxcnt,", Maxcnt, "exceeded"))
+         break
+     }
+     Start <- list(fixed = Start0 * (1 + rnorm(length(Start0),
+         sd = 0.2)), random = RE)
+     icnt <- icnt + 1
+ }
```

```
Success after 1 trie(s).
```

```
> summary(drmod5)$tTable[-grep("^lA", names(fixed.effects(drmod5))),
+     ]

                    Value  Std.Error  DF    t-value      p-value
lD.(Intercept) -1.9325604 0.16098506 909 -12.004595 6.373636e-31
lD.sexM         0.2482529 0.03673843 909   6.757308 2.508749e-11
lg              0.1336830 0.03911416 909   3.417764 6.594050e-04
lTr            -0.2858518 0.06951287 909  -4.112214 4.273822e-05
```

The BMD for males is significantly greater than for females. For convenience, refit the model, estimating a separate BMD value for males in females (instead of an estimate for females and contrast between males and females:

```
> Par <- fixed.effects(drmod5)
> Start0 <- c(getParms("^lA", Par), getParms("^lD", Par) %*% matrix(c(1,
+     0, 1, 1), nrow = 2, ncol = 2), Par["lg"], getParms("^lTr",
+     Par))
> RE <- data.matrix(random.effects(drmod5))
> Start <- list(fixed = Start0, random = RE)
> icnt <- 1
> Maxcnt <- 30
> repeat {
+     drmod6 <- try(nlme(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, lg = lg, lTr = lTr), data = idta, fixed = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ sex - 1, lg ~ 1, lTr ~ 1),
+         random = lD ~ 1 | mrid, weights = varComb(varIdent(form = ~1 |
+             mridXsex), varPower(value = 0.5)), start = Start),
+         silent = TRUE)
+     if (!inherits(drmod6, "try-error") || icnt > Maxcnt) {
+         if (icnt <= Maxcnt)
+             writeLines(paste("Success after", icnt, "trie(s)."))
+         else writeLines(paste("Maxcnt,", Maxcnt, "exceeded"))
+         break
+     }
+     Start <- list(fixed = Start0 * (1 + rnorm(length(Start0),
+         sd = 0.2)), random = RE)
+     icnt <- icnt + 1
+ }

Success after 1 trie(s).

> Ints <- intervals(drmod6, which = "fixed")$fixed
> Ints90 <- intervals(drmod6, which = "fixed", level = 0.9)$fixed
> tTab <- summary(drmod6)$tTable
> summary(drmod6)

Nonlinear mixed-effects model fit by maximum likelihood
  Model: cheact ~ tcmfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr)
 Data: idta
        AIC       BIC   logLik
  -1707.014 -1537.483 888.5071

Random effects:
 Formula: lD ~ 1 | mrid
        lD.(Intercept)   Residual
```

```
StdDev:       0.272704 0.09443928

Combination of variance functions:
 Structure: Different standard deviations per stratum
 Formula: ~1 | mridXsex
 Parameter estimates:
44254401:M 44254401:F 44420301:M 44420301:F 44472001:M 44472001:F  Padilla:M
 1.0000000  0.7927556  1.1386359  0.8430371  0.7109887  0.8275438  1.1128288
 Structure: Power of variance covariate
 Formula: ~fitted(.)
 Parameter estimates:
     power
-0.4254700
Fixed effects: list(lA ~ mridXsexXtmpstds - 1, lD ~ sex - 1, lg ~ 1, lTr ~ 1)
                                                  Value  Std.Error  DF
lA.mridXsexXtmpstds44420301:M:0.5               0.1183431 0.00914230 909
lA.mridXsexXtmpstds44420301:F:0.5               0.1982051 0.00670079 909
lA.mridXsexXtmpstds44254401:M:1                 0.1090786 0.01901339 909
lA.mridXsexXtmpstds44254401:M:24                0.1798184 0.01186871 909
lA.mridXsexXtmpstds44254401:M:360               0.1050355 0.01303773 909
lA.mridXsexXtmpstds44254401:F:1                 0.2050935 0.01402828 909
lA.mridXsexXtmpstds44254401:F:24                0.1947441 0.00909505 909
lA.mridXsexXtmpstds44254401:F:360               0.1095268 0.01026977 909
lA.mridXsexXtmpstds44472001:M:0.5               0.1053297 0.01769167 909
lA.mridXsexXtmpstds44472001:M:2                 0.1776157 0.01354677 909
lA.mridXsexXtmpstds44472001:M:3                 0.2158759 0.01194154 909
lA.mridXsexXtmpstds44472001:M:4                 0.1773699 0.01209072 909
lA.mridXsexXtmpstds44472001:F:0.5               0.1985987 0.01838884 909
lA.mridXsexXtmpstds44472001:F:2                 0.1749666 0.01605949 909
lA.mridXsexXtmpstds44472001:F:3                 0.2156778 0.01402500 909
lA.mridXsexXtmpstds44472001:F:4                 0.2381255 0.01298009 909
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.3125956 0.01853877 909
lA.mridXsexXtmpstdsPadilla:M:0.5                0.0187179 0.08543651 909
lA.mridXsexXtmpstdsPadilla:M:1                  0.0932435 0.06073171 909
lA.mridXsexXtmpstdsPadilla:M:1.5                0.0814831 0.05230606 909
lA.mridXsexXtmpstdsPadilla:M:4                  0.0315470 0.04281781 909
lA.mridXsexXtmpstdsPadilla:M:24                 0.1015947 0.04123874 909
lD.sexF                                        -1.9326443 0.16092719 909
lD.sexM                                        -1.6843837 0.16011499 909
lg                                              0.1336977 0.03911360 909
lTr                                            -0.2860210 0.06950068 909
                                                  t-value p-value
lA.mridXsexXtmpstds44420301:M:0.5               12.944569  0.0000
lA.mridXsexXtmpstds44420301:F:0.5               29.579360  0.0000
lA.mridXsexXtmpstds44254401:M:1                  5.736938  0.0000
lA.mridXsexXtmpstds44254401:M:24                15.150631  0.0000
lA.mridXsexXtmpstds44254401:M:360                8.056270  0.0000
lA.mridXsexXtmpstds44254401:F:1                 14.619999  0.0000
lA.mridXsexXtmpstds44254401:F:24                21.412099  0.0000
lA.mridXsexXtmpstds44254401:F:360               10.664972  0.0000
lA.mridXsexXtmpstds44472001:M:0.5                5.953632  0.0000
lA.mridXsexXtmpstds44472001:M:2                 13.111298  0.0000
lA.mridXsexXtmpstds44472001:M:3                 18.077731  0.0000
lA.mridXsexXtmpstds44472001:M:4                 14.669916  0.0000
```

```
lA.mridXsexXtmpstds44472001:F:0.5                10.799956  0.0000
lA.mridXsexXtmpstds44472001:F:2                  10.894905  0.0000
lA.mridXsexXtmpstds44472001:F:3                  15.378104  0.0000
lA.mridXsexXtmpstds44472001:F:4                  18.345448  0.0000
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  16.861721  0.0000
lA.mridXsexXtmpstdsPadilla:M:0.5                  0.219085  0.8266
lA.mridXsexXtmpstdsPadilla:M:1                    1.535335  0.1250
lA.mridXsexXtmpstdsPadilla:M:1.5                  1.557813  0.1196
lA.mridXsexXtmpstdsPadilla:M:4                    0.736773  0.4615
lA.mridXsexXtmpstdsPadilla:M:24                   2.463574  0.0139
lD.sexF                                         -12.009434  0.0000
lD.sexM                                         -10.519838  0.0000
lg                                                3.418189  0.0007
lTr                                              -4.115369  0.0000
 Correlation:
                                                lA.XX44420301:M lA.XX44420301:F
lA.mridXsexXtmpstds44420301:F:0.5                0.140
lA.mridXsexXtmpstds44254401:M:1                  0.056           0.038
lA.mridXsexXtmpstds44254401:M:24                 0.000           0.000
lA.mridXsexXtmpstds44254401:M:360                0.000           0.000
lA.mridXsexXtmpstds44254401:F:1                  0.028           0.096
lA.mridXsexXtmpstds44254401:F:24                 0.000           0.000
lA.mridXsexXtmpstds44254401:F:360                0.000           0.000
lA.mridXsexXtmpstds44472001:M:0.5                0.038          -0.011
lA.mridXsexXtmpstds44472001:M:2                  0.034           0.017
lA.mridXsexXtmpstds44472001:M:3                  0.021           0.015
lA.mridXsexXtmpstds44472001:M:4                  0.010           0.009
lA.mridXsexXtmpstds44472001:F:0.5               -0.033           0.004
lA.mridXsexXtmpstds44472001:F:2                 -0.003           0.025
lA.mridXsexXtmpstds44472001:F:3                  0.003           0.019
lA.mridXsexXtmpstds44472001:F:4                  0.004           0.011
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.050           0.079
lA.mridXsexXtmpstdsPadilla:M:0.5                 0.002           0.002
lA.mridXsexXtmpstdsPadilla:M:1                   0.009           0.012
lA.mridXsexXtmpstdsPadilla:M:1.5                 0.012           0.016
lA.mridXsexXtmpstdsPadilla:M:4                   0.004           0.006
lA.mridXsexXtmpstdsPadilla:M:24                  0.000           0.000
lD.sexF                                         -0.093          -0.232
lD.sexM                                         -0.154          -0.190
lg                                              -0.277          -0.461
lTr                                              0.043           0.065
                                                lA.XX44254401:M:1
lA.mridXsexXtmpstds44420301:F:0.5
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24                 0.000
lA.mridXsexXtmpstds44254401:M:360                0.000
lA.mridXsexXtmpstds44254401:F:1                  0.145
lA.mridXsexXtmpstds44254401:F:24                 0.000
lA.mridXsexXtmpstds44254401:F:360                0.000
lA.mridXsexXtmpstds44472001:M:0.5                0.017
lA.mridXsexXtmpstds44472001:M:2                  0.000
lA.mridXsexXtmpstds44472001:M:3                 -0.003
lA.mridXsexXtmpstds44472001:M:4                 -0.002
lA.mridXsexXtmpstds44472001:F:0.5               -0.008
```

