Dose-Time Response Modeling of Rat RBC 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 RBC. via gavage dosing. It includes only an acute study.

All the data used for this DR model are in `AggData` (44487501 and 44472001) and `PadillaData`. For mrid 44487501, groups with missing values for `tmpstds` are pre-dose groups. One question is which values to use as controls in this case. Change the NAs to 0. The activity data in `PadillaData` are about a sixth of those 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" & sctn == "RBC", select = c("mrid",
+     "dose", "cheact", "sd", "n", "tmonstdy", "tmpstds", "sex")))
> dta$tmpstds[is.na(dta$tmpstds)] <- 0
> Pdta <- subset(PadillaData, chemical %in% "methomyl", select = c("dose",
+     "RBC.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 * 6
> dta <- rbind(dta, Pdta[, names(dta)])
```

Summaries of this dataset:

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

dta$mrid: 44472001
       mrid         dose         cheact           sd              n
 44472001:16   Min.   :0.0   Min.   : 920   Min.   :188.0   Min.   :10
 44487501: 0   1st Qu.:0.0   1st Qu.:2029   1st Qu.:271.8   1st Qu.:10
 Padilla : 0   Median :1.5   Median :2083   Median :330.5   Median :10
               Mean   :1.5   Mean   :2019   Mean   :349.8   Mean   :10
               3rd Qu.:3.0   3rd Qu.:2261   3rd Qu.:419.2   3rd Qu.:10
               Max.   :3.0   Max.   :2430   Max.   :515.0   Max.   :10
    tmonstdy    tmpstds      sex
 Min.   :1   Min.   :0.500   F:8
 1st Qu.:1   1st Qu.:1.625   M:8
 Median :1   Median :2.500
 Mean   :1   Mean   :2.375
 3rd Qu.:1   3rd Qu.:3.250
 Max.   :1   Max.   :4.000
------------------------------------------------------------
dta$mrid: 44487501
       mrid         dose          cheact           sd              n
 44472001: 0   Min.   :0.00   Min.   : 928   Min.   :167.0   Min.   :10
 44487501:30   1st Qu.:0.25   1st Qu.:1832   1st Qu.:309.2   1st Qu.:10
 Padilla : 0   Median :0.50   Median :2009   Median :339.5   Median :10
               Mean   :0.70   Mean   :1907   Mean   :342.3   Mean   :10
               3rd Qu.:0.75   3rd Qu.:2072   3rd Qu.:381.0   3rd Qu.:10
               Max.   :2.00   Max.   :2426   Max.   :586.0   Max.   :10
    tmonstdy    tmpstds       sex
 Min.   :0   Min.   : 0.000   F:15
 1st Qu.:0   1st Qu.: 0.000   M:15
 Median :1   Median : 0.500
 Mean   :1   Mean   : 8.167
 3rd Qu.:2   3rd Qu.:24.000
 Max.   :2   Max.   :24.000
------------------------------------------------------------
dta$mrid: Padilla
       mrid         dose            cheact              sd          n
 44472001: 0   Min.   :0.000   Min.   : 757.7   Min.   :0   Min.   :1
 44487501: 0   1st Qu.:0.175   1st Qu.:1527.1   1st Qu.:0   1st Qu.:1
```

```
 Padilla :59   Median :1.250   Median :1951.2   Median :0   Median :1
               Mean   :1.619   Mean   :2137.1   Mean   :0   Mean   :1
               3rd Qu.:3.000   3rd Qu.:2662.4   3rd Qu.:0   3rd Qu.:1
               Max.   :3.000   Max.   :5290.9   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, exclude = NULL)))

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 0.5 24
  0    2 2   2
  0.25 2 2   2
  0.5  2 2   2
  0.75 2 2   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, 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$tmpstds > 0])
> initfile <- paste("initvals-RBC-DR-1.RData", sep = "")
> if (!file.exists(initfile)) {
+     lA.start <- lm(I(log(cheact)) ~ mridXftimeXsex - 1, data = CleanUp(subset(dta,
+         dose %in% 0)))
+     Start <- c(coef(lA.start), rep(log(0.1), nlevels(dta$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       143.11 38.31 22.68 13.53 5.65
mu                0.02  0.06  0.10  0.17 0.41
lD.mrid44472001   0.81  0.01  0.16  0.01 0.00
lD.mrid44487501   0.78  0.01  0.18  0.01 0.00
lD.mridPadilla    0.76  0.01  0.12  0.09 0.01
lD.sexM           0.68  0.18  0.10  0.03 0.00
tz.(Intercept)    0.90  0.05  0.05  0.00 0.00
tz.sexM           0.03  0.79  0.06  0.12 0.00
```

```
lg.(Intercept)    0.97  0.03  0.00  0.00 0.00
lg.sexM           0.95  0.05  0.00  0.00 0.00
lTr               0.00  0.00  0.00  0.01 0.83
```

The high-dose shape parameter `tz` ends up being set very small, where continued reduction yields no change in fit, so set it to -10 in the subsequent analysis. As usual, `lD` and `lg` are potentially redundant, but in this dataset the condition index of their eigenvector does not seem to be extremely large, so it may be possible to fit both parameters.

```
> Parm <- init1$start$beta
> Start <- Start0 <- Parm[-grep("^tz", names(Parm))]
> idta <- init1$data
> formals(tcmfn4)$tz <- -10
> icnt <- 1
> Maxcnt <- 60
> repeat {
+     drmod1 <- try(gnls(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, lg = lg, lTr = lTr), data = idta, params = list(lA ~
+         mridXftimeXsex - 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))
+ }
```

This fails with the error:

```
Error in gnls(cheact ~ tcmfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg,  :
        Step halving factor reduced below minimum in NLS step
```

So, try estimating a single value of `lg`. Also, go straight to estimating separate standard deviations for each mridXsex:

```
> Parm <- init1$start$beta
> Parm <- Parm[-grep("^tz", names(Parm))]
> Parm <- Parm[-grep("lg.sexM", names(Parm))]
> Start <- Start0 <- Parm
> idta <- init1$data
> formals(tcmfn4)$tz <- -10
> icnt <- 1
> Maxcnt <- 70
> repeat {
+     drmod1 <- try(gnls(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, lg = lg, lTr = lTr), data = idta, params = list(lA ~
+         mridXftimeXsex - 1, lD ~ mrid + sex - 1, lg ~ 1, lTr ~
+         1), weights = varIdent(form = ~1 | mridXsex), 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(c("Maxcnt exceeded", drmod1))
+         break
+     }
+     icnt <- icnt + 1
+     Start <- Start0 * (1 + rnorm(length(Start0), sd = 0.2))
+ }

Successful in  8 tries
```

Now try the same model for the mean, but include `varPower()` in the error model.

```
> Start <- Start0 <- coef(drmod1)
> formals(tcmfn4)$tz <- -10
> icnt <- 1
> Maxcnt <- 70
> repeat {
+     drmod2 <- try(gnls(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, lg = lg, lTr = lTr), data = idta, params = list(lA ~
+         mridXftimeXsex - 1, lD ~ mrid + sex - 1, lg ~ 1, lTr ~
+         1), weights = varComb(varIdent(form = ~1 | mridXsex),
+         varPower(value = 1)), 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(c("Maxcnt exceeded", drmod2))
+         break
+     }
+     icnt <- icnt + 1
+     Start <- Start0 * (1 + rnorm(length(Start0), sd = 0.2))
+ }

Successful in  1 try

> anova(drmod1, drmod2)

       Model df      AIC      BIC    logLik   Test  L.Ratio p-value
drmod1     1 31 7636.867 7768.676 -3787.434
drmod2     2 32 7604.692 7740.753 -3770.346 1 vs 2 34.17556  <.0001
```

We need to allow standard deviations to vary among mridXsex, and include `varPower()`.

