Dose-Time Response Modeling of Rat Brain AChE Activity: Methomyl 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` and `PadillaData`. 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 only an acute study.

All the data used for this DR model are in `AggData` (4487501 and 44472001) and `PadillaData`. The activity data in `PadillaData` are about 500-fold greater than in the other two datasets, so rescale them to be more similar in magnitude. Now, set up the analysis dataset.

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

Summaries of this dataset:

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

dta$mrid: 44472001
       mrid         dose         cheact            sd               n
 44472001:16   Min.   :0.0   Min.   : 6.65   Min.   :0.3300   Min.   :10
 44487501: 0   1st Qu.:0.0   1st Qu.:11.14   1st Qu.:0.4400   1st Qu.:10
 Padilla : 0   Median :1.5   Median :11.89   Median :0.5300   Median :10
               Mean   :1.5   Mean   :11.15   Mean   :0.5619   Mean   :10
               3rd Qu.:3.0   3rd Qu.:12.10   3rd Qu.:0.6700   3rd Qu.:10
               Max.   :3.0   Max.   :12.46   Max.   :0.9200   Max.   :10
    tmonstdy    tmpstds      sex
 Min.   :1   Min.   :0.500   F:8
 1st Qu.:1   1st Qu.:1.625   M:8
 Median :1   Median :2.500
 Mean   :1   Mean   :2.375
 3rd Qu.:1   3rd Qu.:3.250
 Max.   :1   Max.   :4.000
------------------------------------------------------------
dta$mrid: 44487501
       mrid         dose          cheact             sd               n
 44472001: 0   Min.   :0.00   Min.   : 6.080   Min.   :0.3700   Min.   :10
 44487501:20   1st Qu.:0.25   1st Qu.: 9.815   1st Qu.:0.4400   1st Qu.:10
 Padilla : 0   Median :0.50   Median :11.870   Median :0.5950   Median :10
               Mean   :0.70   Mean   :10.840   Mean   :0.6500   Mean   :10
               3rd Qu.:0.75   3rd Qu.:12.110   3rd Qu.:0.7125   3rd Qu.:10
               Max.   :2.00   Max.   :12.440   Max.   :1.7500   Max.   :10
    tmonstdy      tmpstds      sex
 Min.   :1.0   Min.   : 0.50   F:10
 1st Qu.:1.0   1st Qu.: 0.50   M:10
 Median :1.5   Median :12.25
 Mean   :1.5   Mean   :12.25
 3rd Qu.:2.0   3rd Qu.:24.00
 Max.   :2.0   Max.   :24.00
------------------------------------------------------------
dta$mrid: Padilla
       mrid         dose           cheact             sd          n
 44472001: 0   Min.   :0.000   Min.   : 5.256   Min.   :0   Min.   :1
 44487501: 0   1st Qu.:0.175   1st Qu.: 9.217   1st Qu.:0   1st Qu.:1
 Padilla :59   Median :1.250   Median :11.200   Median :0   Median :1
```

```
                Mean   :1.619   Mean   :10.626   Mean   :0   Mean   :1
                3rd Qu.:3.000   3rd Qu.:12.604   3rd Qu.:0   3rd Qu.:1
                Max.   :3.000   Max.   :14.026   Max.   :0   Max.   :1
    tmonstdy    tmpstds        sex
 Min.   :1   Min.   : 0.5000   F: 0
 1st Qu.:1   1st Qu.: 0.6667   M:59
 Median :1   Median : 0.6667
 Mean   :1   Mean   : 3.0847
 3rd Qu.:1   3rd Qu.: 1.5000
 Max.   :1   Max.   :24.0000

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

dta$mrid: 44472001
    tmpstds
dose 0.5 2 3 4
   0 2   2 2 2
   3 2   2 2 2
------------------------------------------------------------
dta$mrid: 44487501
      tmpstds
dose   0.5 24
  0    2   2
  0.25 2   2
  0.5  2   2
  0.75 2   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
  0.1  0   5                 0 0   0 0
  0.25 0   5                 0 0   0 0
  0.6  0   5                 0 0   0 0
  1.25 0   5                 0 0   0 0
  2.5  0   5                 0 0   0 0
  3    5   0                 5 5   5 4
```

The study 44472001 has multiple time points (0.5 to 4 hr) at 0 and 3 mg/kg, and 44487501 has multiple doses at 0.5 and 24 hr.

There are multiple time points at only one dose, 3 mg/kg, so we can only estimate the recovery half-life at that dose level.

Padilla's data are from an acute study, with multiple doses at 2/3 hr, and multiple timepoints for 3 mg/kg.

There is a control for each time point in each study, so we need to set up a factor that captures those levels.

```
> dta$mridXftimeXsex <- with(dta, interaction(mrid, tmpstds, sex,
+     drop = TRUE, sep = ":"))
> dta$mridXsex <- with(dta, interaction(mrid, sex, 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 whether we can estimate `lg` and `tz` of the dose-response parameters.

2. Next, fit `tcmfn4()` using the parameterizations determined in the previous step. Since this has no repeated measures, but involves multiple datasets, initially use `gnls()` (modeling

   ```
   lD \~ mrid + sex - 1
   ```

3. Try fitting with other variance models the same model for fixed and random effects, using AIC to identify the best variance model. Once the best model for the error variance is found, refit using `nlme()`, allowing the random effect:

   ```
   lD ~ 1 | mrid
   ```

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$tmpstds > 0])
> initfile <- paste("initvals-brain-DR-1.RData", sep = "")
> if (!file.exists(initfile)) {
+     lA.start <- lm(I(log(cheact)) ~ mridXftimeXsex - 1, data = CleanUp(subset(dta,
+         dose %in% 0)))
+     Start <- c(coef(lA.start), rep(log(0.1), nlevels(dta$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 ~ mridXftimeXsex -
+         1, lD ~ mrid + sex - 1, tz ~ sex, lg ~ sex, lTr ~ 1),
+         start = Start, weights = varComb(varIdent(form = ~1 |
+             mridXsex), 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       34.38 11.70 8.34 4.92 4.77
mu               0.07  0.19 0.27 0.46 0.47
lD.mrid44472001  0.83  0.07 0.04 0.00 0.02
lD.mrid44487501  0.85  0.03 0.08 0.00 0.02
lD.mridPadilla   0.68  0.02 0.09 0.14 0.00
lD.sexM          0.76  0.19 0.03 0.00 0.00
tz.(Intercept)   0.73  0.08 0.14 0.01 0.01
tz.sexM          0.72  0.01 0.22 0.02 0.01
```

```
lg.(Intercept)   0.92  0.07 0.00 0.00 0.00
lg.sexM          0.84  0.13 0.01 0.01 0.00
lTr              0.00  0.00 0.00 0.27 0.35
```

Try fitting all the paramters in the above parameterization, first.

```
> Parm <- init1$start$beta
> Start <- Start0 <- Parm
> idta <- init1$data
> icnt <- 1
> Maxcnt <- 20
> repeat {
+     drmod1 <- try(gnls(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, tz = tz, lg = lg, lTr = lTr), data = idta, params = list(lA ~
+         mridXftimeXsex - 1, lD ~ mrid + sex - 1, tz ~ sex, lg ~
+         sex, lTr ~ 1), start = Start))
+     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
```

Try the same model for the mean, allowing the standard deviation to vary among mrid and sex:

```
> Parm <- coef(drmod1)
> Start <- Start0 <- Parm
> icnt <- 1
> Maxcnt <- 20
> repeat {
+     drmod2 <- try(gnls(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, tz = tz, lg = lg, lTr = lTr), data = idta, params = list(lA ~
+         mridXftimeXsex - 1, lD ~ mrid + sex - 1, tz ~ sex, lg ~
+         sex, lTr ~ 1), weights = varIdent(form = ~1 | mridXsex),
+         start = Start))
+     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
```

Finally, do we need to add a `varPower()` component to the error function?

```
> Parm <- coef(drmod1)
> Start <- Start0 <- Parm
> icnt <- 1
> Maxcnt <- 20
> repeat {
+     drmod3 <- try(gnls(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, tz = tz, lg = lg, lTr = lTr), data = idta, params = list(lA ~
+         mridXftimeXsex - 1, lD ~ mrid + sex - 1, tz ~ sex, lg ~
+         sex, lTr ~ 1), weights = varComb(varIdent(form = ~1 |
+         mridXsex), varPower(value = 1)), start = Start))
+     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 with `anova()`:

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

```
       Model df     AIC      BIC    logLik   Test  L.Ratio p-value
drmod1     1 28 928.323 1041.383 -436.1615
drmod2     2 32 923.910 1053.122 -429.9550 1 vs 2 12.41292  0.0145
drmod3     3 33 914.921 1048.171 -424.4605 2 vs 3 10.98907  0.0009
```

AIC and tests definitely prefer the last model.