```
lA.mridXsexXtmpstds44472001:F:2                -0.013
lA.mridXsexXtmpstds44472001:F:3                -0.009
lA.mridXsexXtmpstds44472001:F:4                -0.005
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.024
lA.mridXsexXtmpstdsPadilla:M:0.5                0.005
lA.mridXsexXtmpstdsPadilla:M:1                  0.001
lA.mridXsexXtmpstdsPadilla:M:1.5               -0.002
lA.mridXsexXtmpstdsPadilla:M:4                 -0.002
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lD.sexF                                        -0.087
lD.sexM                                        -0.107
lg                                             -0.116
lTr                                            -0.026
                                               lA.XX44254401:M:2
lA.mridXsexXtmpstds44420301:F:0.5
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360               0.000
lA.mridXsexXtmpstds44254401:F:1                 0.000
lA.mridXsexXtmpstds44254401:F:24                0.000
lA.mridXsexXtmpstds44254401:F:360               0.000
lA.mridXsexXtmpstds44472001:M:0.5               0.000
lA.mridXsexXtmpstds44472001:M:2                 0.000
lA.mridXsexXtmpstds44472001:M:3                 0.000
lA.mridXsexXtmpstds44472001:M:4                 0.000
lA.mridXsexXtmpstds44472001:F:0.5               0.000
lA.mridXsexXtmpstds44472001:F:2                 0.000
lA.mridXsexXtmpstds44472001:F:3                 0.000
lA.mridXsexXtmpstds44472001:F:4                 0.000
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.000
lA.mridXsexXtmpstdsPadilla:M:0.5                0.000
lA.mridXsexXtmpstdsPadilla:M:1                  0.000
lA.mridXsexXtmpstdsPadilla:M:1.5                0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.000
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lD.sexF                                         0.000
lD.sexM                                         0.000
lg                                              0.000
lTr                                             0.000
                                               lA.XX44254401:M:3
lA.mridXsexXtmpstds44420301:F:0.5
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:1                 0.000
lA.mridXsexXtmpstds44254401:F:24                0.000
lA.mridXsexXtmpstds44254401:F:360               0.000
lA.mridXsexXtmpstds44472001:M:0.5               0.000
lA.mridXsexXtmpstds44472001:M:2                 0.000
lA.mridXsexXtmpstds44472001:M:3                 0.000
lA.mridXsexXtmpstds44472001:M:4                 0.000
lA.mridXsexXtmpstds44472001:F:0.5               0.000
lA.mridXsexXtmpstds44472001:F:2                 0.000
lA.mridXsexXtmpstds44472001:F:3                 0.000
```

```
lA.mridXsexXtmpstds44472001:F:4                  0.000
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.000
lA.mridXsexXtmpstdsPadilla:M:0.5                 0.000
lA.mridXsexXtmpstdsPadilla:M:1                   0.000
lA.mridXsexXtmpstdsPadilla:M:1.5                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                   0.000
lA.mridXsexXtmpstdsPadilla:M:24                  0.000
lD.sexF                                          0.000
lD.sexM                                          0.000
lg                                               0.000
lTr                                              0.000
                                                lA.XX44254401:F:1
lA.mridXsexXtmpstds44420301:F:0.5
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:1
lA.mridXsexXtmpstds44254401:F:24                 0.000
lA.mridXsexXtmpstds44254401:F:360                0.000
lA.mridXsexXtmpstds44472001:M:0.5               -0.003
lA.mridXsexXtmpstds44472001:M:2                  0.003
lA.mridXsexXtmpstds44472001:M:3                  0.003
lA.mridXsexXtmpstds44472001:M:4                  0.002
lA.mridXsexXtmpstds44472001:F:0.5                0.004
lA.mridXsexXtmpstds44472001:F:2                  0.007
lA.mridXsexXtmpstds44472001:F:3                  0.005
lA.mridXsexXtmpstds44472001:F:4                  0.003
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.034
lA.mridXsexXtmpstdsPadilla:M:0.5                 0.003
lA.mridXsexXtmpstdsPadilla:M:1                   0.006
lA.mridXsexXtmpstdsPadilla:M:1.5                 0.006
lA.mridXsexXtmpstdsPadilla:M:4                   0.002
lA.mridXsexXtmpstdsPadilla:M:24                  0.000
lD.sexF                                         -0.138
lD.sexM                                         -0.120
lg                                              -0.176
lTr                                              0.015
                                                lA.XX44254401:F:2
lA.mridXsexXtmpstds44420301:F:0.5
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:1
lA.mridXsexXtmpstds44254401:F:24
lA.mridXsexXtmpstds44254401:F:360                0.000
lA.mridXsexXtmpstds44472001:M:0.5                0.000
lA.mridXsexXtmpstds44472001:M:2                  0.000
lA.mridXsexXtmpstds44472001:M:3                  0.000
lA.mridXsexXtmpstds44472001:M:4                  0.000
lA.mridXsexXtmpstds44472001:F:0.5                0.000
lA.mridXsexXtmpstds44472001:F:2                  0.000
lA.mridXsexXtmpstds44472001:F:3                  0.000
lA.mridXsexXtmpstds44472001:F:4                  0.000
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.000
```

```
lA.mridXsexXtmpstdsPadilla:M:0.5                0.000
lA.mridXsexXtmpstdsPadilla:M:1                  0.000
lA.mridXsexXtmpstdsPadilla:M:1.5                0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.000
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lD.sexF                                         0.000
lD.sexM                                         0.000
lg                                              0.000
lTr                                             0.000
                                               lA.XX44254401:F:3
lA.mridXsexXtmpstds44420301:F:0.5
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:1
lA.mridXsexXtmpstds44254401:F:24
lA.mridXsexXtmpstds44254401:F:360
lA.mridXsexXtmpstds44472001:M:0.5               0.000
lA.mridXsexXtmpstds44472001:M:2                 0.000
lA.mridXsexXtmpstds44472001:M:3                 0.000
lA.mridXsexXtmpstds44472001:M:4                 0.000
lA.mridXsexXtmpstds44472001:F:0.5               0.000
lA.mridXsexXtmpstds44472001:F:2                 0.000
lA.mridXsexXtmpstds44472001:F:3                 0.000
lA.mridXsexXtmpstds44472001:F:4                 0.000
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.000
lA.mridXsexXtmpstdsPadilla:M:0.5                0.000
lA.mridXsexXtmpstdsPadilla:M:1                  0.000
lA.mridXsexXtmpstdsPadilla:M:1.5                0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.000
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lD.sexF                                         0.000
lD.sexM                                         0.000
lg                                              0.000
lTr                                             0.000
                                               lA.XX44472001:M:0
lA.mridXsexXtmpstds44420301:F:0.5
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:1
lA.mridXsexXtmpstds44254401:F:24
lA.mridXsexXtmpstds44254401:F:360
lA.mridXsexXtmpstds44472001:M:0.5
lA.mridXsexXtmpstds44472001:M:2                 0.032
lA.mridXsexXtmpstds44472001:M:3                 0.009
lA.mridXsexXtmpstds44472001:M:4                 0.001
lA.mridXsexXtmpstds44472001:F:0.5               0.064
lA.mridXsexXtmpstds44472001:F:2                 0.015
lA.mridXsexXtmpstds44472001:F:3                 0.000
lA.mridXsexXtmpstds44472001:F:4                -0.003
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.007
lA.mridXsexXtmpstdsPadilla:M:0.5                0.005
lA.mridXsexXtmpstdsPadilla:M:1                 -0.004
```