Next, fit a random effects model:

```
> Parm <- coef(drmod2)
> Start0 <- c(getParms("^lA", Parm), mean(getParms("^lD\\.mrid",
+     Parm)), 0, Parm["lg"], Parm["lTr"])
> RE <- matrix(getParms("^lD\\.mrid", Parm) - mean(getParms("^lD\\.mrid",
+     Parm)), ncol = 1, dimnames = list(levels(idta$mrid), NULL))
> Start <- list(fixed = Start0, random = RE)
```

```
> formals(tcmfn4)$tz <- -10
> icnt <- 1
> Maxcnt <- 20
> repeat {
+     drmod3 <- try(nlme(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, lg = lg, lTr = lTr), data = idta, fixed = list(lA ~
+         mridXftimeXsex - 1, lD ~ sex, lg ~ 1, lTr ~ 1), random = lD ~
+         1 | mrid, weights = varComb(varIdent(form = ~1 | mridXsex),
+         varPower(value = 1)), 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 <- list(fixed = Start0 * (1 + rnorm(length(Start0),
+         sd = 0.2)), random = RE)
+ }
```

```
Successful in  1 try
```

Can we simplify the model? Are there differences between the sexes in `lD`, and is `lg` different from 0?

```
> L <- diag(2)
> colnames(L) <- c("lD.sexM", "lg")
> anova(drmod3, L = L)
```

```
F-test for linear combination(s)
  lD.sexM lg
1       1  0
2       0  1
  numDF denDF   F-value p-value
1     2   493 0.5655468  0.5684
```

Neither coefficient differs significantly from zero, so refit without them:

```
> Parm <- fixed.effects(drmod3)
> Start0 <- c(getParms("^lA", Parm), Parm["lD.(Intercept)"], Parm["lTr"])
> RE <- data.matrix(random.effects(drmod3))
> Start <- list(fixed = Start0, random = RE)
> formals(tcmfn4)$tz <- -10
> formals(tcmfn4)$lg <- 0
> icnt <- 1
> Maxcnt <- 20
> repeat {
+     drmod4 <- try(nlme(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, lTr = lTr), data = idta, fixed = list(lA ~ mridXftimeXsex -
+         1, lD ~ 1, lTr ~ 1), random = lD ~ 1 | mrid, weights = varComb(varIdent(form = ~1 |
+         mridXsex), varPower(value = 1)), start = Start), silent = TRUE)
+     if (!inherits(drmod4, "try-error") || icnt > Maxcnt) {
+         if (icnt <= Maxcnt)
+             writeLines(paste("Successful in ", icnt, if (icnt >
```

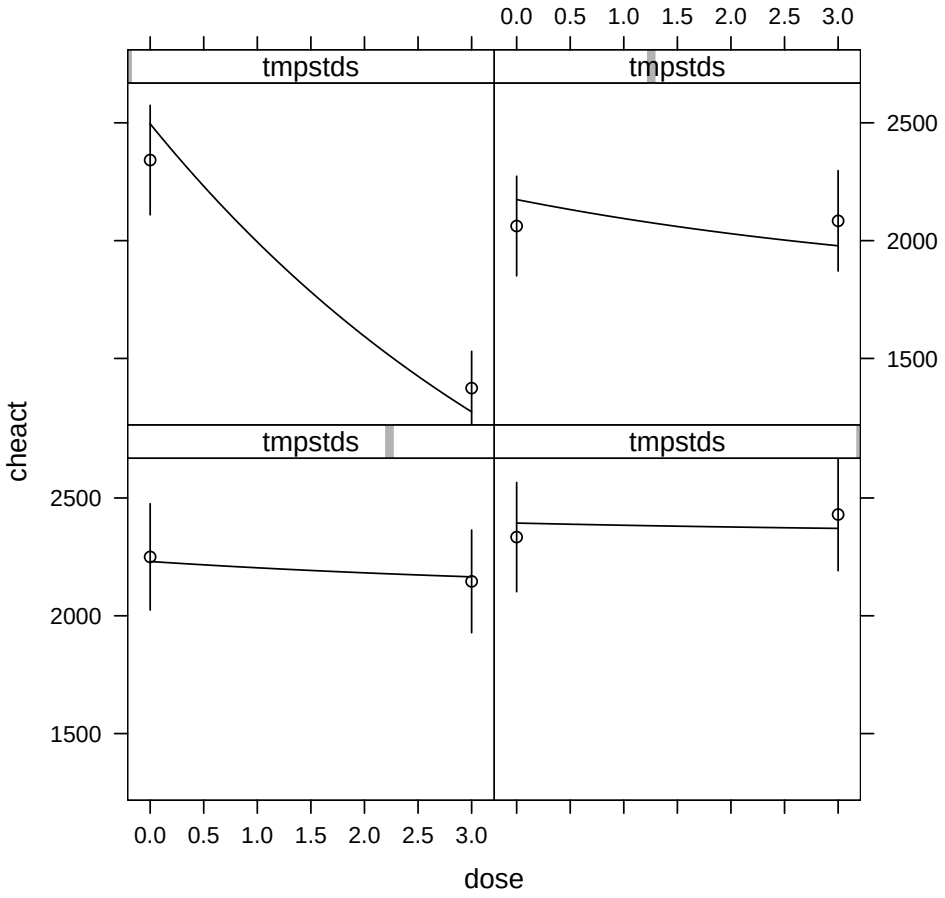
```
+                 1)
+                 "tries"
+             else "try"))
+         else writeLines("Maxcnt exceeded")
+         break
+     }
+     icnt <- icnt + 1
+     Start <- list(fixed = Start0 * (1 + rnorm(length(Start0),
+         sd = 0.2)), random = RE)
+ }
```

```
Successful in  1 try
```

