Dose-Time Response Modeling of Rat RBC 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` 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 red blood cells. via gavage dosing. It includes acute and subchronic 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 = RBC.R) added to the Padilla dataset.

Now, set up the analysis dataset.

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

Summary of the relevant variables in this dataset:

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

dta$mrid: 44254401
     cheact           sd              n               dose          tmonstdy
 Min.   : 606   Min.   :132.0   Min.   : 9.000   Min.   :0.000   Min.   :0.00
 1st Qu.:1666   1st Qu.:287.8   1st Qu.:10.000   1st Qu.:0.075   1st Qu.:0.75
 Median :1817   Median :345.5   Median :10.000   Median :0.550   Median :1.00
 Mean   :1739   Mean   :352.4   Mean   : 9.969   Mean   :0.775   Mean   :0.75
 3rd Qu.:2012   3rd Qu.:404.2   3rd Qu.:10.000   3rd Qu.:1.250   3rd Qu.:1.00
 Max.   :2298   Max.   :570.0   Max.   :10.000   Max.   :2.000   Max.   :1.00
    tmpstds      sex          mrid    species
 Min.   : -1.0   F:16   44254401:32   RAT:32
 1st Qu.:  0.5   M:16   44472001: 0
 Median : 12.5          Padilla : 0
 Mean   : 96.0
 3rd Qu.:108.0
 Max.   :360.0
------------------------------------------------------------
dta$mrid: 44472001
     cheact           sd              n           dose        tmonstdy
 Min.   : 740   Min.   :172.0   Min.   :10   Min.   :0.0   Min.   :1
 1st Qu.:1776   1st Qu.:281.5   1st Qu.:10   1st Qu.:0.0   1st Qu.:1
 Median :1877   Median :320.0   Median :10   Median :0.5   Median :1
 Mean   :1820   Mean   :323.0   Mean   :10   Mean   :0.5   Mean   :1
 3rd Qu.:2038   3rd Qu.:355.2   3rd Qu.:10   3rd Qu.:1.0   3rd Qu.:1
 Max.   :2456   Max.   :472.0   Max.   :10   Max.   :1.0   Max.   :1
    tmpstds      sex         mrid    species
 Min.   :0.500   F:8   44254401: 0   RAT:16
 1st Qu.:1.625   M:8   44472001:16
 Median :2.500         Padilla : 0
 Mean   :2.375
 3rd Qu.:3.250
 Max.   :4.000
------------------------------------------------------------
```

```
dta$mrid: Padilla
     cheact             sd          n          dose           tmonstdy
 Min.   : 32.76   Min.   :0   Min.   :1   Min.   :0.0000   Min.   :1
 1st Qu.:113.44   1st Qu.:0   1st Qu.:1   1st Qu.:0.0833   1st Qu.:1
 Median :267.32   Median :0   Median :1   Median :1.0000   Median :1
 Mean   :259.49   Mean   :0   Mean   :1   Mean   :0.6751   Mean   :1
 3rd Qu.:409.32   3rd Qu.:0   3rd Qu.:1   3rd Qu.:1.0000   3rd Qu.:1
 Max.   :563.89   Max.   :0   Max.   :1   Max.   :1.5000   Max.   :1
    tmpstds        sex          mrid    species
 Min.   : 0.5000   F: 0   44254401: 0   RAT:59
 1st Qu.: 0.6667   M:59   44472001: 0
 Median : 0.6667          Padilla :59
 Mean   : 3.0847
 3rd Qu.: 1.5000
 Max.   :24.0000
```

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

         mrid tmonstdy     tmpstds
1083 44254401        0  -1.0000000
1087 44254401        1   1.0000000
1091 44254401        1  24.0000000
1095 44254401        1 360.0000000
1139 44472001        1   0.5000000
1140 44472001        1   2.0000000
1141 44472001        1   3.0000000
1142 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$mrid: 44254401
     tmpstds
dose  -1 1 24 360
  0   2  2 2  2
  0.1 2  2 2  2
  1   2  2 2  2
  2   2  2 2  2
------------------------------------------------------------
dta$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 and 44472001 are acute studies. Also, in 44254401, only the 1 hour time point is likely to be useful, since AChE activity should be at background by the next time point, 24 hours. Note the negative time in 44254401. This indicates pre-study baseline values (dose == 0). Set up a new dose variable, `dose2` that is 0 when `tmpstds` is negative. Since this study does not involve repeated measures, these extra groups are only useful for estimating variance.