Use this error model, and try to fit an mixed effects model:

```
> Parm <- coef(drmod3)
> Start0 <- c(getParms("^lA", Parm), mean(getParms("^lD\\.mrid",
+     Parm)), Parm["lD.sexM"], getParms("^tz", Parm), getParms("^lg",
+     Parm), Parm["lTr"])
> Start <- list(fixed = Start0, random = matrix(getParms("^lD\\.mrid",
+     Parm) - mean(getParms("^lD\\.mrid", Parm)), ncol = 1, dimnames = list(levels(idta$mrid),
+     NULL)))
> icnt <- 1
> Maxcnt <- 20
> repeat {
+     drmod4 <- try(nlme(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, tz = tz, lg = lg, lTr = lTr), data = idta, fixed = list(lA ~
+         mridXftimeXsex - 1, lD ~ sex, tz ~ sex, lg ~ sex, lTr ~
+         1), random = lD ~ 1 | mrid, weights = varComb(varIdent(form = ~1 |
+         mridXsex), varPower(value = 1)), start = Start))
```

```
+     if (!inherits(drmod4, "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 <- list(fixed = Start0 * (1 + rnorm(length(Start0),
+         sd = 0.2)), random = Start$random)
+ }

Successful in  1 try
```

Look at the relevant parameter values, standard errors, etc.:

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

                     Value  Std.Error  DF    t-value     p-value
lD.(Intercept) -0.68311746 0.27399768 392 -2.4931505 0.013073161
lD.sexM        -0.06294029 0.21361473 392 -0.2946440 0.768421854
tz.(Intercept)  0.24765954 0.18603800 392  1.3312309 0.183886718
tz.sexM        -0.06364338 0.25585787 392 -0.2487451 0.803688262
lg.(Intercept)  0.42527500 0.19016864 392  2.2363046 0.025893780
lg.sexM        -0.02402499 0.23984735 392 -0.1001678 0.920262295
lTr            -0.21328723 0.07447676 392 -2.8638093 0.004410781
```

Note that none of the gender differences is individually significant. Test for joint non-significance, to see if we can simplify the model:

```
> L <- diag(3)
> colnames(L) <- c("lD.sexM", "tz.sexM", "lg.sexM")
> anova(drmod4, L = L)

F-test for linear combination(s)
  lD.sexM tz.sexM lg.sexM
1       1       0       0
2       0       1       0
3       0       0       1
  numDF denDF   F-value p-value
1     3   392 0.1595313  0.9235
```

Yes, we can. Fit the new, simpler model:

```
> Parm <- fixed.effects(drmod4)
> Start0 <- c(getParms("^lA", Parm), Parm["lD.(Intercept)"], Parm["tz.(Intercept)"],
+     Parm["lg.(Intercept)"], Parm["lTr"])
> Start <- list(fixed = Start0, random = data.matrix(random.effects(drmod4)))
> icnt <- 1
> Maxcnt <- 20
> repeat {
+     drmod5 <- try(nlme(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, tz = tz, lg = lg, lTr = lTr), data = idta, fixed = list(lA ~
```

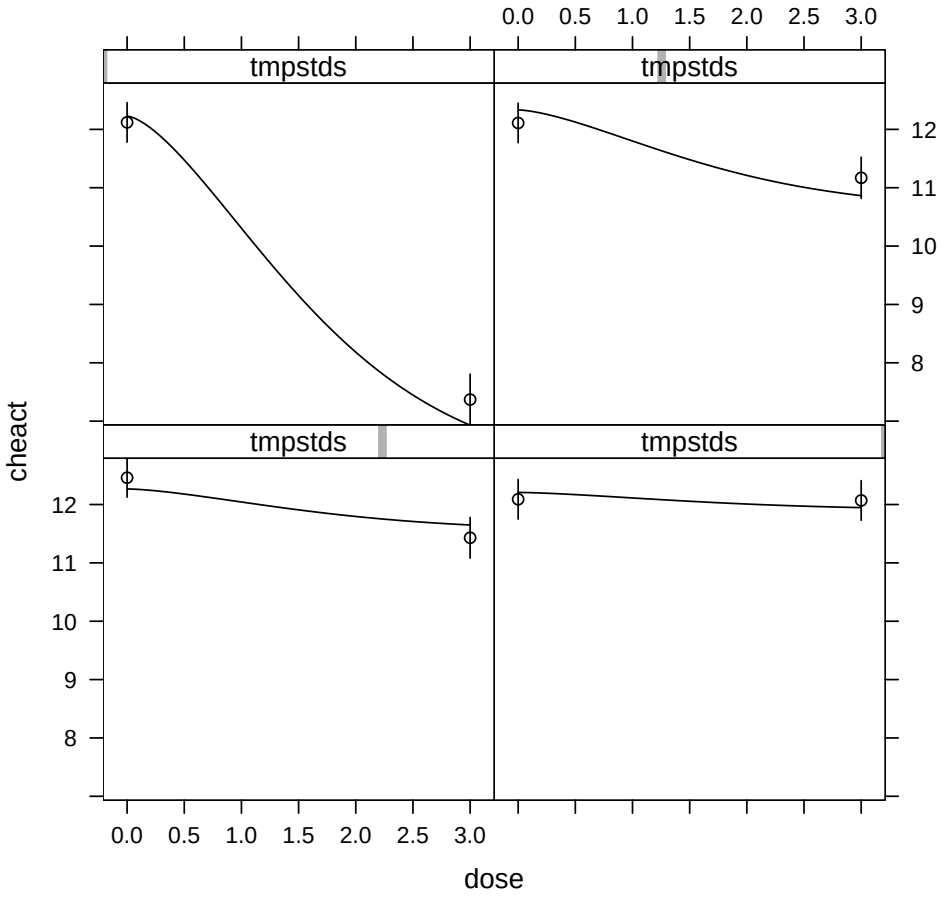
```
+         mridXftimeXsex - 1, lD ~ 1, tz ~ 1, lg ~ 1, lTr ~ 1),
+         random = lD ~ 1 | mrid, weights = varComb(varIdent(form = ~1 |
+             mridXsex), varPower(value = 1)), start = Start),
+         silent = TRUE)
+     if (!inherits(drmod5, "try-error") || icnt > Maxcnt) {
+         if (icnt <= Maxcnt)
+             writeLines(paste("Successful in ", icnt, if (icnt >
+                 1)
+                 "tries"
+             else "try"))
+         else writeLines("Maxcnt exceeded")
+         break
+     }
+     icnt <- icnt + 1
+     Start <- list(fixed = Start0 * (1 + rnorm(length(Start0),
+         sd = 0.2)), random = Start$random)
+ }