```
lA.mridXsexXtmpstdsPadilla:M:1.5                -0.010
lA.mridXsexXtmpstdsPadilla:M:4                  -0.005
lA.mridXsexXtmpstdsPadilla:M:24                  0.000
lD.sexF                                         -0.026
lD.sexM                                         -0.054
lg                                              -0.021
lTr                                             -0.059
                                                lA.XX44472001:M:2
lA.mridXsexXtmpstds44420301:F:0.5
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:1
lA.mridXsexXtmpstds44254401:F:24
lA.mridXsexXtmpstds44254401:F:360
lA.mridXsexXtmpstds44472001:M:0.5
lA.mridXsexXtmpstds44472001:M:2
lA.mridXsexXtmpstds44472001:M:3                  0.091
lA.mridXsexXtmpstds44472001:M:4                  0.049
lA.mridXsexXtmpstds44472001:F:0.5                0.012
lA.mridXsexXtmpstds44472001:F:2                  0.115
lA.mridXsexXtmpstds44472001:F:3                  0.090
lA.mridXsexXtmpstds44472001:F:4                  0.054
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.005
lA.mridXsexXtmpstdsPadilla:M:0.5                -0.017
lA.mridXsexXtmpstdsPadilla:M:1                   0.032
lA.mridXsexXtmpstdsPadilla:M:1.5                 0.060
lA.mridXsexXtmpstdsPadilla:M:4                   0.027
lA.mridXsexXtmpstdsPadilla:M:24                  0.000
lD.sexF                                          0.016
lD.sexM                                          0.002
lg                                              -0.061
lTr                                              0.312
                                                lA.XX44472001:M:3
lA.mridXsexXtmpstds44420301:F:0.5
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:1
lA.mridXsexXtmpstds44254401:F:24
lA.mridXsexXtmpstds44254401:F:360
lA.mridXsexXtmpstds44472001:M:0.5
lA.mridXsexXtmpstds44472001:M:2
lA.mridXsexXtmpstds44472001:M:3
lA.mridXsexXtmpstds44472001:M:4                  0.038
lA.mridXsexXtmpstds44472001:F:0.5               -0.001
lA.mridXsexXtmpstds44472001:F:2                  0.088
lA.mridXsexXtmpstds44472001:F:3                  0.070
lA.mridXsexXtmpstds44472001:F:4                  0.043
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.003
lA.mridXsexXtmpstdsPadilla:M:0.5                -0.014
lA.mridXsexXtmpstdsPadilla:M:1                   0.026
lA.mridXsexXtmpstdsPadilla:M:1.5                 0.048
lA.mridXsexXtmpstdsPadilla:M:4                   0.022
```

```
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lD.sexF                                         0.016
lD.sexM                                         0.010
lg                                             -0.045
lTr                                             0.253
                                               lA.XX44472001:M:4
lA.mridXsexXtmpstds44420301:F:0.5
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:1
lA.mridXsexXtmpstds44254401:F:24
lA.mridXsexXtmpstds44254401:F:360
lA.mridXsexXtmpstds44472001:M:0.5
lA.mridXsexXtmpstds44472001:M:2
lA.mridXsexXtmpstds44472001:M:3
lA.mridXsexXtmpstds44472001:M:4
lA.mridXsexXtmpstds44472001:F:0.5              -0.003
lA.mridXsexXtmpstds44472001:F:2                 0.048
lA.mridXsexXtmpstds44472001:F:3                 0.039
lA.mridXsexXtmpstds44472001:F:4                 0.024
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.001
lA.mridXsexXtmpstdsPadilla:M:0.5               -0.008
lA.mridXsexXtmpstdsPadilla:M:1                  0.014
lA.mridXsexXtmpstdsPadilla:M:1.5                0.027
lA.mridXsexXtmpstdsPadilla:M:4                  0.012
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lD.sexF                                         0.010
lD.sexM                                         0.007
lg                                             -0.024
lTr                                             0.143
                                               lA.XX44472001:F:0
lA.mridXsexXtmpstds44420301:F:0.5
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:1
lA.mridXsexXtmpstds44254401:F:24
lA.mridXsexXtmpstds44254401:F:360
lA.mridXsexXtmpstds44472001:M:0.5
lA.mridXsexXtmpstds44472001:M:2
lA.mridXsexXtmpstds44472001:M:3
lA.mridXsexXtmpstds44472001:M:4
lA.mridXsexXtmpstds44472001:F:0.5
lA.mridXsexXtmpstds44472001:F:2                 0.020
lA.mridXsexXtmpstds44472001:F:3                 0.003
lA.mridXsexXtmpstds44472001:F:4                -0.002
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667 -0.003
lA.mridXsexXtmpstdsPadilla:M:0.5                0.004
lA.mridXsexXtmpstdsPadilla:M:1                 -0.006
lA.mridXsexXtmpstdsPadilla:M:1.5               -0.011
lA.mridXsexXtmpstdsPadilla:M:4                 -0.005
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lD.sexF                                        -0.026
```

```
lD.sexM                                          -0.005
lg                                                0.028
lTr                                              -0.059
                                                 lA.XX44472001:F:2
lA.mridXsexXtmpstds44420301:F:0.5
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:1
lA.mridXsexXtmpstds44254401:F:24
lA.mridXsexXtmpstds44254401:F:360
lA.mridXsexXtmpstds44472001:M:0.5
lA.mridXsexXtmpstds44472001:M:2
lA.mridXsexXtmpstds44472001:M:3
lA.mridXsexXtmpstds44472001:M:4
lA.mridXsexXtmpstds44472001:F:0.5
lA.mridXsexXtmpstds44472001:F:2
lA.mridXsexXtmpstds44472001:F:3                   0.093
lA.mridXsexXtmpstds44472001:F:4                   0.056
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667    0.000
lA.mridXsexXtmpstdsPadilla:M:0.5                 -0.019
lA.mridXsexXtmpstdsPadilla:M:1                    0.032
lA.mridXsexXtmpstdsPadilla:M:1.5                  0.060
lA.mridXsexXtmpstdsPadilla:M:4                    0.027
lA.mridXsexXtmpstdsPadilla:M:24                   0.000
lD.sexF                                           0.015
lD.sexM                                           0.026
lg                                               -0.036
lTr                                               0.316
                                                 lA.XX44472001:F:3
lA.mridXsexXtmpstds44420301:F:0.5
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:1
lA.mridXsexXtmpstds44254401:F:24
lA.mridXsexXtmpstds44254401:F:360
lA.mridXsexXtmpstds44472001:M:0.5
lA.mridXsexXtmpstds44472001:M:2
lA.mridXsexXtmpstds44472001:M:3
lA.mridXsexXtmpstds44472001:M:4
lA.mridXsexXtmpstds44472001:F:0.5
lA.mridXsexXtmpstds44472001:F:2
lA.mridXsexXtmpstds44472001:F:3
lA.mridXsexXtmpstds44472001:F:4                   0.045
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667    0.001
lA.mridXsexXtmpstdsPadilla:M:0.5                 -0.015
lA.mridXsexXtmpstdsPadilla:M:1                    0.026
lA.mridXsexXtmpstdsPadilla:M:1.5                  0.050
lA.mridXsexXtmpstdsPadilla:M:4                    0.023
lA.mridXsexXtmpstdsPadilla:M:24                   0.000
lD.sexF                                           0.017
lD.sexM                                           0.022
lg                                               -0.034
```

```
lTr                                          0.263
                                            lA.XX44472001:F:4 lA.XXP:M:0.6
lA.mridXsexXtmpstds44420301:F:0.5
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:1
lA.mridXsexXtmpstds44254401:F:24
lA.mridXsexXtmpstds44254401:F:360
lA.mridXsexXtmpstds44472001:M:0.5
lA.mridXsexXtmpstds44472001:M:2
lA.mridXsexXtmpstds44472001:M:3
lA.mridXsexXtmpstds44472001:M:4
lA.mridXsexXtmpstds44472001:F:0.5
lA.mridXsexXtmpstds44472001:F:2
lA.mridXsexXtmpstds44472001:F:3
lA.mridXsexXtmpstds44472001:F:4
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.000
lA.mridXsexXtmpstdsPadilla:M:0.5               -0.010             0.121
lA.mridXsexXtmpstdsPadilla:M:1                  0.016             0.126
lA.mridXsexXtmpstdsPadilla:M:1.5                0.031             0.092
lA.mridXsexXtmpstdsPadilla:M:4                  0.014             0.011
lA.mridXsexXtmpstdsPadilla:M:24                 0.000             0.000
lD.sexF                                         0.011            -0.129
lD.sexM                                         0.013            -0.130
lg                                             -0.022            -0.173
lTr                                             0.163             0.005
                                            lA.XXP:M:0.5 lA.mXXP:M:1
lA.mridXsexXtmpstds44420301:F:0.5
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:1
lA.mridXsexXtmpstds44254401:F:24
lA.mridXsexXtmpstds44254401:F:360
lA.mridXsexXtmpstds44472001:M:0.5
lA.mridXsexXtmpstds44472001:M:2
lA.mridXsexXtmpstds44472001:M:3
lA.mridXsexXtmpstds44472001:M:4
lA.mridXsexXtmpstds44472001:F:0.5
lA.mridXsexXtmpstds44472001:F:2
lA.mridXsexXtmpstds44472001:F:3
lA.mridXsexXtmpstds44472001:F:4
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667
lA.mridXsexXtmpstdsPadilla:M:0.5
lA.mridXsexXtmpstdsPadilla:M:1                  0.070
lA.mridXsexXtmpstdsPadilla:M:1.5                0.044        0.075
lA.mridXsexXtmpstdsPadilla:M:4                  0.001        0.015
lA.mridXsexXtmpstdsPadilla:M:24                 0.000        0.000
lD.sexF                                        -0.041       -0.029
lD.sexM                                        -0.042       -0.031
lg                                             -0.004       -0.028
lTr                                            -0.059        0.100
                                            lA.XXP:M:1. lA.XXP:M:4
```