```
> dta$dose2 <- ifelse(dta$tmpstds < 0, 0, dta$dose)
```

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 = ":"))
```

We only have useful time course data at a single dose, 1 mg/kg, in both the Padilla study and in 44472001. Thus, only a single value for `lTr` will be estimated.

2 Dose-Response Modeling

2.1 strategy

Use the model with simple exponential recovery (`tcmfn4()`). 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 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-RBC-DR-1.RData", sep = "")
> if (!file.exists(initfile)) {
```

```
+     lA.start <- lm(I(log(cheact)) ~ mridXsexXtmpstds - 1, data = CleanUp(subset(dta,
+         dose2 %in% 0)))
+     Start <- c(coef(lA.start), rep(log(0.5), nlevels(dta$mrid)),
+         0, -2, 0, log(1), 0, log(1.5))
+     init1 <- GetInitialValues(cbind(resp = cheact, sd = sd, n = n) ~
+         tcmfn4(dose2, tmpstds, lA = lA, tz = tz, lD = lD, lg = lg,
+             lTr = lTr), data = dta, params = list(lA ~ mridXsexXtmpstds -
+         1, lD ~ mrid + sex - 1, tz ~ sex, lg ~ sex, lTr ~ 1),
+         start = Start, weights = varComb(varIdent(form = ~1 |
+             mridXsex), varPower(value = 1)))
+     save(init1, file = initfile)
+ } else load(initfile)
> tmp <- t(init1$Redundancy[[1]]$Eigens)
> tmp <- tmp[-grep("^lA", rownames(tmp)), ]
> round(tmp[, 1:7], digits = 2)
```

```
                 [,1]  [,2] [,3] [,4] [,5] [,6] [,7]
CondIndex       52.22 20.38 7.53 3.58 2.89 2.76 2.52
mu               0.04  0.10 0.27 0.57 0.71 0.74 0.81
lD.mrid44254401  0.89  0.08 0.00 0.02 0.00 0.01 0.00
lD.mrid44472001  0.98  0.02 0.00 0.00 0.00 0.00 0.00
lD.mridPadilla   0.62  0.06 0.01 0.02 0.21 0.01 0.00
lD.sexM          0.34  0.65 0.00 0.01 0.00 0.00 0.00
tz.(Intercept)   0.10  0.01 0.67 0.10 0.01 0.00 0.02
tz.sexM          0.00  0.10 0.61 0.02 0.04 0.13 0.06
lg.(Intercept)   0.98  0.02 0.00 0.00 0.00 0.00 0.00
lg.sexM          0.63  0.36 0.00 0.00 0.00 0.00 0.00
lTr              0.00  0.00 0.94 0.01 0.00 0.00 0.00
```

The above shows the results of a redundancy analysis. The largest condition index is about 76, 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) -10.2  11.83117
tz.sexM         -4.1 743.96350
```