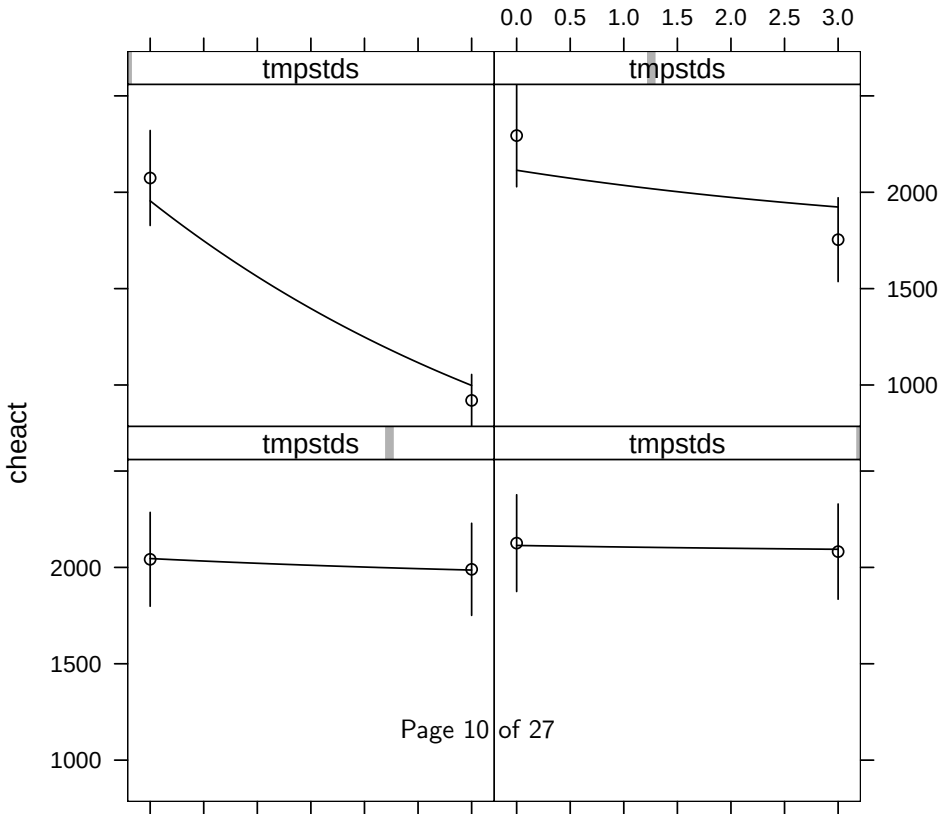
Diagnostic plots for this model: Plots of data with 95% CI and fitted curve for each combination of mrid and sex. First set up the data set and predicted values for plotting.

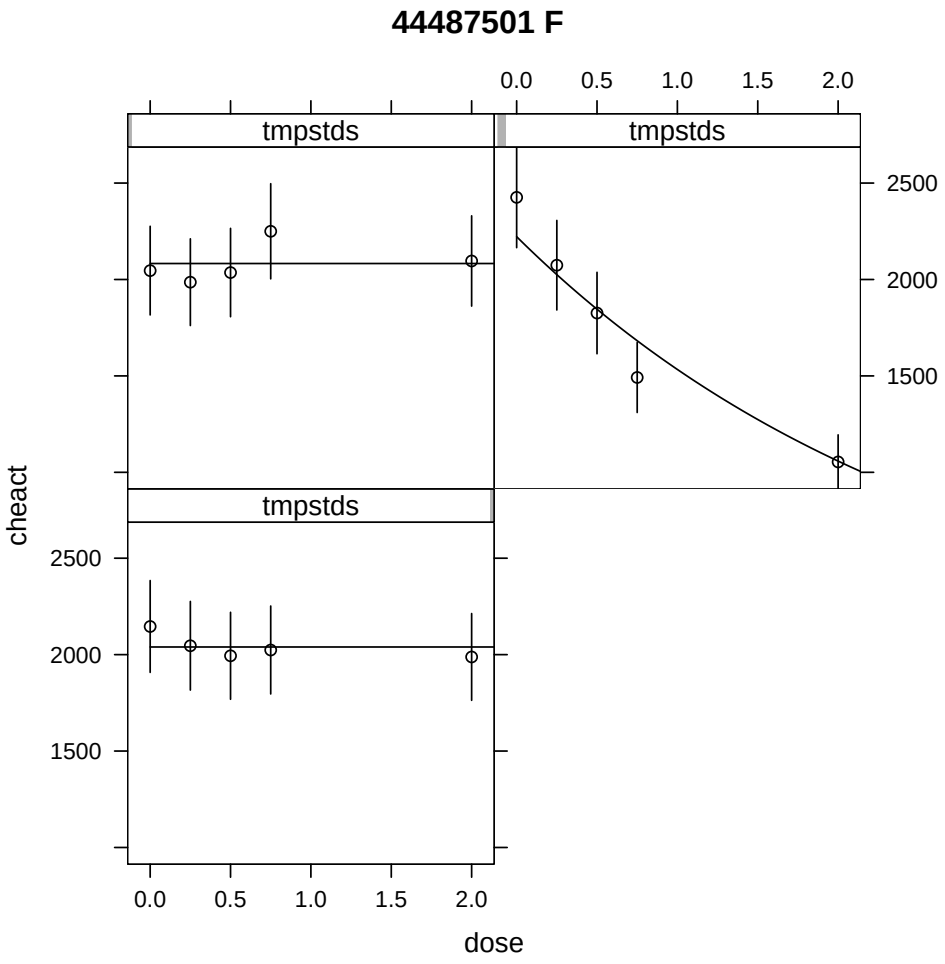
```
> tdta <- local({
+     idta <- with(dta, PhonyDF(dose, n, cheact, sd, "dose", "cheact",
+         Avals = list(mrid = mrid, sex = sex, tmpstds = tmpstds)))
+     idta$mridXsex <- with(idta, interaction(mrid, sex, drop = TRUE,
+         sep = ":"))
+     idta$mridXsexXtmpstdsXdose <- with(idta, interaction(mrid,
+         sex, tmpstds, dose, sep = ":", drop = TRUE))
+     out <- gls(cheact ~ mridXsexXtmpstdsXdose - 1, data = idta,
+         weights = varComb(varIdent(form = ~1 | mridXsex), varPower(value = 1)))
+     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$tmpstds <- as.numeric(sapply(sstr, function(x) x[2]))
> tmp <- drmod4
> tmp$contrasts <- NULL
> ndta$pred <- predict(tmp, newdata = ndta)
```