```
lA.mridXsexXtmpstds44420301:F:0.5
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:1
lA.mridXsexXtmpstds44254401:F:24
lA.mridXsexXtmpstds44254401:F:360
lA.mridXsexXtmpstds44472001:M:0.5
lA.mridXsexXtmpstds44472001:M:2
lA.mridXsexXtmpstds44472001:M:3
lA.mridXsexXtmpstds44472001:M:4
lA.mridXsexXtmpstds44472001:F:0.5
lA.mridXsexXtmpstds44472001:F:2
lA.mridXsexXtmpstds44472001:F:3
lA.mridXsexXtmpstds44472001:F:4
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667
lA.mridXsexXtmpstdsPadilla:M:0.5
lA.mridXsexXtmpstdsPadilla:M:1
lA.mridXsexXtmpstdsPadilla:M:1.5
lA.mridXsexXtmpstdsPadilla:M:4                  0.021
lA.mridXsexXtmpstdsPadilla:M:24                 0.000       0.000
lD.sexF                                        -0.011       0.004
lD.sexM                                        -0.012       0.004
lg                                             -0.038      -0.014
lTr                                             0.189       0.087
                                               lA.XXP:M:2 lD.sxF lD.sxM lg
lA.mridXsexXtmpstds44420301:F:0.5
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:1
lA.mridXsexXtmpstds44254401:F:24
lA.mridXsexXtmpstds44254401:F:360
lA.mridXsexXtmpstds44472001:M:0.5
lA.mridXsexXtmpstds44472001:M:2
lA.mridXsexXtmpstds44472001:M:3
lA.mridXsexXtmpstds44472001:M:4
lA.mridXsexXtmpstds44472001:F:0.5
lA.mridXsexXtmpstds44472001:F:2
lA.mridXsexXtmpstds44472001:F:3
lA.mridXsexXtmpstds44472001:F:4
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667
lA.mridXsexXtmpstdsPadilla:M:0.5
lA.mridXsexXtmpstdsPadilla:M:1
lA.mridXsexXtmpstdsPadilla:M:1.5
lA.mridXsexXtmpstdsPadilla:M:4
lA.mridXsexXtmpstdsPadilla:M:24
lD.sexF                                         0.000
lD.sexM                                         0.000      0.974
lg                                              0.000      0.434  0.431
lTr                                             0.000      0.084  0.083 -0.149

Standardized Within-Group Residuals:
        Min          Q1         Med          Q3         Max
```

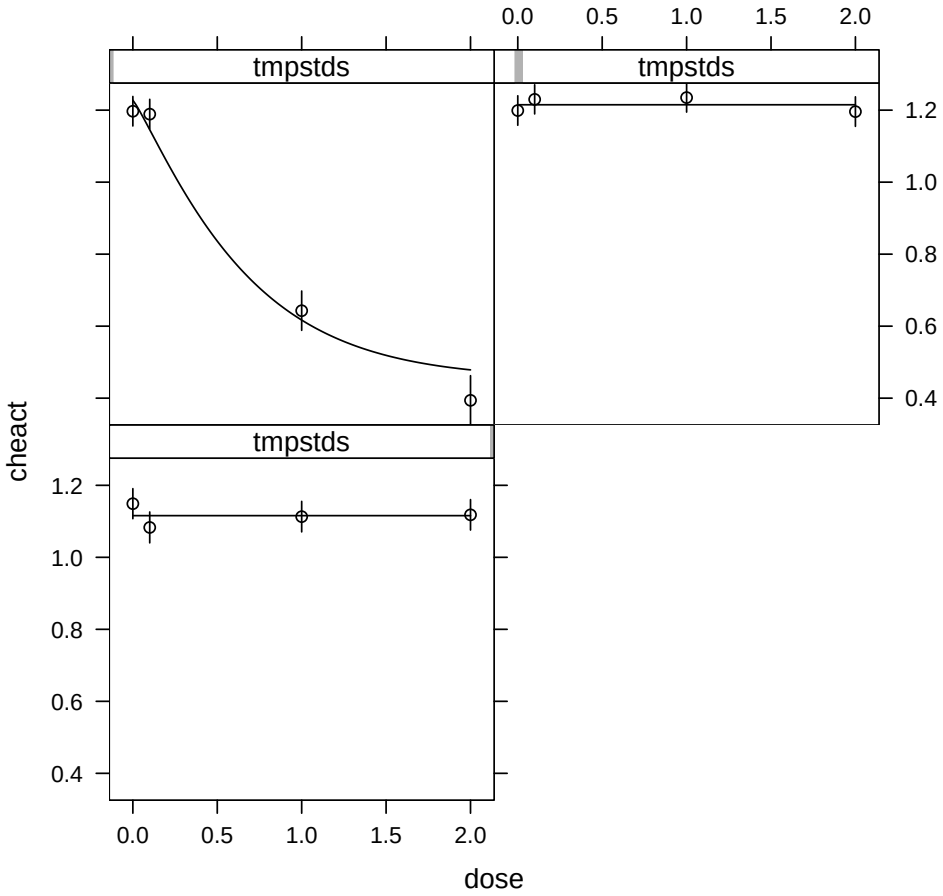
```
-3.06494567 -0.62979728  0.06831742  0.58207261  5.29472137

Number of Observations: 938
Number of Groups: 4
```

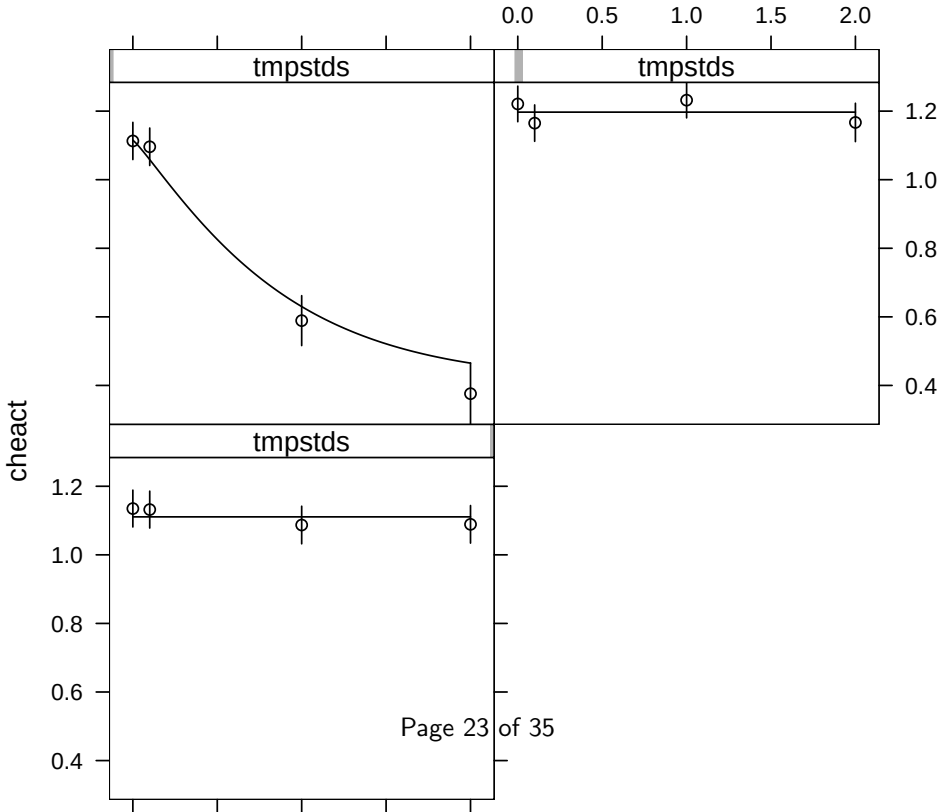
Diagnostic plots for this model: Plots of data with 95% CI and fitted curve for each combination of mrid and sex. First set up the data set and predicted values for plotting.