Successful in  1 try
```

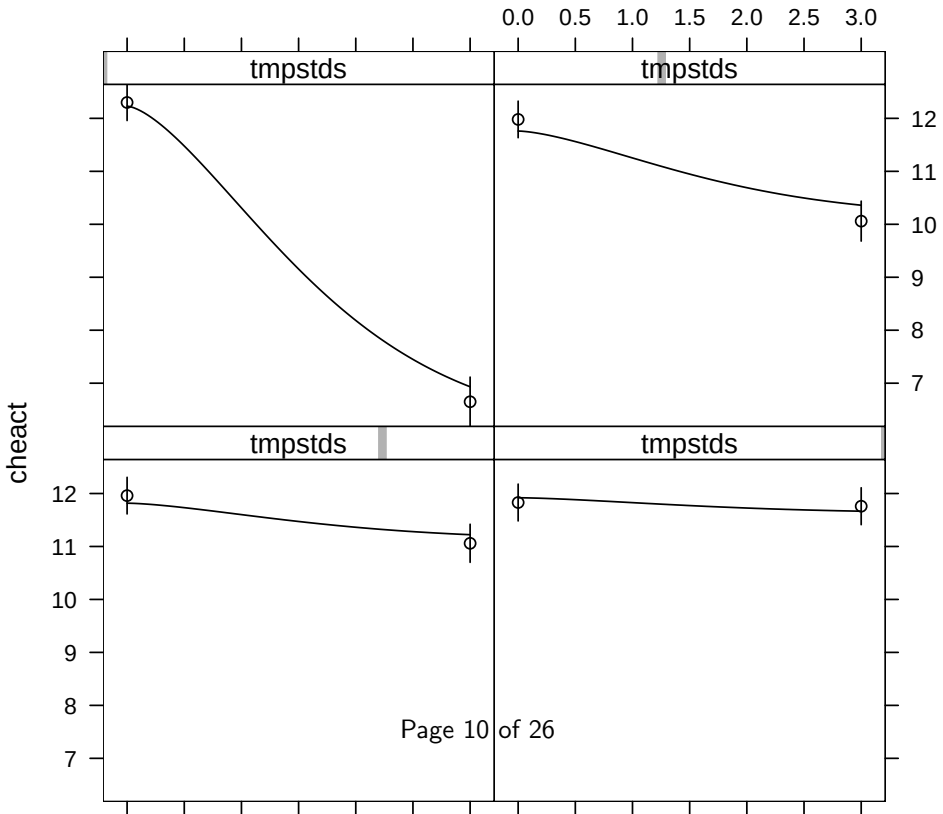
Diagnostic graphics for the model contained in drmod5: Plots of data with 95% CI and fitted curve for each combination of mrid and sex. First set up the data set and predicted values for plotting.

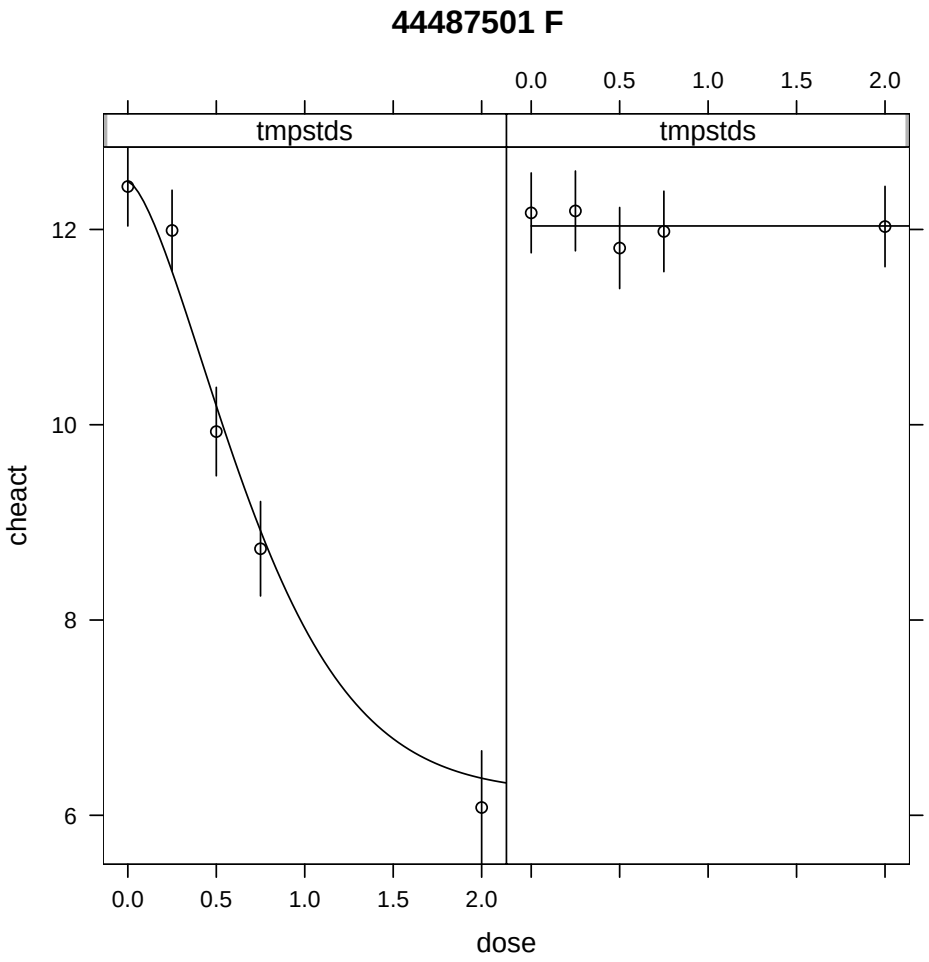
```
> tdta <- local({
+     idta$mridXsexXtmpstdsXdose <- with(idta, interaction(mrid,
+         sex, tmpstds, dose, sep = ":", drop = TRUE))
+     out <- gls(cheact ~ mridXsexXtmpstdsXdose - 1, data = idta,
+         weights = varComb(varIdent(form = ~1 | mridXsex), varPower()))
+     Ints <- intervals(out, which = "coef")$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$dose), length = 101),