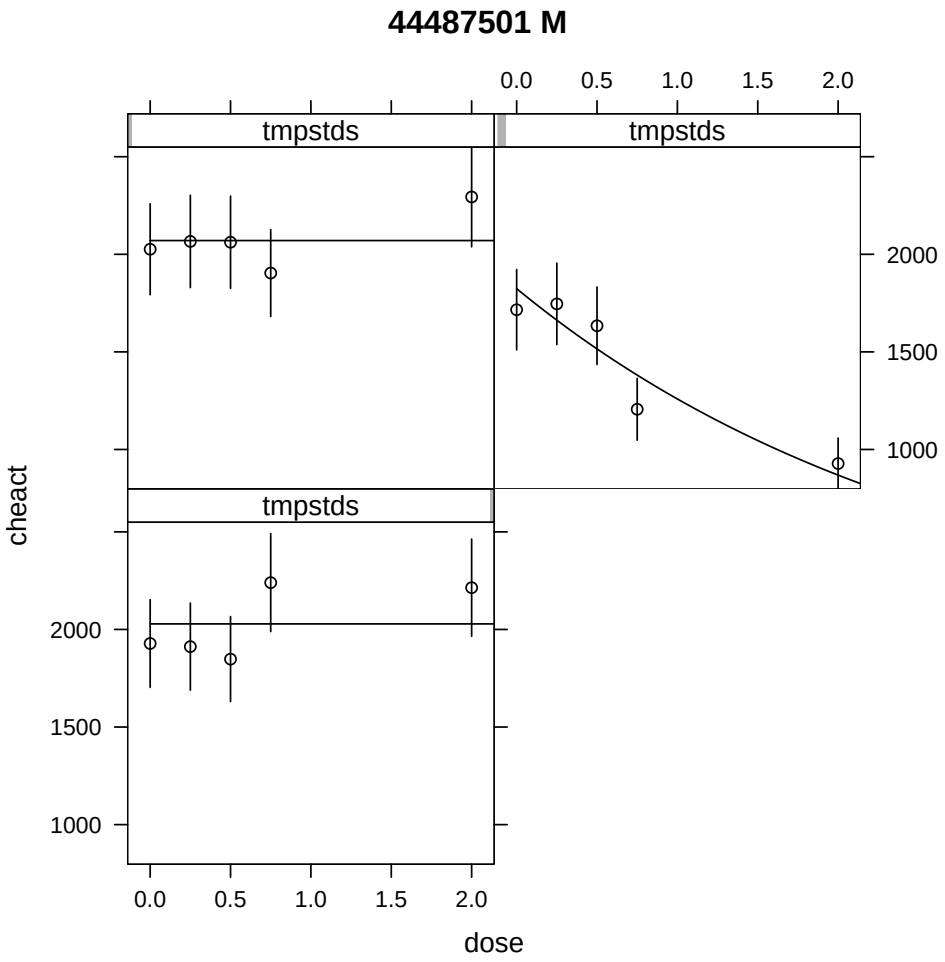
44472001 F

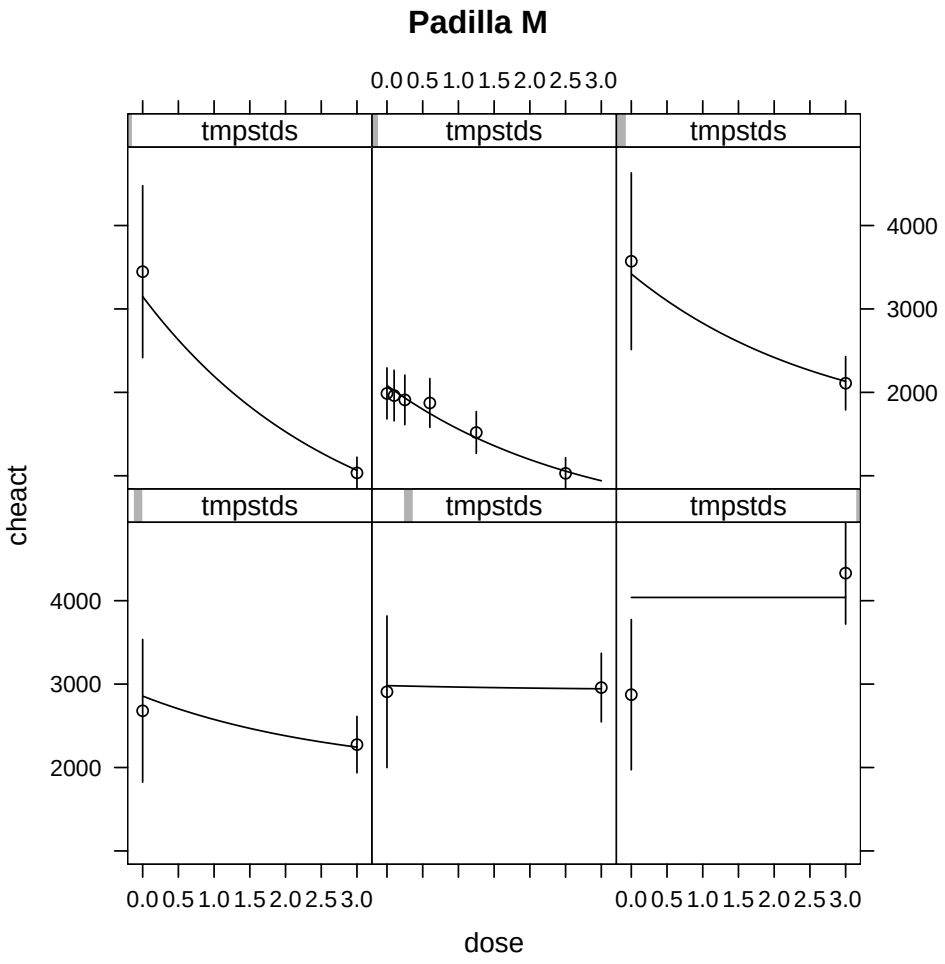


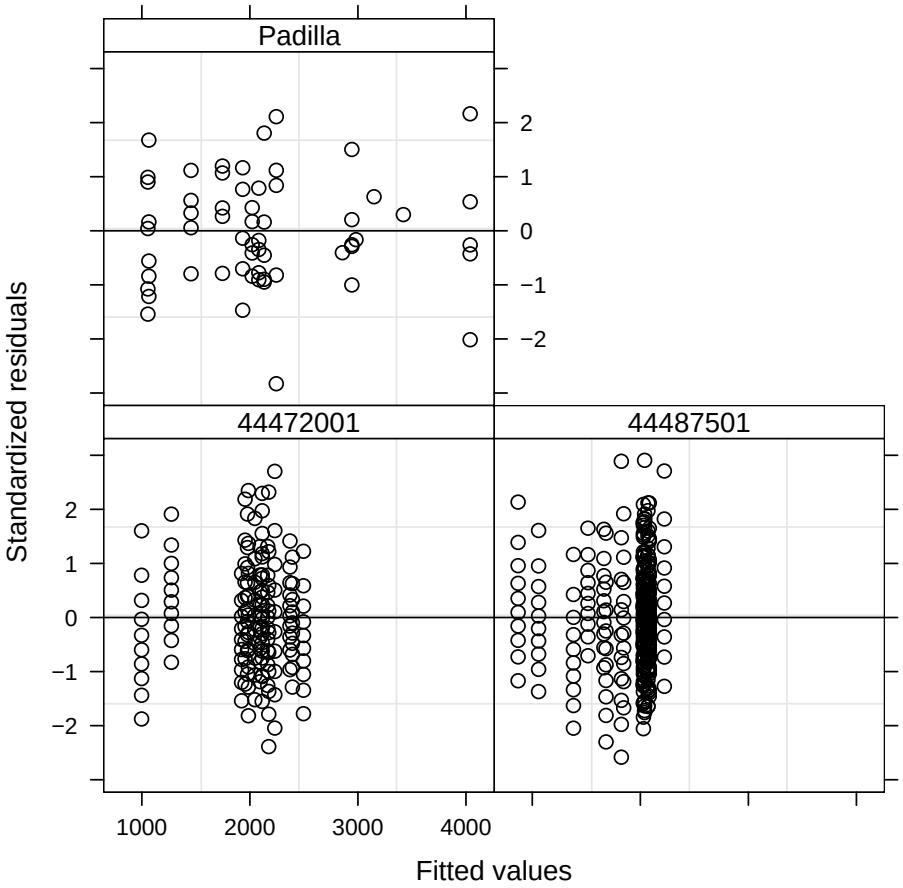
44472001 M

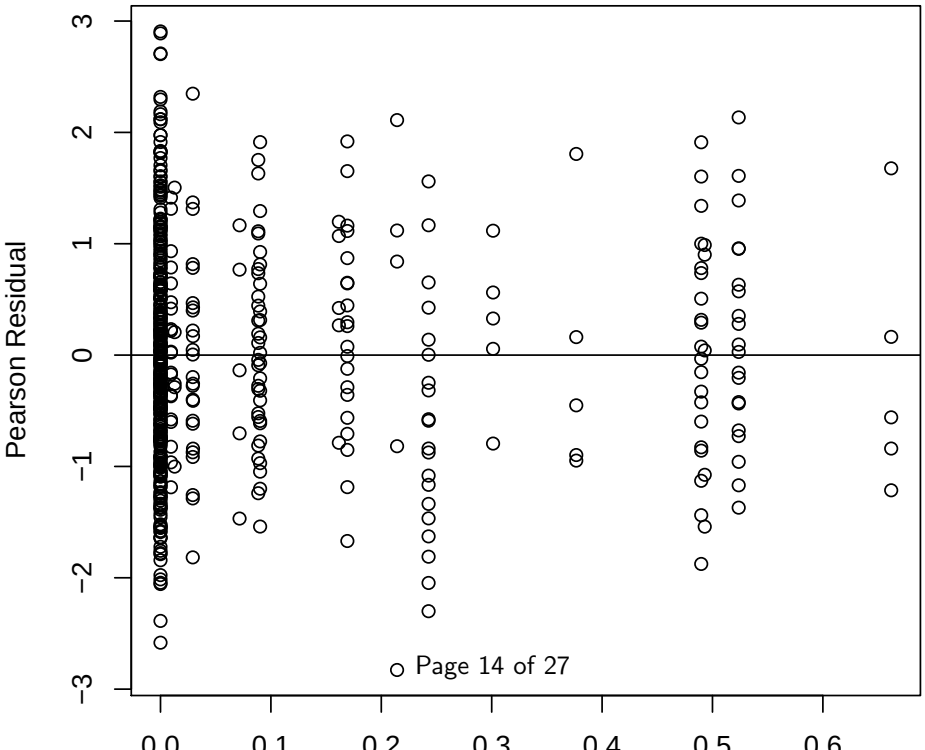


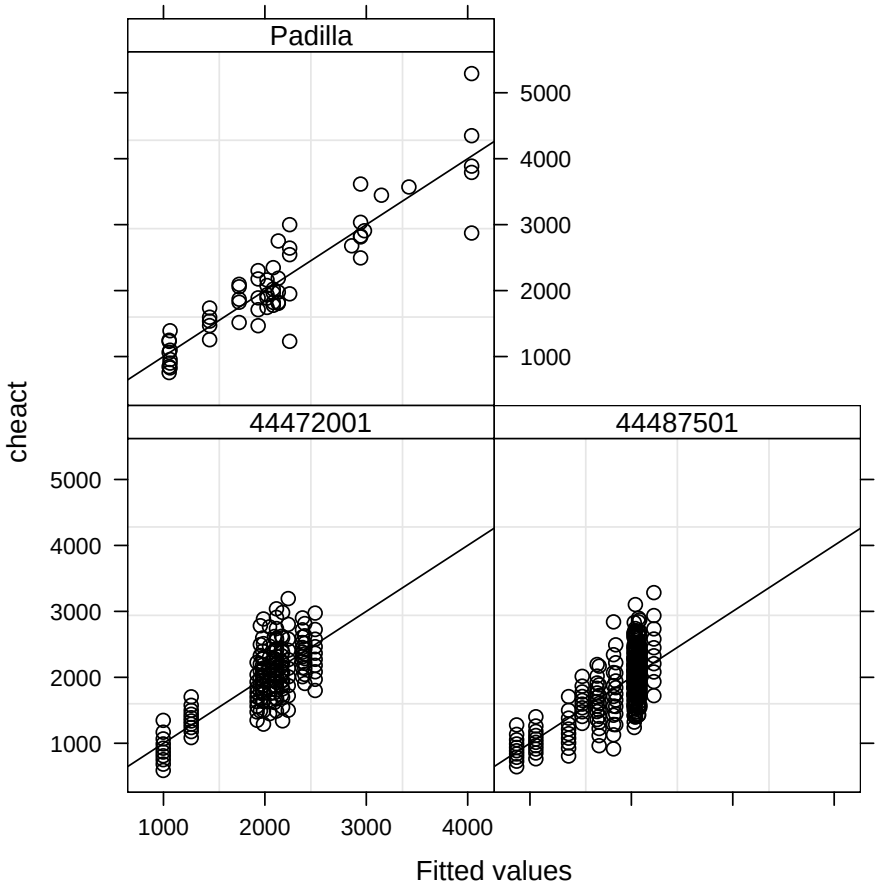

44487501 F
tmpstds
tmpstds
tmpstds
cheact
dose
0.0
0.5
1.0
1.5
2.0
1500
2000
2500

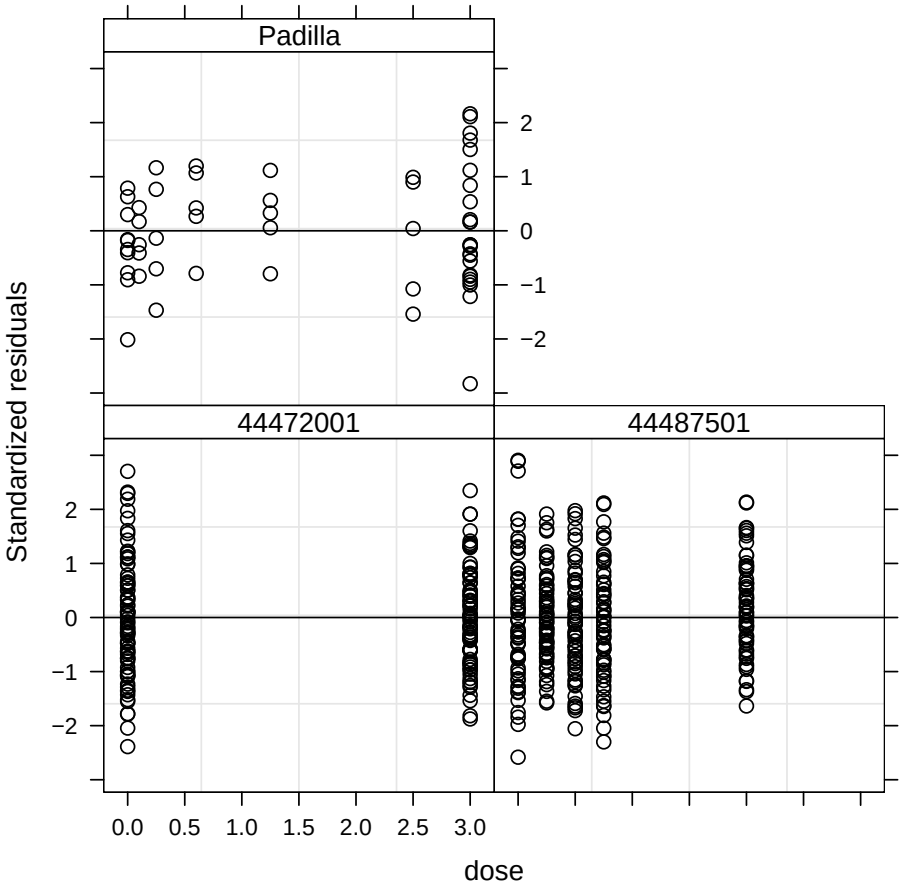