```
> tdta <- local({
+     idta$mridXsexXtmpstdsXdose <- with(idta, interaction(mridXsexXtmpstds,
+         dose, sep = ":", drop = TRUE))
+     out <- gls(cheact ~ mridXsexXtmpstdsXdose - 1, data = idta,
+         weights = varComb(varIdent(form = ~1 | mridXsex), varPower()))
+     Ints <- intervals(out, which = "coef")$coef
+     nms <- gsub("mridXsexXtmpstdsXdose", "", rownames(Ints))
+     sstr <- strsplit(nms, ":")
+     data.frame(cheact = Ints[, "est."], llim = Ints[, "lower"],
+         ulim = Ints[, "upper"], mrid = factor(sapply(sstr, function(x) x[1])),
+         sex = factor(sapply(sstr, function(x) x[2])), tmpstds = as.numeric(sapply(sstr,
+             function(x) x[3])), dose = as.numeric(sapply(sstr,
+             function(x) x[4])))
+ })
> ndta <- expand.grid(dose = seq(0, max(tdta$dose), length = 101),
+     mridXsexXtmpstds = levels(idta$mridXsexXtmpstds))
> nms <- as.character(ndta$mridXsexXtmpstds)
> sstr <- strsplit(nms, ":")
> ndta$mrid <- factor(sapply(sstr, function(x) x[1]))
> ndta$sex <- factor(sapply(sstr, function(x) x[2]))
> ndta$tmpstds <- as.numeric(sapply(sstr, function(x) x[3]))
> tmp <- drmod6
> tmp$contrasts <- NULL
> ndta$pred <- predict(tmp, newdata = ndta)
```

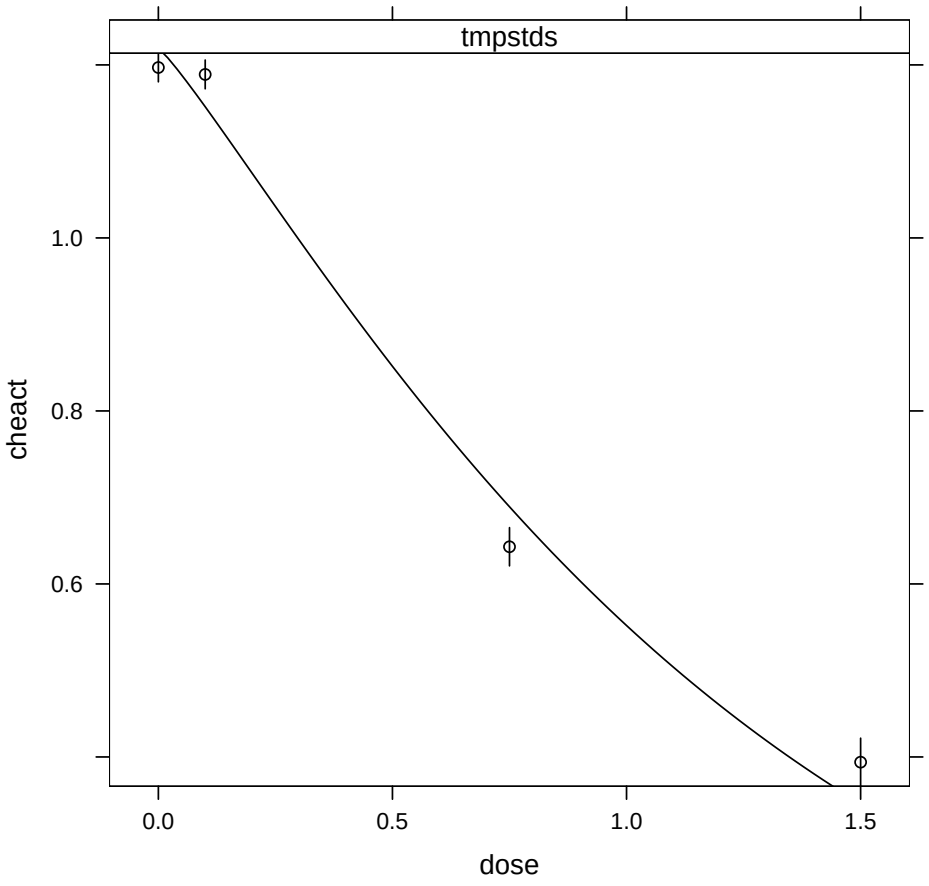