+     mridXftimeXsex = levels(idta$mridXftimeXsex))
> nms <- as.character(ndta$mridXftimeXsex)
> sstr <- strsplit(nms, ":")
> ndta$mrid <- factor(sapply(sstr, function(x) x[1]))
> ndta$sex <- factor(sapply(sstr, function(x) x[3]))
> ndta$tmpstds <- as.numeric(sapply(sstr, function(x) x[2]))
> tmp <- drmod5
> tmp$contrasts <- NULL
> ndta$pred <- predict(tmp, newdata = ndta)
```

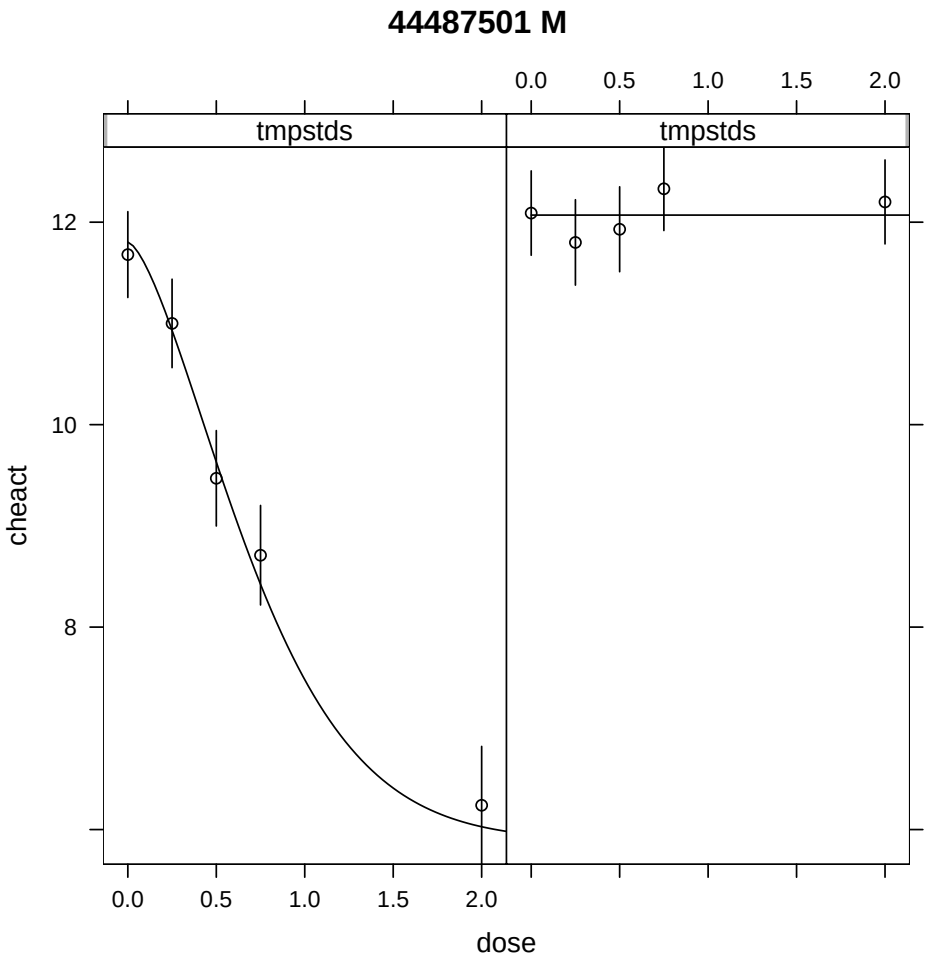
44472001 F

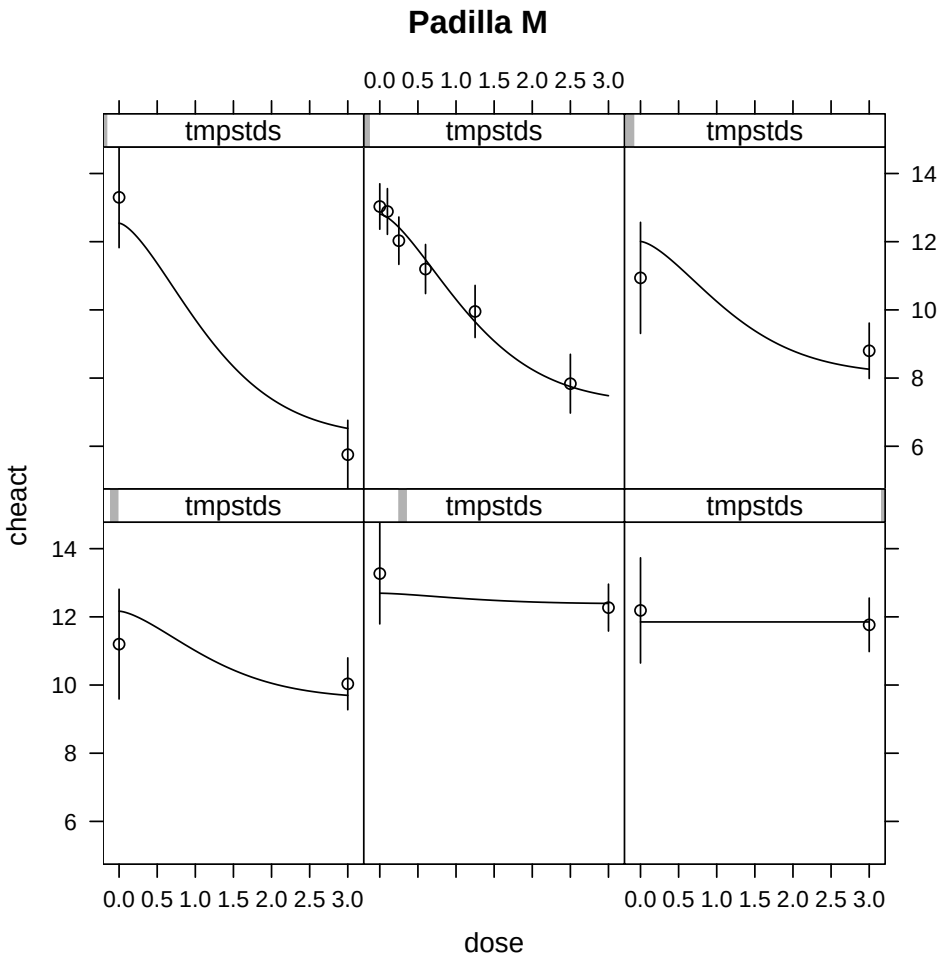


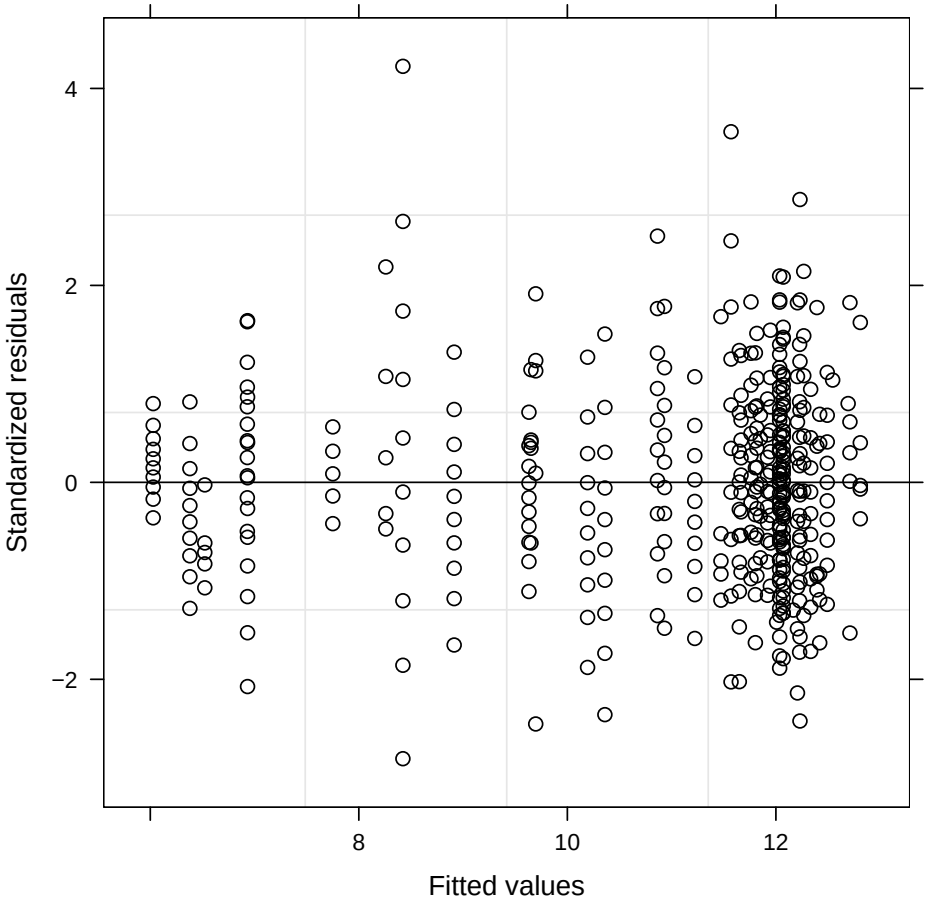
44472001 M

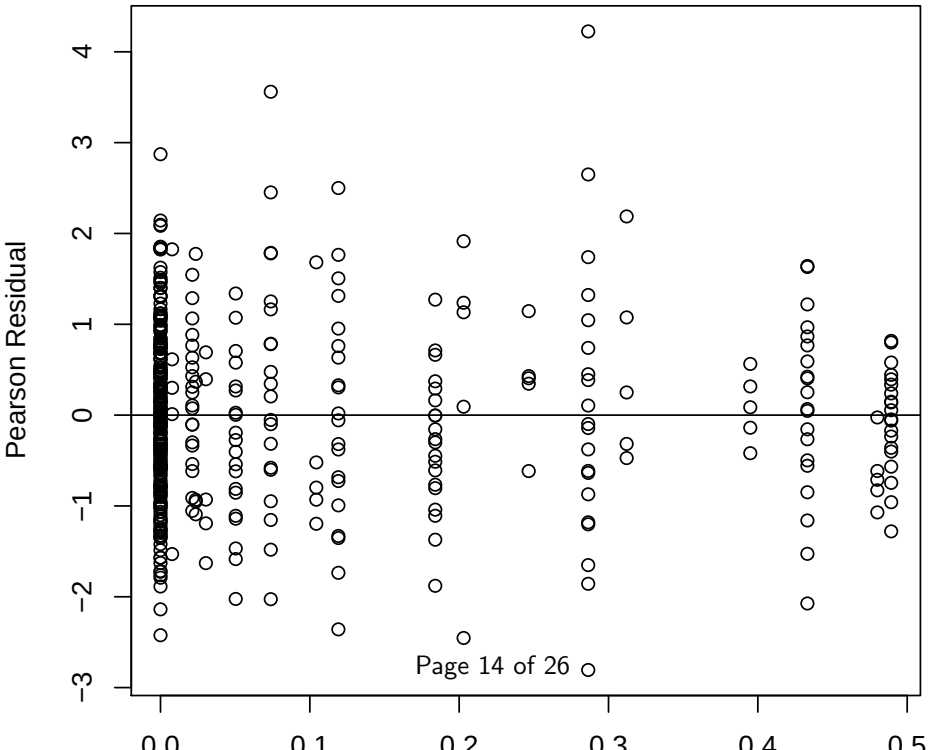


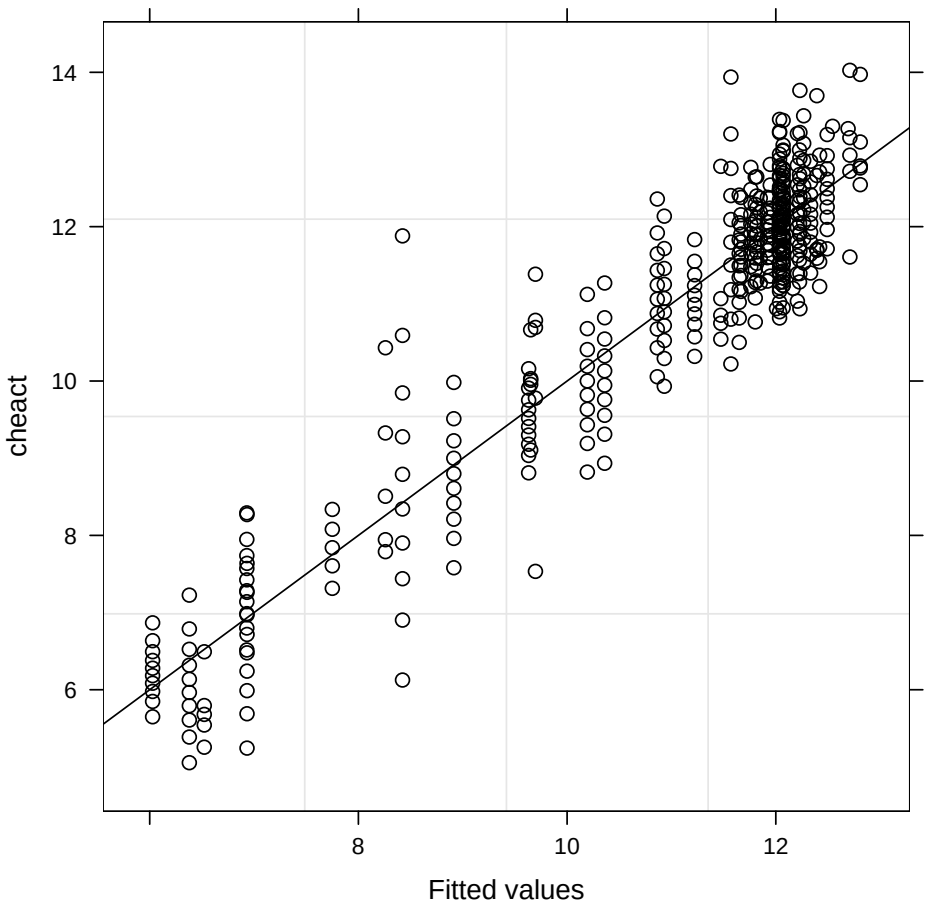

44487501 F
tmpstds