44487501 M
tmpstds
tmpstds
tmpstds
cheact
dose
0.0
0.5
1.0
1.5
2.0
1000
1500
2000

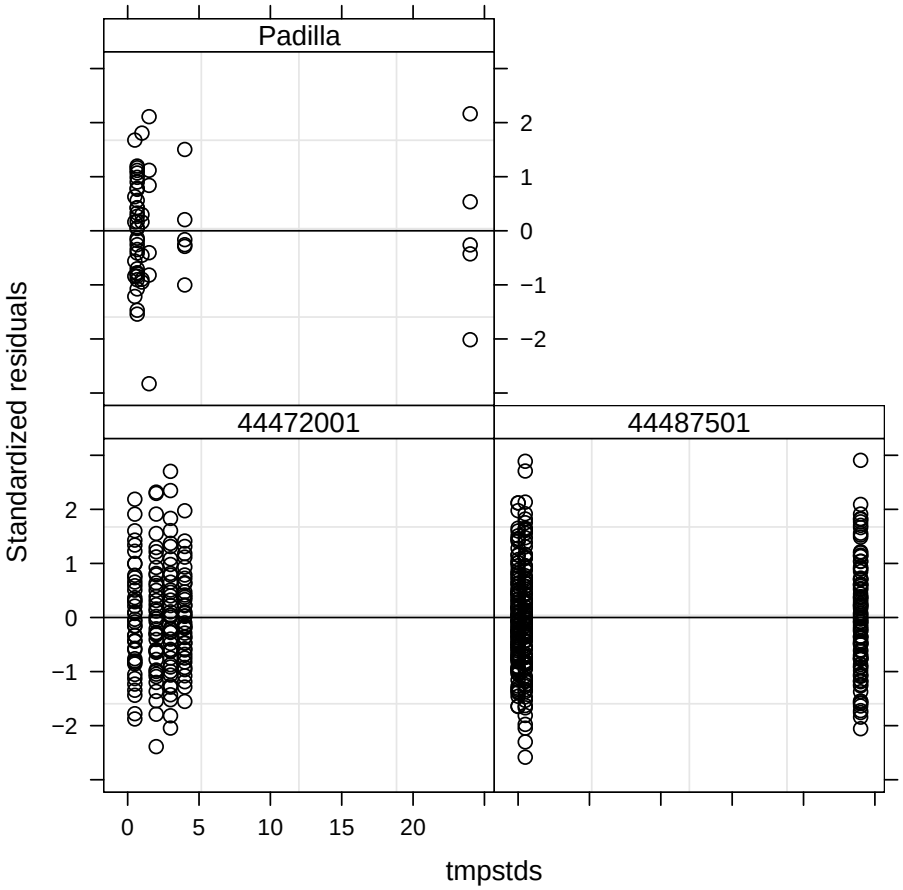

Padilla M
tmpstds
tmpstds
tmpstds
tmpstds
tmpstds
tmpstds
cheact
dose
0.0 0.5 1.0 1.5 2.0 2.5 3.0
2000
3000
4000

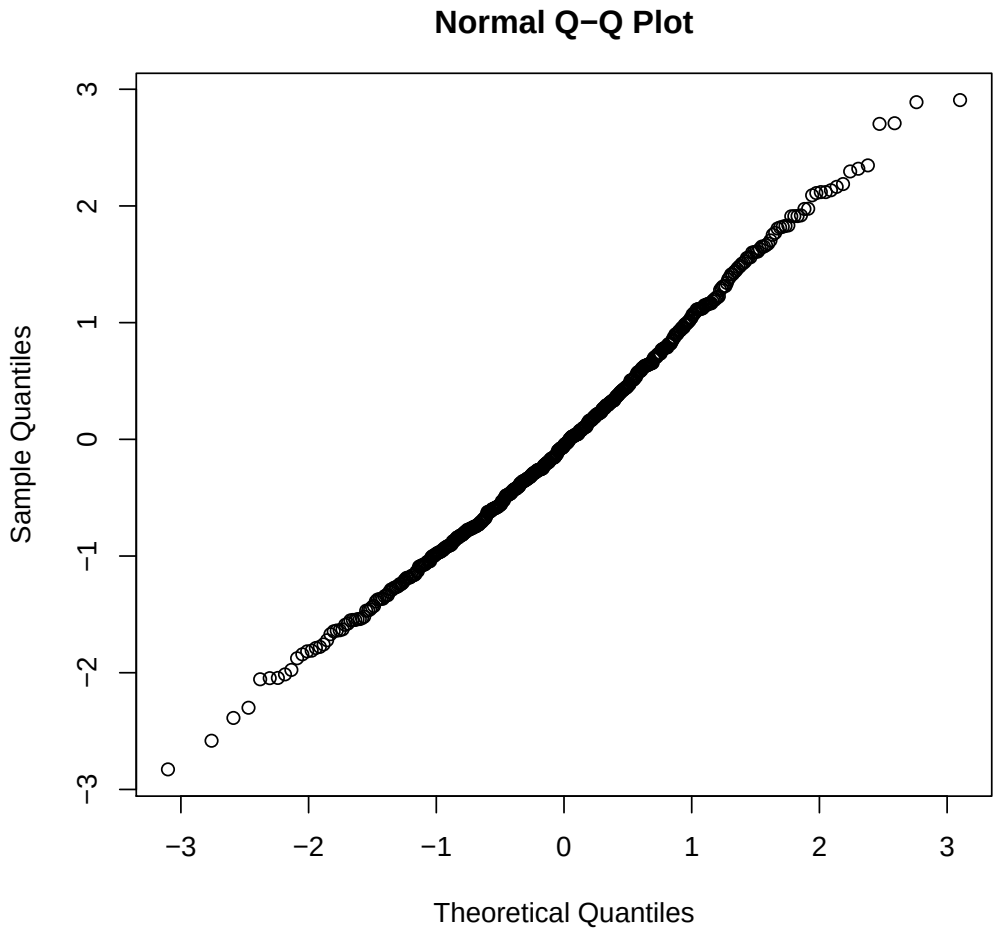

Padilla
44472001
44487501
Standardized residuals
Fitted values
1000
2000
3000
4000
2
1
0
−1
−2


Pearson Residual
3
2
1
0
−1
−2
−3
0.0
0.1
0.2
0.3
0.4
0.5
0.6


Padilla
44472001
44487501
cheact
Fitted values
1000
2000
3000
4000
5000


Padilla
44472001
44487501
Standardized residuals
dose
0.0
0.5
1.0
1.5
2.0
2.5
3.0
2
1
0
−1
−2


Padilla
44472001
44487501
Standardized residuals
tmpstds
2
1
0
−1
−2
0
5
10
15
20