44254401 F

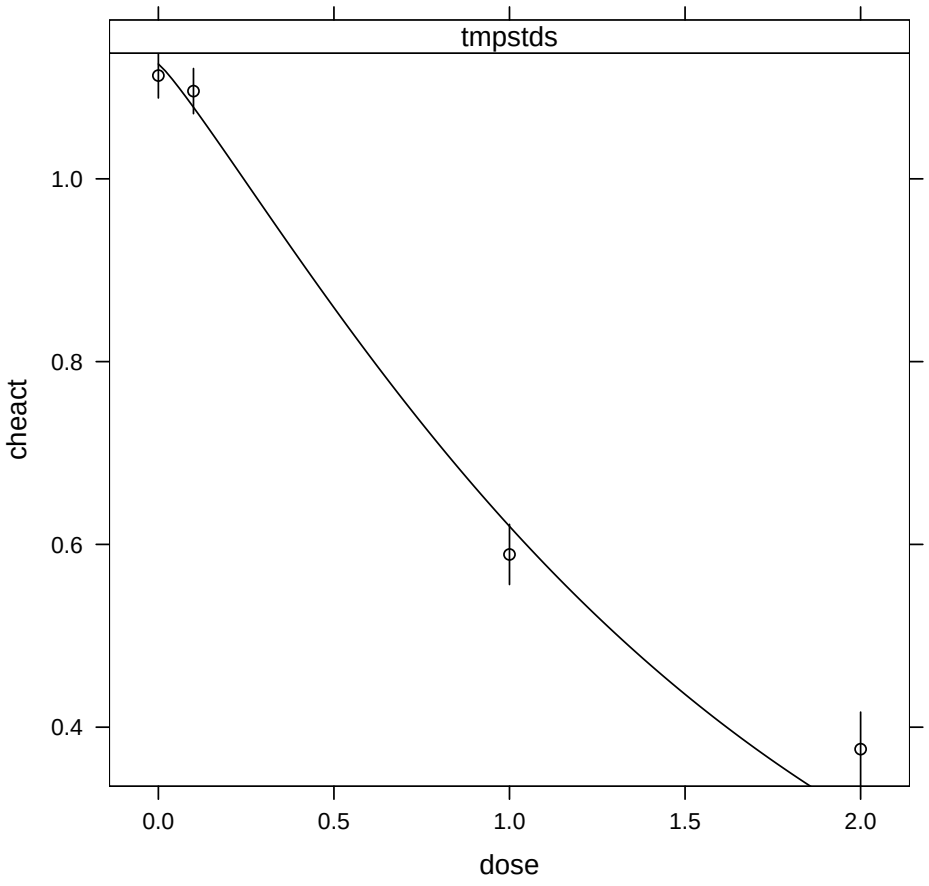


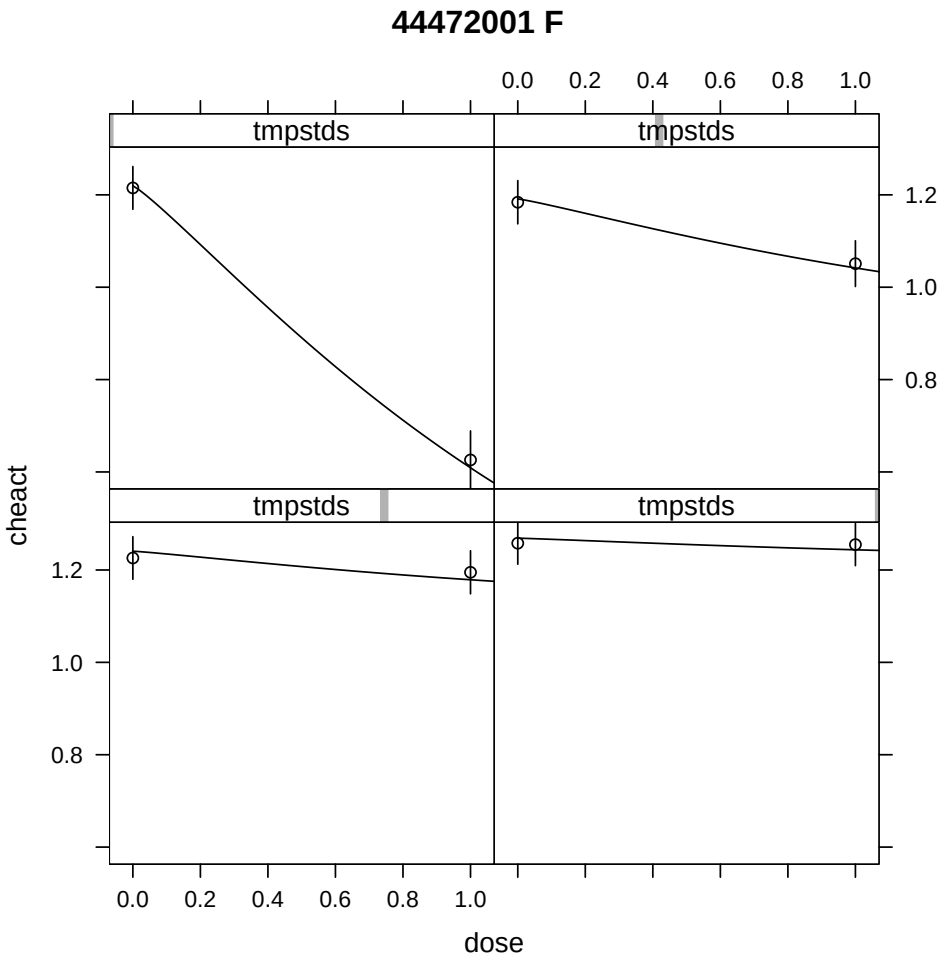
44254401 M

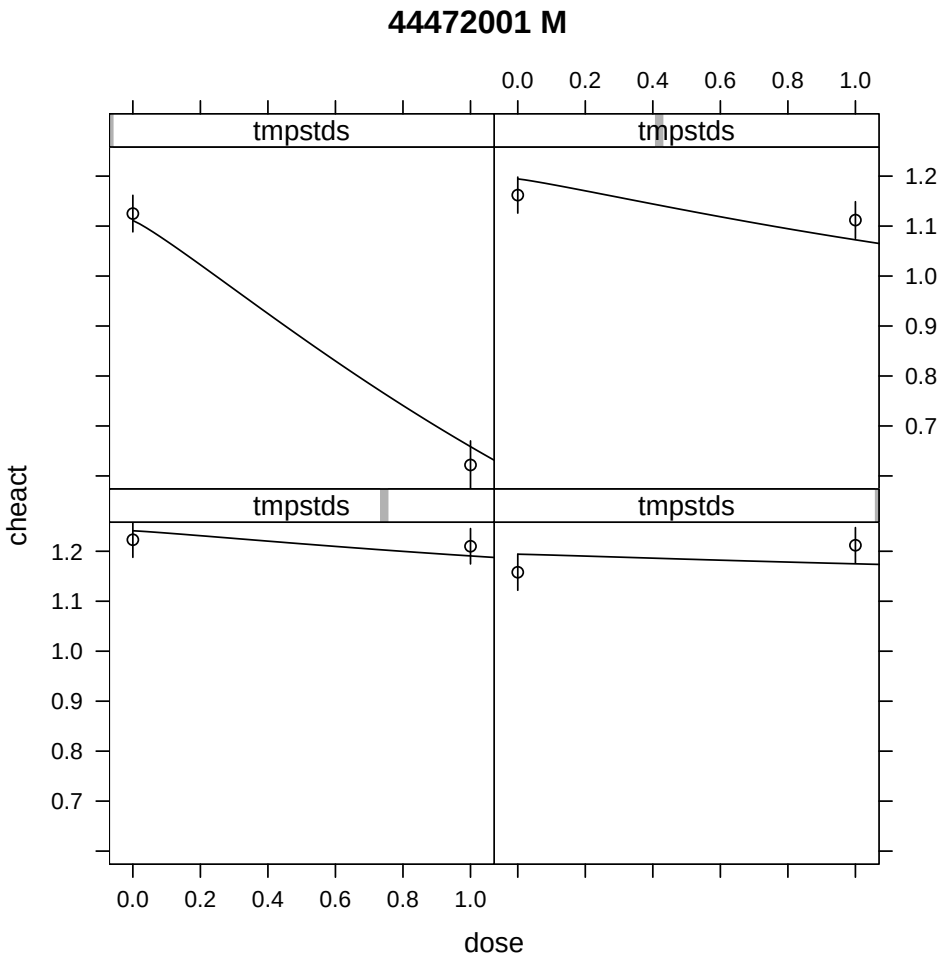


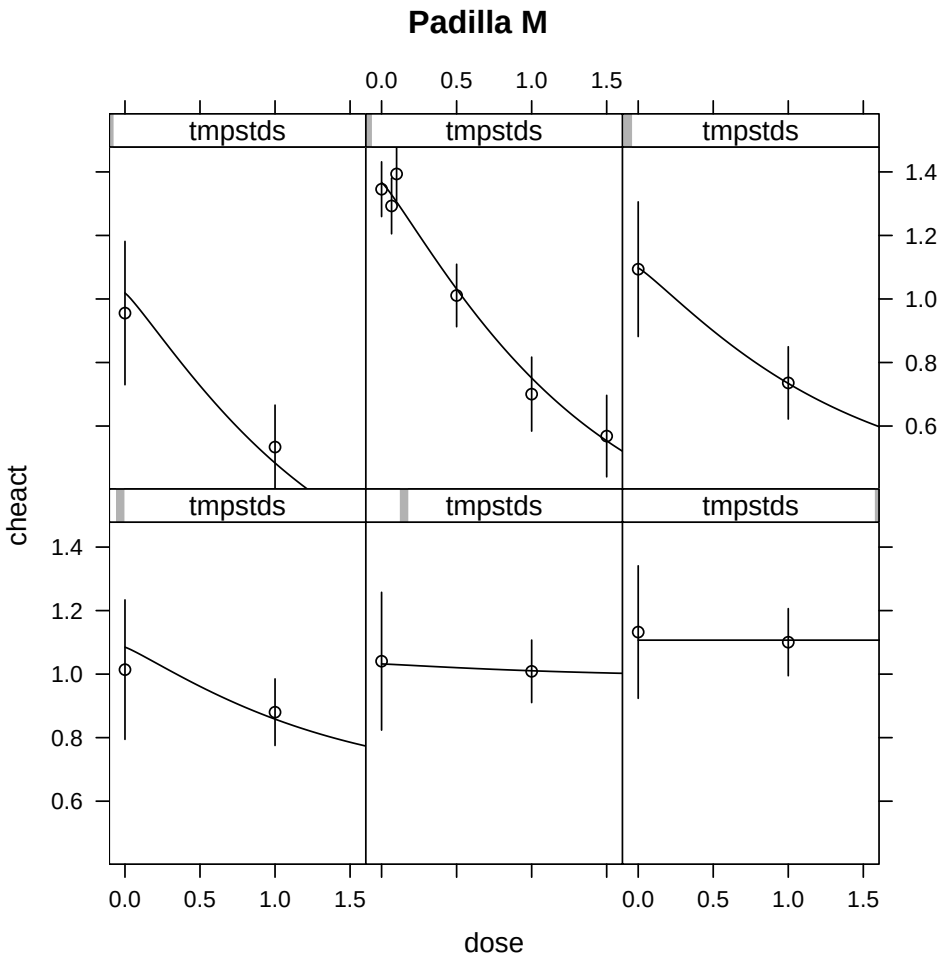
44420301 F

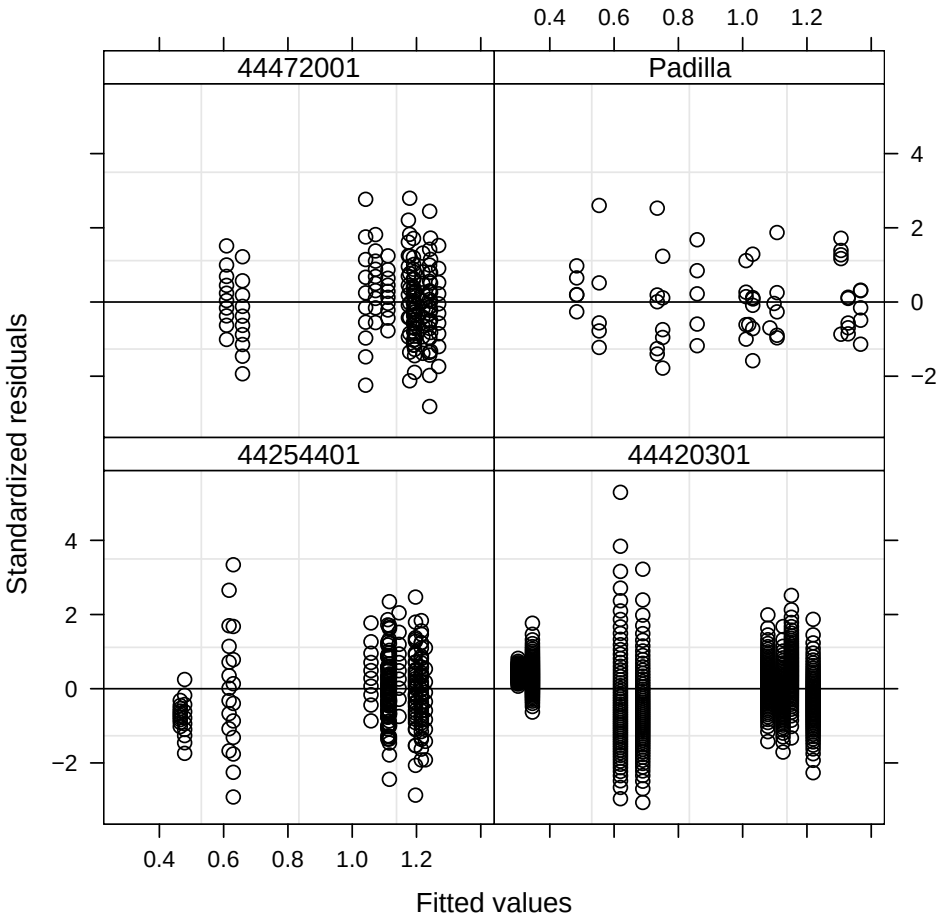


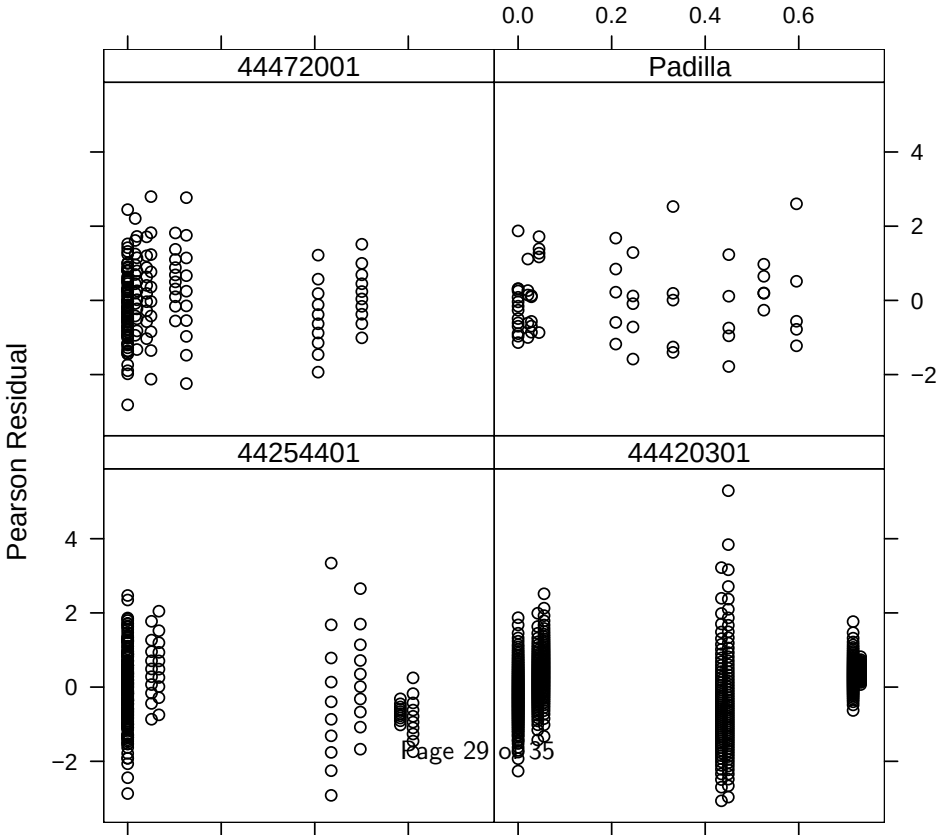

44420301 M
tmpstds
cheact
1.0
0.8
0.6
0.4
0.0
0.5
1.0
1.5
2.0
dose

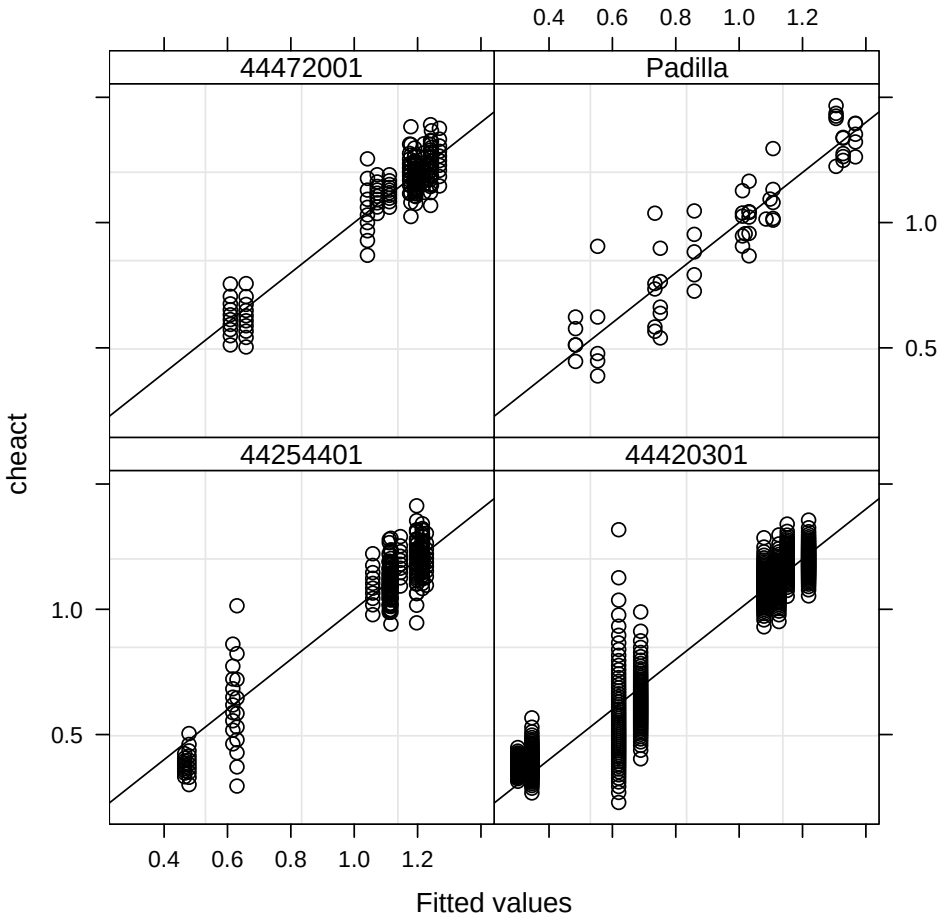

44472001 F
tmpstds
tmpstds
tmpstds
tmpstds
cheact
dose
0.0
0.2
0.4
0.6
0.8
1.0
0.8
1.0
1.2

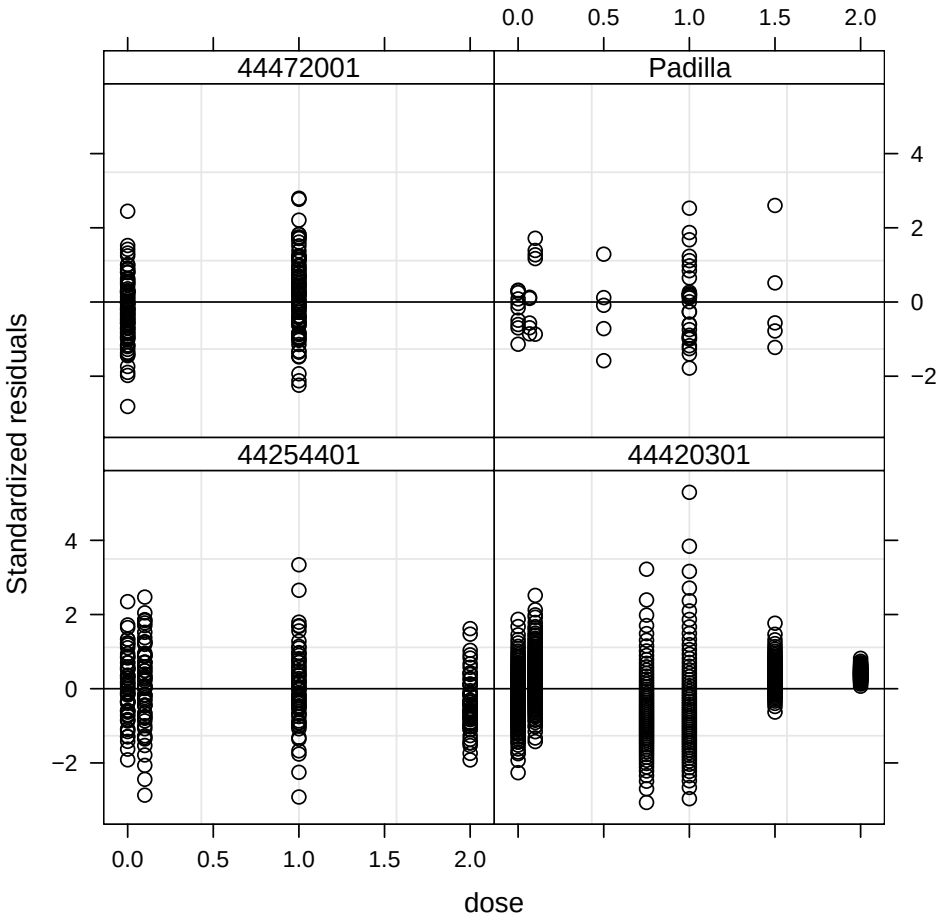

44472001 M
tmpstds
tmpstds
tmpstds
tmpstds
cheact
dose
0.0
0.2
0.4
0.6
0.8
1.0
0.7
0.8
0.9
1.0
1.1
1.2

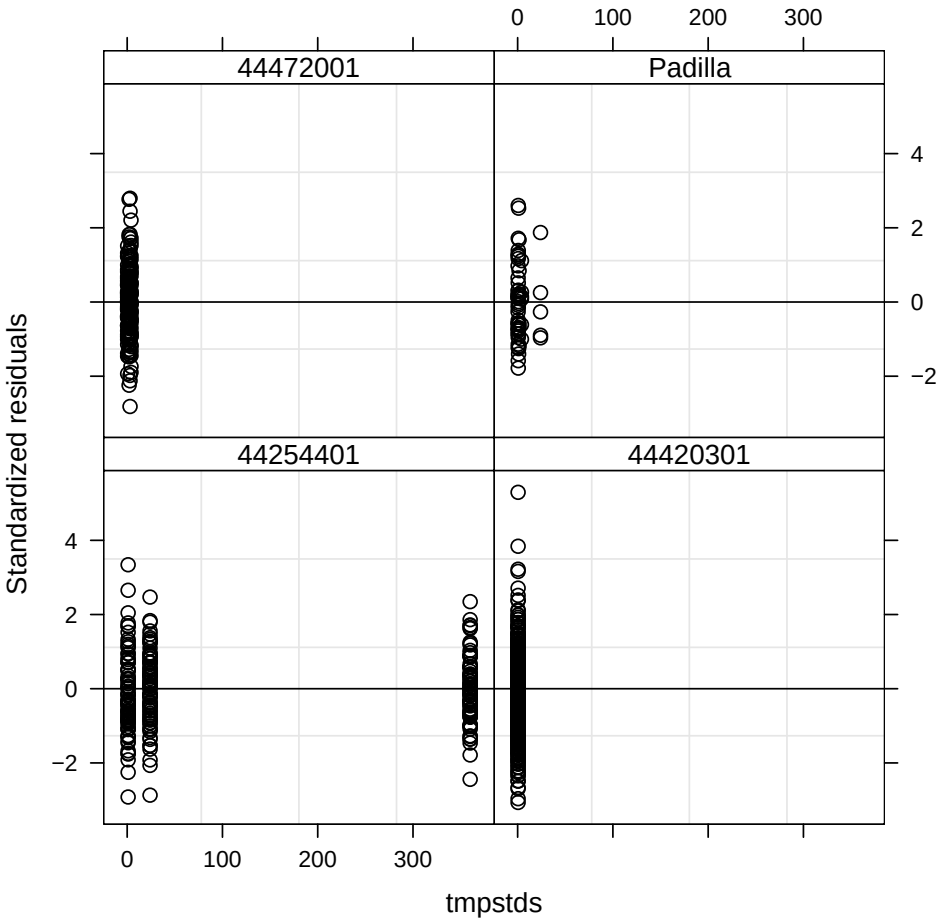

Padilla M
tmpstds
tmpstds
tmpstds
tmpstds
tmpstds
tmpstds
cheact
dose
0.0
0.5
1.0
1.5
0.6
0.8
1.0
1.2
1.4


44472001
Padilla
44254401
44420301
Standardized residuals
Fitted values
0.4
0.6
0.8
1.0
1.2
4
2
0
−2


44472001
Padilla
44254401
44420301
Pearson Residual
0.0
0.2
0.4
0.6
4
2
0
−2

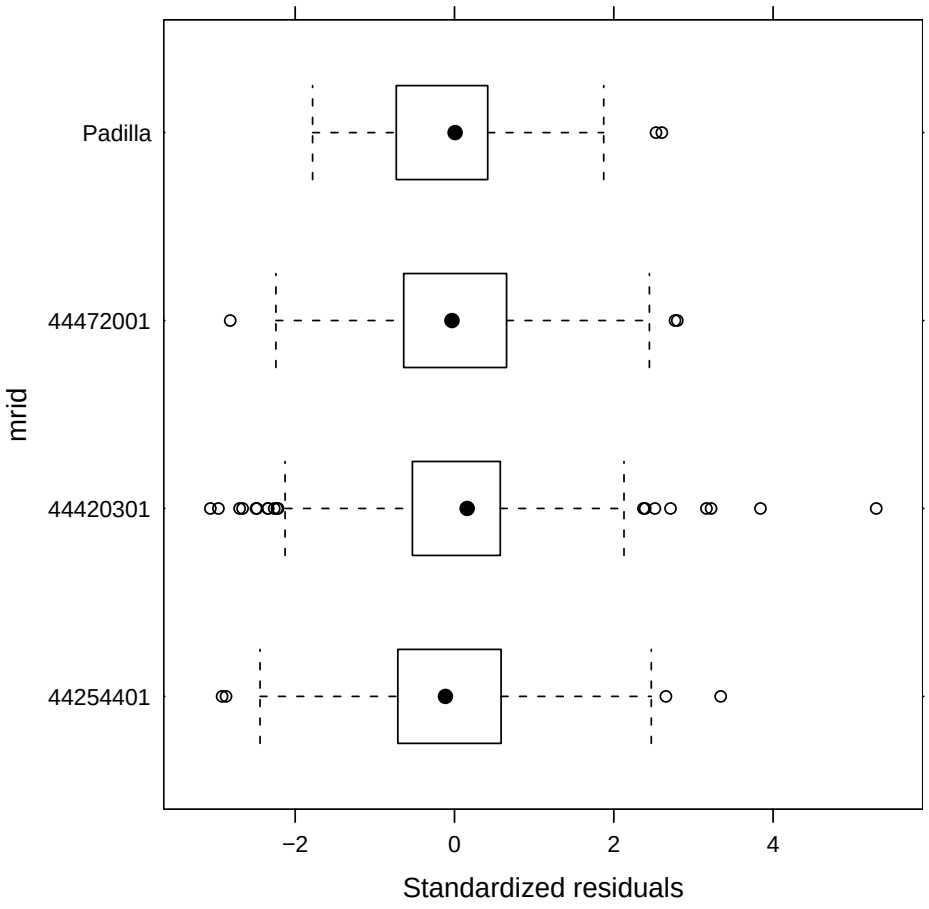

44472001
Padilla
44254401
44420301
cheact
Fitted values
0.4
0.6
0.8
1.0
1.2
0.5
1.0

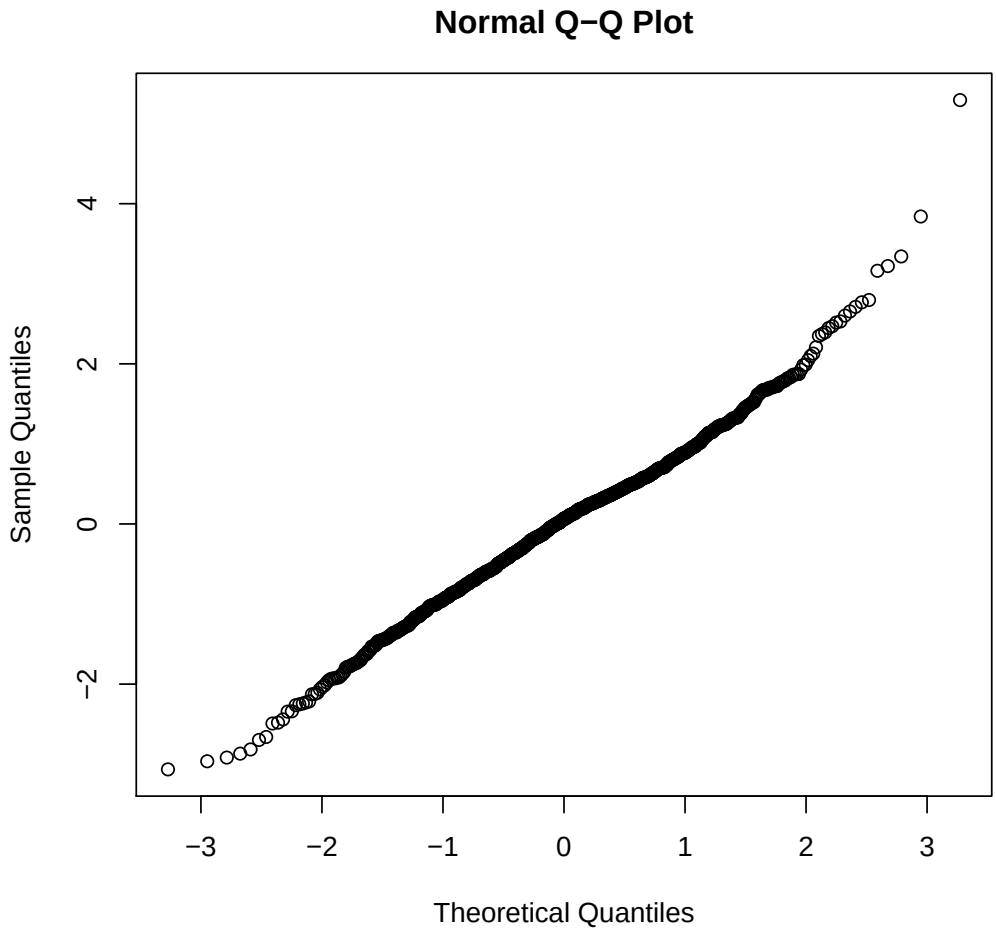

44472001
Padilla
44254401
44420301
Standardized residuals
dose
0.0
0.5
1.0
1.5
2.0
4
2
0
−2



Some more graphs:

Pearson residuals split by mrid and sex, and QQ plots for the Pearson residuals and random effects:


Padilla
44472001
44420301
44254401
mrid
−2
0
2
4
Standardized residuals



sectionSummary The critical estimates from this analysis are listed below. They are printed with greater than usual precision, in case they are to be used in further computation. For reporting, round to two or three significant digits. In these data, the BMD differs between sexes, and only a single value for recovery half life, pooled over doses and sexes, was estimated. BMD has units mg/kg, and times are in hours.

species RAT

mrid `[1] "44254401" "44420301" "44472001" "Padilla"`

Female `lD` **(standard error)** -1.93264434916771 (0.160927185098833)

Male `lD` **(standard error)** -1.68438367803855 (0.160114985263852)

Female BMD (95% CI) 0.144764882999124 (0.106026267971059, 0.197657351812765)

Female BMDL, the one-sided lower 95% CL 0.111479124254806

Male BMD (95% CI) 0.185558760660040 (0.136117611632972, 0.252958109127955)

Male BMDL, the one-sided lower 95% CL 0.143081824568725

`lTr (standard error)` -0.286020958649306 (0.0695006760582325)

Recovery Half-life (95% CI) 0.751246870662182 (0.656706753088121, 0.85939707186777)

Save everything:

```
> save.image(file = "RatBrainDR.RData")
```

Save the results for incorporating into a database:

```
> oxamyl.oral.brain <- list(mrid = levels(dta$mrid), species = "RAT",
+     BMDs = list(female = list(lD = tTab["lD.sexF", "Value"],
+         lD.se = tTab["lD.sexF", "Std.Error"], BMD = exp(Ints["lD.sexF",
+             "est."]), BMD.CI = exp(Ints["lD.sexF", c("lower",
+             "upper")]), BMDL = exp(Ints90["lD.sexF", "lower"])),
+         male = list(lD = tTab["lD.sexM", "Value"], lD.se = tTab["lD.sexM",
+             "Std.Error"], BMD = exp(Ints["lD.sexM", "est."]),
+             BMD.CI = exp(Ints["lD.sexM", c("lower", "upper")]),
+             BMDL = exp(Ints90["lD.sexM", "lower"]))), HalfLives = list(lTr = tTab["lTr",
+         "Value"], lTr.se = tTab["lTr", "Std.Error"], Tr = exp(Ints["lTr",
+         "est."]), Tr.CI = exp(Ints["lTr", c("lower", "upper")])))
> save(oxamyl.oral.brain, file = file.path("..", "..", "01Summaries",
+     "oxamyl.oral.brain.RData"))
```