Set `tz` to -10, and do not estimate it. Rerun `GetInitialValues()` with this reduced model:

```
> formals(tcmfn4)$tz <- -10
> initfile <- paste("initvals-RBC-DR-2.RData", sep = "")
> if (!file.exists(initfile)) {
+     Start <- init1$start$beta
+     Start <- Start[-grep("^tz", names(Start))]
+     init2 <- GetInitialValues(cbind(resp = cheact, sd = sd, n = n) ~
+         tcmfn4(dose2, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr),
+         data = dta, params = list(lA ~ mridXsexXtmpstds - 1,
+             lD ~ mrid + sex - 1, lg ~ sex, lTr ~ 1), start = Start,
+         weights = varComb(varIdent(form = ~1 | mridXsex), varPower(value = 1)))
+     save(init2, file = initfile)
+ } else load(initfile)
> tmp <- t(init2$Redundancy[[1]]$Eigens)
> tmp <- tmp[-grep("^lA", rownames(tmp)), ]
> round(tmp[, 1:7], digits = 2)
```

```
                 [,1]  [,2] [,3] [,4] [,5] [,6] [,7]
CondIndex       53.78 21.53 4.11 3.59 3.13 2.84 2.53
mu               0.04  0.09 0.49 0.56 0.64 0.71 0.80
lD.mrid44254401  0.93  0.05 0.00 0.01 0.00 0.01 0.00
lD.mrid44472001  0.97  0.02 0.00 0.00 0.00 0.00 0.00
lD.mridPadilla   0.85  0.09 0.04 0.00 0.01 0.00 0.00
lD.sexM          0.46  0.53 0.01 0.00 0.00 0.00 0.00
lg.(Intercept)   0.97  0.03 0.00 0.00 0.00 0.00 0.00
lg.sexM          0.66  0.33 0.00 0.00 0.00 0.00 0.00
lTr              0.07  0.10 0.02 0.68 0.01 0.05 0.00
```

Fit the model first with `gnls()` to get the variance model right.

```
> Start <- Start0 <- init2$start$beta
> idta <- init2$data
> icnt <- 1
> Maxcnt <- 50
> repeat {
+     drmod1 <- try(gnls(cheact ~ tcmfn4(dose2, 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))
+ }
```

That fails with the error:

```
Error in gnls(cheact ~ tcmfn4(dose2, tmpstds, lA = lA, tz = tz, lD = lD,  :
        Step halving factor reduced below minimum in NLS step
```

Perhaps fitting a single value for `lg` would help?

```
> Start0 <- init2$start$beta
> Start0 <- Start0[-grep("lg\\.sexM", names(Start0))]
> Start <- Start0
> idta <- init2$data
> icnt <- 1
> Maxcnt <- 50
> repeat {
+     drmod1 <- try(gnls(cheact ~ tcmfn4(dose2, tmpstds, lA = lA,
+         lD = lD, lg = lg, lTr = lTr), data = idta, params = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ mrid + sex - 1, lg ~ 1, 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  6 tries
```

Now, two more models. The next one allows standard deviation to vary among studies, and the one after includes a power function in the model for the standard deviation:

```
> Start0 <- coef(drmod1)
> Start <- Start0
> idta <- init2$data
> icnt <- 1
> Maxcnt <- 50
> repeat {
+     drmod2 <- try(gnls(cheact ~ tcmfn4(dose2, tmpstds, lA = lA,
+         lD = lD, lg = lg, lTr = lTr), data = idta, params = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ mrid + sex - 1, lg ~ 1, 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  2 tries

> Start0 <- coef(drmod2)
> Start <- Start0
> idta <- init2$data
> icnt <- 1
> Maxcnt <- 50
> repeat {
+     drmod3 <- try(gnls(cheact ~ tcmfn4(dose2, tmpstds, lA = lA,
+         lD = lD, lg = lg, lTr = lTr), data = idta, params = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ mrid + sex - 1, lg ~ 1, lTr ~
+         1), 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 <- Start0 * (1 + rnorm(length(Start0), sd = 0.2))
+ }
```

```
Successful in  1 try
```

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

```
       Model df      AIC      BIC    logLik   Test   L.Ratio p-value
drmod1     1 29 7866.791 7991.139 -3904.396
drmod2     2 33 7716.478 7857.978 -3825.239 1 vs 2 158.31283  <.0001
drmod3     3 34 7693.675 7839.463 -3812.838 2 vs 3  24.80312  <.0001
```

Yes. We will use the model in `drmod3`.