Details of this final model fit:

```
> tTab <- summary(drmod4)$tTable
> Ints <- intervals(drmod4, which = "fixed")$fixed
> Ints90 <- intervals(drmod4, which = "fixed", level = 0.9)$fixed
> summary(drmod4)
```

```
Nonlinear mixed-effects model fit by maximum likelihood
  Model: cheact ~ tcmfn4(dose, tmpstds, lA = lA, lD = lD, lTr = lTr)
 Data: idta
       AIC      BIC    logLik
  7611.763 7735.069 -3776.882

Random effects:
 Formula: lD ~ 1 | mrid
               lD Residual
StdDev: 0.2384426 0.778159

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
```

```
 1.0000000  0.8472990  0.9852776  0.9348876  0.8466240
 Structure: Power of variance covariate
 Formula: ~fitted(.)
 Parameter estimates:
    power
0.8162613
Fixed effects: list(lA ~ mridXftimeXsex - 1, lD ~ 1, lTr ~ 1)
                                            Value  Std.Error  DF   t-value
lA.mridXftimeXsex44487501:0:M                7.635497 0.02724331 495 280.27053
lA.mridXftimeXsex44487501:0.5:M              7.508787 0.03448780 495 217.72300
lA.mridXftimeXsex44487501:24:M               7.615003 0.02734609 495 278.46766
lA.mridXftimeXsex44487501:0:F                7.641468 0.02582166 495 295.93248
lA.mridXftimeXsex44487501:0.5:F              7.706119 0.03241732 495 237.71612
lA.mridXftimeXsex44487501:24:F               7.620509 0.02592129 495 293.98644
lA.mridXftimeXsex44472001:0.5:M              7.578324 0.05308029 495 142.77096
lA.mridXftimeXsex44472001:2:M                7.656416 0.04778013 495 160.24267
lA.mridXftimeXsex44472001:3:M                7.623601 0.04497220 495 169.51807
lA.mridXftimeXsex44472001:4:M                7.656318 0.04380042 495 174.80010
lA.mridXftimeXsex44472001:0.5:F              7.822381 0.04543314 495 172.17345
lA.mridXftimeXsex44472001:2:F                7.684481 0.04152584 495 185.05298
lA.mridXftimeXsex44472001:3:F                7.709933 0.03787810 495 203.54591
lA.mridXftimeXsex44472001:4:F                7.780510 0.03635425 495 214.01928
lA.mridXftimeXsexPadilla:0.666666666666667:M 7.641348 0.03678141 495 207.75027
lA.mridXftimeXsexPadilla:0.5:M               8.054876 0.11848832 495  67.98034
lA.mridXftimeXsexPadilla:1:M                 8.137470 0.08817492 495  92.28781
lA.mridXftimeXsexPadilla:1.5:M               7.957320 0.08528633 495  93.30124
lA.mridXftimeXsexPadilla:4:M                 8.000297 0.06402963 495 124.94680
lA.mridXftimeXsexPadilla:24:M                8.303702 0.06547436 495 126.82372
lD                                          -1.082329 0.15158199 495  -7.14022
lTr                                         -0.486789 0.22895312 495  -2.12615
                                            p-value
lA.mridXftimeXsex44487501:0:M                 0.000
lA.mridXftimeXsex44487501:0.5:M               0.000
lA.mridXftimeXsex44487501:24:M                0.000
lA.mridXftimeXsex44487501:0:F                 0.000
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
lTr                                           0.034
 Correlation:
```

```
                                            lA.XX44487501:0:M
lA.mridXftimeXsex44487501:0.5:M              0.000
lA.mridXftimeXsex44487501:24:M               0.000
lA.mridXftimeXsex44487501:0:F                0.000
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
lTr                                          0.000
                                            lA.XX44487501:0.5:M
lA.mridXftimeXsex44487501:0.5:M
lA.mridXftimeXsex44487501:24:M               0.000
lA.mridXftimeXsex44487501:0:F                0.000
lA.mridXftimeXsex44487501:0.5:F              0.302
lA.mridXftimeXsex44487501:24:F               0.000
lA.mridXftimeXsex44472001:0.5:M              0.010
lA.mridXftimeXsex44472001:2:M               -0.003
lA.mridXftimeXsex44472001:3:M               -0.002
lA.mridXftimeXsex44472001:4:M               -0.001
lA.mridXftimeXsex44472001:0.5:F              0.012
lA.mridXftimeXsex44472001:2:F               -0.004
lA.mridXftimeXsex44472001:3:F               -0.003
lA.mridXftimeXsex44472001:4:F               -0.001
lA.mridXftimeXsexPadilla:0.666666666666667:M 0.012
lA.mridXftimeXsexPadilla:0.5:M               0.022
lA.mridXftimeXsexPadilla:1:M                 0.001
lA.mridXftimeXsexPadilla:1.5:M              -0.004
lA.mridXftimeXsexPadilla:4:M                -0.002
lA.mridXftimeXsexPadilla:24:M                0.000
lD                                          -0.102
lTr                                         -0.012
                                            lA.XX44487501:24:M
lA.mridXftimeXsex44487501:0.5:M
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0:F                0.000
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
lTr                                            0.000
                                              lA.XX44487501:0:F
lA.mridXftimeXsex44487501:0.5:M
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0:F
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
lTr                                            0.000
                                              lA.XX44487501:0.5:F
lA.mridXftimeXsex44487501:0.5:M
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0:F
lA.mridXftimeXsex44487501:0.5:F
lA.mridXftimeXsex44487501:24:F                 0.000
lA.mridXftimeXsex44472001:0.5:M                0.011
lA.mridXftimeXsex44472001:2:M                 -0.004
lA.mridXftimeXsex44472001:3:M                 -0.002
lA.mridXftimeXsex44472001:4:M                 -0.001
lA.mridXftimeXsex44472001:0.5:F                0.013
lA.mridXftimeXsex44472001:2:F                 -0.004
lA.mridXftimeXsex44472001:3:F                 -0.003
lA.mridXftimeXsex44472001:4:F                 -0.001
lA.mridXftimeXsexPadilla:0.666666666666667:M  0.013
lA.mridXftimeXsexPadilla:0.5:M                 0.023
lA.mridXftimeXsexPadilla:1:M                   0.001
lA.mridXftimeXsexPadilla:1.5:M                 -0.004
lA.mridXftimeXsexPadilla:4:M                   -0.002
lA.mridXftimeXsexPadilla:24:M                  0.000
```

```
lD                                          -0.108
lTr                                         -0.013
                                            lA.XX44487501:24:F
lA.mridXftimeXsex44487501:0.5:M
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0:F
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
lTr                                          0.000
                                            lA.XX44472001:0.5:M
lA.mridXftimeXsex44487501:0.5:M
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0:F
lA.mridXftimeXsex44487501:0.5:F
lA.mridXftimeXsex44487501:24:F
lA.mridXftimeXsex44472001:0.5:M
lA.mridXftimeXsex44472001:2:M                0.009
lA.mridXftimeXsex44472001:3:M               -0.001
lA.mridXftimeXsex44472001:4:M               -0.002
lA.mridXftimeXsex44472001:0.5:F              0.259
lA.mridXftimeXsex44472001:2:F                0.011
lA.mridXftimeXsex44472001:3:F               -0.001
lA.mridXftimeXsex44472001:4:F               -0.002
lA.mridXftimeXsexPadilla:0.666666666666667:M  0.008
lA.mridXftimeXsexPadilla:0.5:M               0.032
lA.mridXftimeXsexPadilla:1:M                -0.021
lA.mridXftimeXsexPadilla:1.5:M              -0.026
lA.mridXftimeXsexPadilla:4:M                -0.007
lA.mridXftimeXsexPadilla:24:M                0.000
lD                                          -0.101
lTr                                         -0.049
                                            lA.XX44472001:2:M
lA.mridXftimeXsex44487501:0.5:M
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0:F
lA.mridXftimeXsex44487501:0.5:F
lA.mridXftimeXsex44487501:24:F
lA.mridXftimeXsex44472001:0.5:M
lA.mridXftimeXsex44472001:2:M
```

```