tmpstds
cheact
dose
12
10
8
6
0.0
0.5
1.0
1.5
2.0

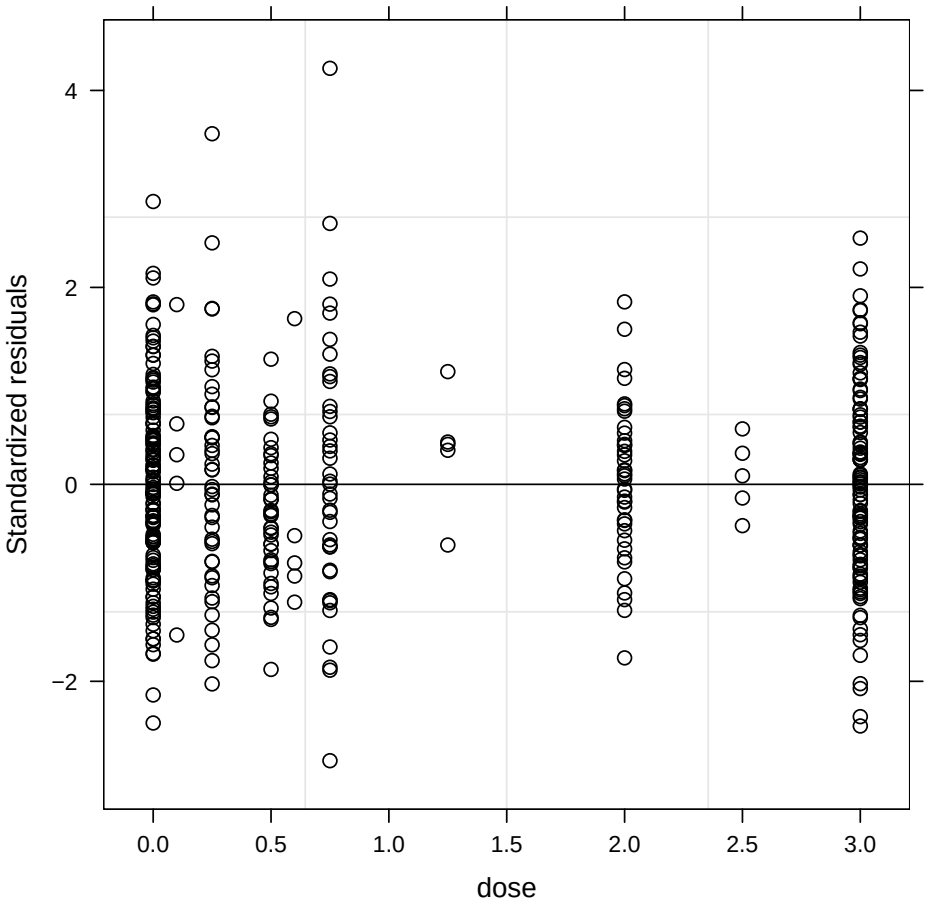

44487501 M
tmpstds
tmpstds
0.0
0.5
1.0
1.5
2.0
12
10
8
cheact
dose

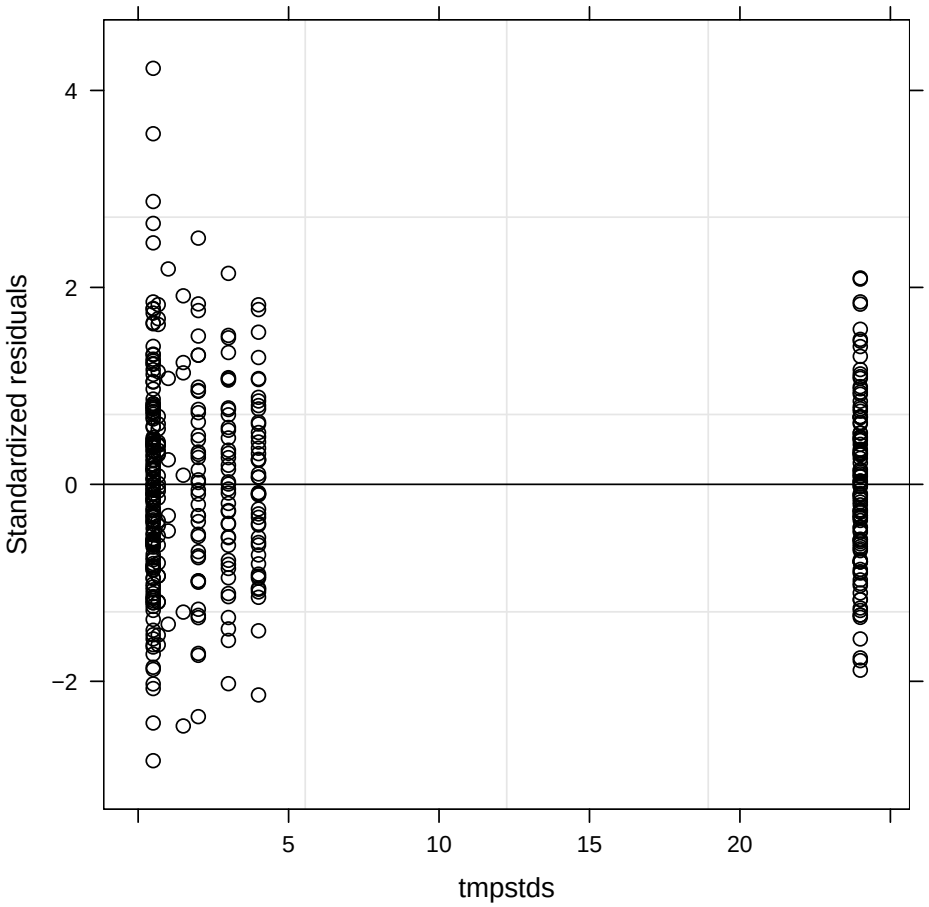

Padilla M
tmpstds
tmpstds
tmpstds
tmpstds
tmpstds
tmpstds
cheact
dose
0.0 0.5 1.0 1.5 2.0 2.5 3.0
6
8
10
12
14

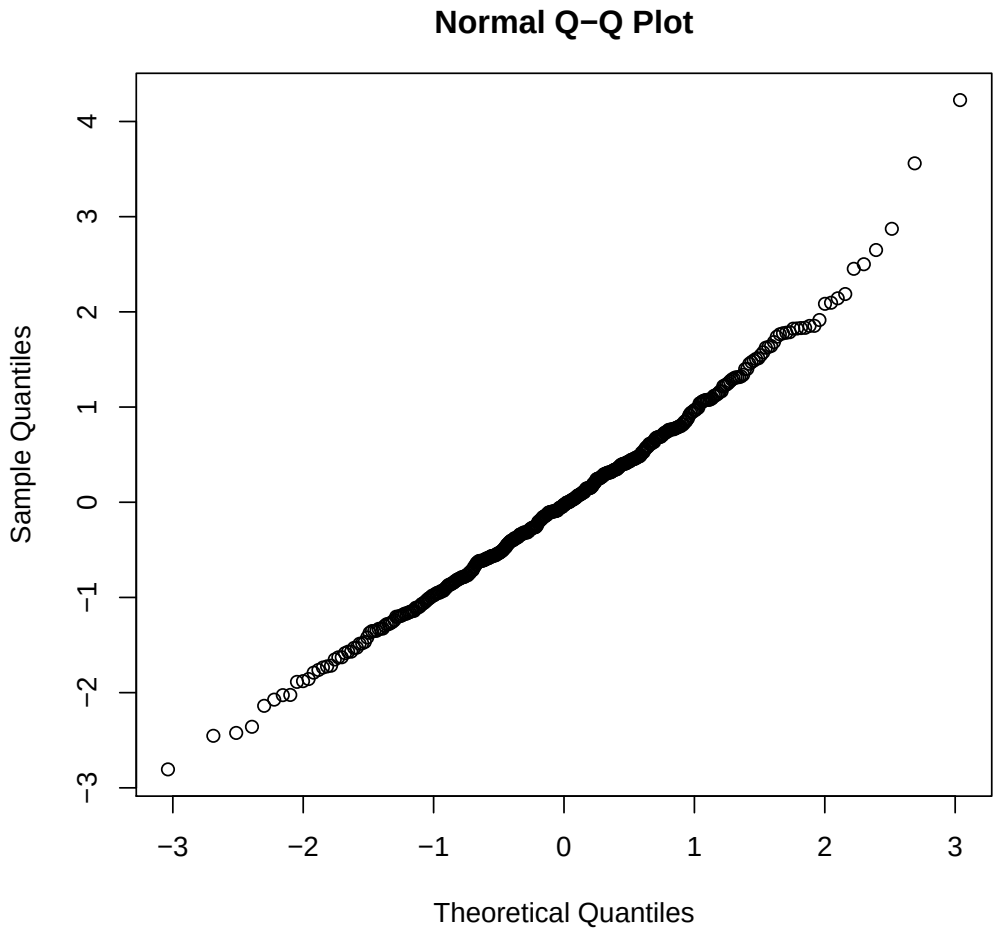

Standardized residuals
Fitted values
4
2
0
−2
8
10
12


Pearson Residual
4
3
2
1
0
−1
−2
−3
0.0
0.1
0.2
0.3
0.4
0.5


14
12
10
8
6
cheact
8
10
12
Fitted values


Standardized residuals
4
2
0
−2
0.0
0.5
1.0
1.5
2.0
2.5
3.0
dose


Standardized residuals
4
2
0
−2
5
10
15
20
tmpstds



Details of this final model fit:

```
> tTab <- summary(drmod5)$tTable
> Ints <- intervals(drmod5, which = "fixed")$fixed
> Ints90 <- intervals(drmod5, which = "fixed", level = 0.9)$fixed
> summary(drmod5)
```

```
Nonlinear mixed-effects model fit by maximum likelihood
  Model: cheact ~ tcmfn4(dose, tmpstds, lA = lA, lD = lD, tz = tz, lg = lg,      lTr = lTr)
 Data: idta
       AIC      BIC    logLik
  921.5666 1038.665 -431.7833

Random effects:
 Formula: lD ~ 1 | mrid
               lD Residual
StdDev: 0.3459616 3.430972

Combination of variance functions:
 Structure: Different standard deviations per stratum
 Formula: ~1 | mridXsex
 Parameter estimates:
44472001:M 44472001:F 44487501:M 44487501:F  Padilla:M
```

```
  1.000000   1.024296   1.161377   1.195078   1.388550
 Structure: Power of variance covariate
 Formula: ~fitted(.)
 Parameter estimates:
     power
-0.7427421
Fixed effects: list(lA ~ mridXftimeXsex - 1, lD ~ 1, tz ~ 1, lg ~ 1, lTr ~ 1)
                                                 Value  Std.Error  DF  t-value
lA.mridXftimeXsex44487501:0.5:M               2.4683653 0.01397865 395 176.5811
lA.mridXftimeXsex44487501:24:M                2.4907230 0.00754190 395 330.2516
lA.mridXftimeXsex44487501:0.5:F               2.5250995 0.01342616 395 188.0731
lA.mridXftimeXsex44487501:24:F                2.4879022 0.00779899 395 319.0031
lA.mridXftimeXsex44472001:0.5:M               2.5039646 0.01374311 395 182.1978
lA.mridXftimeXsex44472001:2:M                 2.4647710 0.01282067 395 192.2498
lA.mridXftimeXsex44472001:3:M                 2.4695640 0.01172352 395 210.6504
lA.mridXftimeXsex44472001:4:M                 2.4781744 0.01092788 395 226.7754
lA.mridXftimeXsex44472001:0.5:F               2.5036765 0.01406270 395 178.0366
lA.mridXftimeXsex44472001:2:F                 2.5123067 0.01219718 395 205.9743
lA.mridXftimeXsex44472001:3:F                 2.5069158 0.01129968 395 221.8573
lA.mridXftimeXsex44472001:4:F                 2.5019932 0.01074650 395 232.8193
lA.mridXftimeXsexPadilla:0.666666666666667:M  2.5501701 0.01634656 395 156.0065
lA.mridXftimeXsexPadilla:0.5:M                2.5292675 0.04992196 395  50.6644
lA.mridXftimeXsexPadilla:1:M                  2.4854749 0.04361841 395  56.9822
lA.mridXftimeXsexPadilla:1.5:M                2.4986428 0.03692145 395  67.6746
lA.mridXftimeXsexPadilla:4:M                  2.5410374 0.02507381 395 101.3423
lA.mridXftimeXsexPadilla:24:M                 2.4723852 0.02944069 395  83.9785
lD                                           -0.7204569 0.24006798 395  -3.0011
tz                                            0.2194194 0.12414890 395   1.7674
lg                                            0.4194159 0.12860190 395   3.2614
lTr                                          -0.2165573 0.07464935 395  -2.9010
                                             p-value
lA.mridXftimeXsex44487501:0.5:M               0.0000
lA.mridXftimeXsex44487501:24:M                0.0000
lA.mridXftimeXsex44487501:0.5:F               0.0000
lA.mridXftimeXsex44487501:24:F                0.0000
lA.mridXftimeXsex44472001:0.5:M               0.0000
lA.mridXftimeXsex44472001:2:M                 0.0000
lA.mridXftimeXsex44472001:3:M                 0.0000
lA.mridXftimeXsex44472001:4:M                 0.0000
lA.mridXftimeXsex44472001:0.5:F               0.0000
lA.mridXftimeXsex44472001:2:F                 0.0000
lA.mridXftimeXsex44472001:3:F                 0.0000
lA.mridXftimeXsex44472001:4:F                 0.0000
lA.mridXftimeXsexPadilla:0.666666666666667:M  0.0000
lA.mridXftimeXsexPadilla:0.5:M                0.0000
lA.mridXftimeXsexPadilla:1:M                  0.0000
lA.mridXftimeXsexPadilla:1.5:M                0.0000
lA.mridXftimeXsexPadilla:4:M                  0.0000
lA.mridXftimeXsexPadilla:24:M                 0.0000
lD                                            0.0029
tz                                            0.0779
lg                                            0.0012
lTr                                           0.0039
 Correlation:
```

	lA.XX44487501:0.5:M
lA.mridXftimeXsex44487501:24:M	0.000
lA.mridXftimeXsex44487501:0.5:F	0.426
lA.mridXftimeXsex44487501:24:F	0.000
lA.mridXftimeXsex44472001:0.5:M	0.000
lA.mridXftimeXsex44472001:2:M	0.000
lA.mridXftimeXsex44472001:3:M	0.000
lA.mridXftimeXsex44472001:4:M	0.000
lA.mridXftimeXsex44472001:0.5:F	0.000
lA.mridXftimeXsex44472001:2:F	0.000
lA.mridXftimeXsex44472001:3:F	0.000
lA.mridXftimeXsex44472001:4:F	0.000
lA.mridXftimeXsexPadilla:0.666666666666667:M	0.107
lA.mridXftimeXsexPadilla:0.5:M	0.021
lA.mridXftimeXsexPadilla:1:M	0.020
lA.mridXftimeXsexPadilla:1.5:M	0.016
lA.mridXftimeXsexPadilla:4:M	0.003
lA.mridXftimeXsexPadilla:24:M	0.000
lD	-0.204
tz	-0.285
lg	-0.377
lTr	0.000

	lA.XX44487501:24:M
lA.mridXftimeXsex44487501:24:M	
lA.mridXftimeXsex44487501:0.5:F	0.000
lA.mridXftimeXsex44487501:24:F	0.000
lA.mridXftimeXsex44472001:0.5:M	0.000
lA.mridXftimeXsex44472001:2:M	0.000
lA.mridXftimeXsex44472001:3:M	0.000
lA.mridXftimeXsex44472001:4:M	0.000
lA.mridXftimeXsex44472001:0.5:F	0.000
lA.mridXftimeXsex44472001:2:F	0.000
lA.mridXftimeXsex44472001:3:F	0.000
lA.mridXftimeXsex44472001:4:F	0.000
lA.mridXftimeXsexPadilla:0.666666666666667:M	0.000
lA.mridXftimeXsexPadilla:0.5:M	0.000
lA.mridXftimeXsexPadilla:1:M	0.000
lA.mridXftimeXsexPadilla:1.5:M	0.000
lA.mridXftimeXsexPadilla:4:M	0.000
lA.mridXftimeXsexPadilla:24:M	0.000
lD	0.000
tz	0.000
lg	0.000
lTr	0.000

	lA.XX44487501:0.5:F
lA.mridXftimeXsex44487501:24:M	
lA.mridXftimeXsex44487501:0.5:F	
lA.mridXftimeXsex44487501:24:F	0.000
lA.mridXftimeXsex44472001:0.5:M	0.000
lA.mridXftimeXsex44472001:2:M	0.000
lA.mridXftimeXsex44472001:3:M	0.000
lA.mridXftimeXsex44472001:4:M	0.000
lA.mridXftimeXsex44472001:0.5:F	0.000
lA.mridXftimeXsex44472001:2:F	0.000

```
lA.mridXftimeXsex44472001:3:F                 0.000
lA.mridXftimeXsex44472001:4:F                 0.000
lA.mridXftimeXsexPadilla:0.666666666666667:M  0.112
lA.mridXftimeXsexPadilla:0.5:M                0.021
lA.mridXftimeXsexPadilla:1:M                  0.021
lA.mridXftimeXsexPadilla:1.5:M                0.016
lA.mridXftimeXsexPadilla:4:M                  0.003
lA.mridXftimeXsexPadilla:24:M                 0.000
lD                                           -0.213
tz                                           -0.297
lg                                           -0.393
lTr                                           0.000
                                             lA.XX44487501:24:F
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0.5:F
lA.mridXftimeXsex44487501:24:F
lA.mridXftimeXsex44472001:0.5:M               0.000
lA.mridXftimeXsex44472001:2:M                 0.000
lA.mridXftimeXsex44472001:3:M                 0.000
lA.mridXftimeXsex44472001:4:M                 0.000
lA.mridXftimeXsex44472001:0.5:F               0.000
lA.mridXftimeXsex44472001:2:F                 0.000
lA.mridXftimeXsex44472001:3:F                 0.000
lA.mridXftimeXsex44472001:4:F                 0.000
lA.mridXftimeXsexPadilla:0.666666666666667:M  0.000
lA.mridXftimeXsexPadilla:0.5:M                0.000
lA.mridXftimeXsexPadilla:1:M                  0.000
lA.mridXftimeXsexPadilla:1.5:M                0.000
lA.mridXftimeXsexPadilla:4:M                  0.000
lA.mridXftimeXsexPadilla:24:M                 0.000
lD                                            0.000
tz                                            0.000
lg                                            0.000
lTr                                           0.000
                                             lA.XX44472001:0.5:M
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0.5:F
lA.mridXftimeXsex44487501:24:F
lA.mridXftimeXsex44472001:0.5:M
lA.mridXftimeXsex44472001:2:M                 0.009
lA.mridXftimeXsex44472001:3:M                -0.006
lA.mridXftimeXsex44472001:4:M                -0.007
lA.mridXftimeXsex44472001:0.5:F               0.062
lA.mridXftimeXsex44472001:2:F                 0.009
lA.mridXftimeXsex44472001:3:F                -0.006
lA.mridXftimeXsex44472001:4:F                -0.007
lA.mridXftimeXsexPadilla:0.666666666666667:M  0.003
lA.mridXftimeXsexPadilla:0.5:M                0.004
lA.mridXftimeXsexPadilla:1:M                 -0.011
lA.mridXftimeXsexPadilla:1.5:M               -0.020
lA.mridXftimeXsexPadilla:4:M                 -0.013
lA.mridXftimeXsexPadilla:24:M                 0.000
lD                                           -0.027
tz                                           -0.003
```

```
lg                                          0.005
lTr                                        -0.075
                                           lA.XX44472001:2:M
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0.5:F
lA.mridXftimeXsex44487501:24:F
lA.mridXftimeXsex44472001:0.5:M
lA.mridXftimeXsex44472001:2:M
lA.mridXftimeXsex44472001:3:M               0.119
lA.mridXftimeXsex44472001:4:M               0.077
lA.mridXftimeXsex44472001:0.5:F             0.009
lA.mridXftimeXsex44472001:2:F               0.153
lA.mridXftimeXsex44472001:3:F               0.123
lA.mridXftimeXsex44472001:4:F               0.078
lA.mridXftimeXsexPadilla:0.666666666666667:M -0.005
lA.mridXftimeXsexPadilla:0.5:M             -0.011
lA.mridXftimeXsexPadilla:1:M                0.057
lA.mridXftimeXsexPadilla:1.5:M              0.100
lA.mridXftimeXsexPadilla:4:M                0.061
lA.mridXftimeXsexPadilla:24:M               0.000
lD                                          0.000
tz                                          0.013
lg                                         -0.003
lTr                                         0.352
                                           lA.XX44472001:3:M
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0.5:F
lA.mridXftimeXsex44487501:24:F
lA.mridXftimeXsex44472001:0.5:M
lA.mridXftimeXsex44472001:2:M
lA.mridXftimeXsex44472001:3:M
lA.mridXftimeXsex44472001:4:M               0.066
lA.mridXftimeXsex44472001:0.5:F            -0.005
lA.mridXftimeXsex44472001:2:F               0.125
lA.mridXftimeXsex44472001:3:F               0.104
lA.mridXftimeXsex44472001:4:F               0.067
lA.mridXftimeXsexPadilla:0.666666666666667:M -0.004
lA.mridXftimeXsexPadilla:0.5:M             -0.010
lA.mridXftimeXsexPadilla:1:M                0.050
lA.mridXftimeXsexPadilla:1.5:M              0.087
lA.mridXftimeXsexPadilla:4:M                0.054
lA.mridXftimeXsexPadilla:24:M               0.000
lD                                          0.006
tz                                          0.011
lg                                         -0.004
lTr                                         0.308
                                           lA.XX44472001:4:M
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0.5:F
lA.mridXftimeXsex44487501:24:F
lA.mridXftimeXsex44472001:0.5:M
lA.mridXftimeXsex44472001:2:M
lA.mridXftimeXsex44472001:3:M
lA.mridXftimeXsex44472001:4:M
```