lA.mridXftimeXsex44472001:3:M                 0.084
lA.mridXftimeXsex44472001:4:M                 0.038
lA.mridXftimeXsex44472001:0.5:F               0.011
lA.mridXftimeXsex44472001:2:F                 0.178
lA.mridXftimeXsex44472001:3:F                 0.100
lA.mridXftimeXsex44472001:4:F                 0.046
lA.mridXftimeXsexPadilla:0.666666666666667:M  0.033
lA.mridXftimeXsexPadilla:0.5:M               -0.117
lA.mridXftimeXsexPadilla:1:M                  0.227
lA.mridXftimeXsexPadilla:1.5:M                0.239
lA.mridXftimeXsexPadilla:4:M                  0.058
lA.mridXftimeXsexPadilla:24:M                 0.000
lD                                            0.034
lTr                                           0.389
                                             lA.XX44472001:3:M
lA.mridXftimeXsex44487501:0.5:M
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0:F
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                 0.021
lA.mridXftimeXsex44472001:0.5:F              -0.001
lA.mridXftimeXsex44472001:2:F                 0.097
lA.mridXftimeXsex44472001:3:F                 0.054
lA.mridXftimeXsex44472001:4:F                 0.025
lA.mridXftimeXsexPadilla:0.666666666666667:M  0.018
lA.mridXftimeXsexPadilla:0.5:M               -0.064
lA.mridXftimeXsexPadilla:1:M                  0.124
lA.mridXftimeXsexPadilla:1.5:M                0.131
lA.mridXftimeXsexPadilla:4:M                  0.032
lA.mridXftimeXsexPadilla:24:M                 0.000
lD                                            0.021
lTr                                           0.213
                                             lA.XX44472001:4:M
lA.mridXftimeXsex44487501:0.5:M
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0:F
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              -0.002
lA.mridXftimeXsex44472001:2:F                 0.044
lA.mridXftimeXsex44472001:3:F                 0.025
lA.mridXftimeXsex44472001:4:F                 0.012
lA.mridXftimeXsexPadilla:0.666666666666667:M  0.008
lA.mridXftimeXsexPadilla:0.5:M               -0.030
lA.mridXftimeXsexPadilla:1:M                  0.057
lA.mridXftimeXsexPadilla:1.5:M                0.060
```

```
lA.mridXftimeXsexPadilla:4:M                  0.014
lA.mridXftimeXsexPadilla:24:M                 0.000
lD                                            0.010
lTr                                           0.098
                                             lA.XX44472001:0.5:F
lA.mridXftimeXsex44487501:0.5:M
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0:F
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                 0.013
lA.mridXftimeXsex44472001:3:F                -0.002
lA.mridXftimeXsex44472001:4:F                -0.002
lA.mridXftimeXsexPadilla:0.666666666666667:M  0.010
lA.mridXftimeXsexPadilla:0.5:M                0.037
lA.mridXftimeXsexPadilla:1:M                 -0.024
lA.mridXftimeXsexPadilla:1.5:M               -0.031
lA.mridXftimeXsexPadilla:4:M                 -0.008
lA.mridXftimeXsexPadilla:24:M                 0.000
lD                                           -0.118
lTr                                          -0.057
                                             lA.XX44472001:2:F
lA.mridXftimeXsex44487501:0.5:M
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0:F
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                 0.115
lA.mridXftimeXsex44472001:4:F                 0.053
lA.mridXftimeXsexPadilla:0.666666666666667:M  0.038
lA.mridXftimeXsexPadilla:0.5:M               -0.134
lA.mridXftimeXsexPadilla:1:M                  0.261
lA.mridXftimeXsexPadilla:1.5:M                0.275
lA.mridXftimeXsexPadilla:4:M                  0.066
lA.mridXftimeXsexPadilla:24:M                 0.000
lD                                            0.039
lTr                                           0.447
                                             lA.XX44472001:3:F
lA.mridXftimeXsex44487501:0.5:M
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0:F
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                 0.030
lA.mridXftimeXsexPadilla:0.666666666666667:M  0.021
lA.mridXftimeXsexPadilla:0.5:M               -0.076
lA.mridXftimeXsexPadilla:1:M                  0.147
lA.mridXftimeXsexPadilla:1.5:M                0.155
lA.mridXftimeXsexPadilla:4:M                  0.037
lA.mridXftimeXsexPadilla:24:M                 0.000
lD                                            0.025
lTr                                           0.253
                                             lA.XX44472001:4:F lA.XXP:0.6
lA.mridXftimeXsex44487501:0.5:M
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0:F
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  0.010
lA.mridXftimeXsexPadilla:0.5:M               -0.036             0.348
lA.mridXftimeXsexPadilla:1:M                  0.069             0.209
lA.mridXftimeXsexPadilla:1.5:M                0.072             0.126
lA.mridXftimeXsexPadilla:4:M                  0.017             0.017
lA.mridXftimeXsexPadilla:24:M                 0.000             0.000
lD                                            0.012            -0.116
lTr                                           0.118             0.081
                                             lA.XXP:0.5 lA.XXP:1: lA.XXP:1.
lA.mridXftimeXsex44487501:0.5:M
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0:F
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                  0.049
lA.mridXftimeXsexPadilla:1.5:M               -0.080      0.404
lA.mridXftimeXsexPadilla:4:M                 -0.038      0.089     0.092
lA.mridXftimeXsexPadilla:24:M                 0.000      0.000     0.000
lD                                           -0.212     -0.007     0.037
lTr                                          -0.306      0.581     0.614
                                             lA.XXP:4 lA.XXP:2 lD
lA.mridXftimeXsex44487501:0.5:M
lA.mridXftimeXsex44487501:24:M
lA.mridXftimeXsex44487501:0:F
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                                            0.015    0.000
lTr                                           0.148    0.000    0.119

Standardized Within-Group Residuals:
        Min          Q1         Med          Q3         Max
-2.82790046 -0.73202320 -0.05672426  0.64691508  2.90729312

Number of Observations: 519
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] "1"   "2"   "3"   "4"   "5"   "6"   "7"   "8"   "9"   "10"  "11"  "12"
[13] "13"  "14"  "15"  "16"  "17"  "18"  "19"  "20"  "21"  "22"  "23"  "24"
[25] "25"  "26"  "27"  "28"  "29"  "30"  "31"  "32"  "33"  "34"  "35"  "36"
[37] "37"  "38"  "39"  "40"  "41"  "42"  "43"  "44"  "45"  "46"  "47"  "48"
[49] "49"  "50"  "51"  "52"  "53"  "54"  "55"  "56"  "57"  "58"  "59"  "60"
[61] "61"  "62"  "63"  "64"  "65"  "66"  "67"  "68"  "69"  "70"  "71"  "72"
[73] "73"  "74"  "75"  "76"  "77"  "78"  "79"  "80"  "81"  "82"  "83"  "84"
[85] "85"  "86"  "87"  "88"  "89"  "90"  "91"  "92"  "93"  "94"  "95"  "96"
[97] "97"  "98"  "99"  "100" "101" "102" "103" "104" "105"
```

`lD` **(standard error)** -1.08232907909048 (0.151581991363741)

BMD (95% CI) 0.338805501178803 (0.253150292707659, 0.453442760825009)

BMDL, the one-sided lower 95% CL 0.265331557566138

`lTr (standard error)` -0.486788598178087 (0.228953123745829)

Recovery Half-life (95% CI) 0.614596946126359 (0.395742728365004, 0.954482240895292)

Save everything:

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

Save the results for incorporating into a database:

```
> methomyl.oral.rbc <- 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.rbc, file = file.path("..", "..", "01Summaries",
+     "methomyl.oral.rbc.RData"))
```