```
lA.mridXftimeXsex44472001:0.5:F              -0.007
lA.mridXftimeXsex44472001:2:F                 0.081
lA.mridXftimeXsex44472001:3:F                 0.068
lA.mridXftimeXsex44472001:4:F                 0.044
lA.mridXftimeXsexPadilla:0.666666666666667:M -0.003
lA.mridXftimeXsexPadilla:0.5:M               -0.007
lA.mridXftimeXsexPadilla:1:M                  0.033
lA.mridXftimeXsexPadilla:1.5:M                0.058
lA.mridXftimeXsexPadilla:4:M                  0.036
lA.mridXftimeXsexPadilla:24:M                 0.000
lD                                            0.005
tz                                            0.007
lg                                           -0.003
lTr                                           0.205
                                             lA.XX44472001:0.5:F
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0.5:F
lA.mridXftimeXsex44487501:24:F
lA.mridXftimeXsex44472001:0.5:M
lA.mridXftimeXsex44472001:2:M
lA.mridXftimeXsex44472001:3:M
lA.mridXftimeXsex44472001:4:M
lA.mridXftimeXsex44472001:0.5:F
lA.mridXftimeXsex44472001:2:F                 0.009
lA.mridXftimeXsex44472001:3:F                -0.006
lA.mridXftimeXsex44472001:4:F                -0.007
lA.mridXftimeXsexPadilla:0.666666666666667:M  0.003
lA.mridXftimeXsexPadilla:0.5:M                0.004
lA.mridXftimeXsexPadilla:1:M                 -0.011
lA.mridXftimeXsexPadilla:1.5:M               -0.020
lA.mridXftimeXsexPadilla:4:M                 -0.013
lA.mridXftimeXsexPadilla:24:M                 0.000
lD                                           -0.026
tz                                           -0.003
lg                                            0.005
lTr                                          -0.074
                                             lA.XX44472001:2:F
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0.5:F
lA.mridXftimeXsex44487501:24:F
lA.mridXftimeXsex44472001:0.5:M
lA.mridXftimeXsex44472001:2:M
lA.mridXftimeXsex44472001:3:M
lA.mridXftimeXsex44472001:4:M
lA.mridXftimeXsex44472001:0.5:F
lA.mridXftimeXsex44472001:2:F
lA.mridXftimeXsex44472001:3:F                 0.130
lA.mridXftimeXsex44472001:4:F                 0.082
lA.mridXftimeXsexPadilla:0.666666666666667:M -0.005
lA.mridXftimeXsexPadilla:0.5:M               -0.011
lA.mridXftimeXsexPadilla:1:M                  0.060
lA.mridXftimeXsexPadilla:1.5:M                0.105
lA.mridXftimeXsexPadilla:4:M                  0.064
lA.mridXftimeXsexPadilla:24:M                 0.000
```

```
lD                                          0.000
tz                                          0.013
lg                                         -0.003
lTr                                         0.370
                                           lA.XX44472001:3:F
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0.5:F
lA.mridXftimeXsex44487501:24:F
lA.mridXftimeXsex44472001:0.5:M
lA.mridXftimeXsex44472001:2:M
lA.mridXftimeXsex44472001:3:M
lA.mridXftimeXsex44472001:4:M
lA.mridXftimeXsex44472001:0.5:F
lA.mridXftimeXsex44472001:2:F
lA.mridXftimeXsex44472001:3:F
lA.mridXftimeXsex44472001:4:F               0.069
lA.mridXftimeXsexPadilla:0.666666666666667:M -0.005
lA.mridXftimeXsexPadilla:0.5:M             -0.010
lA.mridXftimeXsexPadilla:1:M                0.052
lA.mridXftimeXsexPadilla:1.5:M              0.090
lA.mridXftimeXsexPadilla:4:M                0.056
lA.mridXftimeXsexPadilla:24:M               0.000
lD                                          0.006
tz                                          0.011
lg                                         -0.004
lTr                                         0.319
                                           lA.XX44472001:4:F lA.XXP:0.6
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0.5:F
lA.mridXftimeXsex44487501:24:F
lA.mridXftimeXsex44472001:0.5:M
lA.mridXftimeXsex44472001:2:M
lA.mridXftimeXsex44472001:3:M
lA.mridXftimeXsex44472001:4:M
lA.mridXftimeXsex44472001:0.5:F
lA.mridXftimeXsex44472001:2:F
lA.mridXftimeXsex44472001:3:F
lA.mridXftimeXsex44472001:4:F
lA.mridXftimeXsexPadilla:0.666666666666667:M -0.003
lA.mridXftimeXsexPadilla:0.5:M             -0.007             0.079
lA.mridXftimeXsexPadilla:1:M                0.034             0.072
lA.mridXftimeXsexPadilla:1.5:M              0.059             0.055
lA.mridXftimeXsexPadilla:4:M                0.036             0.007
lA.mridXftimeXsexPadilla:24:M               0.000             0.000
lD                                          0.005            -0.233
tz                                          0.007            -0.121
lg                                         -0.003            -0.283
lTr                                         0.208            -0.016
                                           lA.XXP:0.5 lA.XXP:1: lA.XXP:1.
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0.5:F
lA.mridXftimeXsex44487501:24:F
lA.mridXftimeXsex44472001:0.5:M
lA.mridXftimeXsex44472001:2:M
```

```
lA.mridXftimeXsex44472001:3:M
lA.mridXftimeXsex44472001:4:M
lA.mridXftimeXsex44472001:0.5:F
lA.mridXftimeXsex44472001:2:F
lA.mridXftimeXsex44472001:3:F
lA.mridXftimeXsex44472001:4:F
lA.mridXftimeXsexPadilla:0.666666666666667:M
lA.mridXftimeXsexPadilla:0.5:M
lA.mridXftimeXsexPadilla:1:M                  0.048
lA.mridXftimeXsexPadilla:1.5:M                0.033      0.086
lA.mridXftimeXsexPadilla:4:M                  0.001      0.035     0.054
lA.mridXftimeXsexPadilla:24:M                 0.000      0.000     0.000
lD                                           -0.015     -0.007     0.001
tz                                           -0.152     -0.139    -0.105
lg                                           -0.027     -0.029    -0.026
lTr                                          -0.033      0.161     0.282
                                             lA.XXP:4 lA.XXP:2 lD     tz
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0.5:F
lA.mridXftimeXsex44487501:24:F
lA.mridXftimeXsex44472001:0.5:M
lA.mridXftimeXsex44472001:2:M
lA.mridXftimeXsex44472001:3:M
lA.mridXftimeXsex44472001:4:M
lA.mridXftimeXsex44472001:0.5:F
lA.mridXftimeXsex44472001:2:F
lA.mridXftimeXsex44472001:3:F
lA.mridXftimeXsex44472001:4:F
lA.mridXftimeXsexPadilla:0.666666666666667:M
lA.mridXftimeXsexPadilla:0.5:M
lA.mridXftimeXsexPadilla:1:M
lA.mridXftimeXsexPadilla:1.5:M
lA.mridXftimeXsexPadilla:4:M
lA.mridXftimeXsexPadilla:24:M                 0.000
lD                                            0.005    0.000
tz                                           -0.013    0.000    0.193
lg                                           -0.006    0.000    0.451  0.654
lTr                                           0.174    0.000    0.042  0.036
                                             lg
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0.5:F
lA.mridXftimeXsex44487501:24:F
lA.mridXftimeXsex44472001:0.5:M
lA.mridXftimeXsex44472001:2:M
lA.mridXftimeXsex44472001:3:M
lA.mridXftimeXsex44472001:4:M
lA.mridXftimeXsex44472001:0.5:F
lA.mridXftimeXsex44472001:2:F
lA.mridXftimeXsex44472001:3:F
lA.mridXftimeXsex44472001:4:F
lA.mridXftimeXsexPadilla:0.666666666666667:M
lA.mridXftimeXsexPadilla:0.5:M
lA.mridXftimeXsexPadilla:1:M
lA.mridXftimeXsexPadilla:1.5:M
```

```
lA.mridXftimeXsexPadilla:4:M
lA.mridXftimeXsexPadilla:24:M
lD
tz
lg
lTr                                          -0.016

Standardized Within-Group Residuals:
        Min          Q1         Med          Q3         Max
-2.80592883 -0.64554454 -0.02553839  0.62175213  4.22495060

Number of Observations: 419
Number of Groups: 3
```

3 Summary

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. BMD has units mg/kg, and times are in hours.

species RAT

mrid `[1] "44472001" "44487501" "Padilla"`

`lD` **(standard error)** -0.720456946215928 (0.240067984390359)

BMD (95% CI) 0.486529887167675 (0.307318690678700, 0.77024710272136)

BMDL, the one-sided lower 95% CL 0.330968933609935

`lTr (standard error)` -0.216557313853540 (0.0746493462787226)

Recovery Half-life (95% CI) 0.805286379534398 (0.698086544339014, 0.928948077172352)

Save everything:

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

Save the results for incorporating into a database:

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