Fit the same model as above as a mixed effect model, except just allow `lD` to vary among sexes, and include a random effect for the variation of `lD` among studies.

```
> 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(dose2, 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(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 6 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) -1.25703329 0.34184127 510 -3.677243 0.0002607887
lD.sexM        -0.09445415 0.07497211 510 -1.259857 0.2082971050
lg              0.59254674 0.27111108 510  2.185623 0.0292972526
lTr            -0.21498842 0.10713879 510 -2.006635 0.0453159131
```

Note, particularly, that the difference between the sexes in `lD` is not significant. Refit the data with the simpler term for `lD`:

```
> Par <- fixed.effects(drmod4)
> Start0 <- c(getParms("^lA", Par), Par["lD.(Intercept)"], getParms("^lg",
+     Par), 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(dose2, tmpstds, lA = lA,
+         lD = lD, lg = lg, lTr = lTr), data = idta, fixed = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ 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(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 2 trie(s).

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

Nonlinear mixed-effects model fit by maximum likelihood
  Model: cheact ~ tcmfn4(dose2, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr)
 Data: idta
       AIC      BIC    logLik
  7727.391 7864.602 -3831.696

Random effects:
 Formula: lD ~ 1 | mrid
                  lD Residual
StdDev: 1.117708e-05 11.36529

Combination of variance functions:
 Structure: Different standard deviations per stratum
 Formula: ~1 | mridXsex
 Parameter estimates:
```

```
44254401:M 44254401:F 44472001:M 44472001:F  Padilla:M
 1.0000000  0.9792244  0.9197067  0.8270580  0.4239227
 Structure: Power of variance covariate
 Formula: ~fitted(.)
 Parameter estimates:
    power
0.4730126
Fixed effects: list(lA ~ mridXsexXtmpstds - 1, lD ~ 1, lg ~ 1, lTr ~ 1)
                                                  Value Std.Error  DF
lA.mridXsexXtmpstds44254401:M:-1                 7.456166 0.0361749 511
lA.mridXsexXtmpstds44254401:M:1                  7.605601 0.0422251 511
lA.mridXsexXtmpstds44254401:M:24                 7.485578 0.0360723 511
lA.mridXsexXtmpstds44254401:M:360                7.502462 0.0353030 511
lA.mridXsexXtmpstds44254401:F:-1                 7.654680 0.0319048 511
lA.mridXsexXtmpstds44254401:F:1                  7.598350 0.0415990 511
lA.mridXsexXtmpstds44254401:F:24                 7.522400 0.0342082 511
lA.mridXsexXtmpstds44254401:F:360                7.448043 0.0355753 511
lA.mridXsexXtmpstds44472001:M:0.5                7.533742 0.0583052 511
lA.mridXsexXtmpstds44472001:M:2                  7.572896 0.0484468 511
lA.mridXsexXtmpstds44472001:M:3                  7.656083 0.0442008 511
lA.mridXsexXtmpstds44472001:M:4                  7.755198 0.0409054 511
lA.mridXsexXtmpstds44472001:F:0.5                7.727473 0.0483913 511
lA.mridXsexXtmpstds44472001:F:2                  7.663532 0.0420987 511
lA.mridXsexXtmpstds44472001:F:3                  7.557889 0.0419604 511
lA.mridXsexXtmpstds44472001:F:4                  7.583356 0.0402822 511
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  5.585252 0.0586797 511
lA.mridXsexXtmpstdsPadilla:M:0.5                 5.780334 0.1527479 511
lA.mridXsexXtmpstdsPadilla:M:1                   5.967646 0.1134421 511
lA.mridXsexXtmpstdsPadilla:M:1.5                 6.078887 0.0981966 511
lA.mridXsexXtmpstdsPadilla:M:4                   6.149186 0.0805505 511
lA.mridXsexXtmpstdsPadilla:M:24                  6.174154 0.0852413 511
lD                                              -1.279979 0.3502319 511
lg                                               0.605307 0.2727966 511
lTr                                             -0.205322 0.1068452 511
                                                  t-value p-value
lA.mridXsexXtmpstds44254401:M:-1                206.11430  0.0000
lA.mridXsexXtmpstds44254401:M:1                 180.12019  0.0000
lA.mridXsexXtmpstds44254401:M:24                207.51608  0.0000
lA.mridXsexXtmpstds44254401:M:360               212.51629  0.0000
lA.mridXsexXtmpstds44254401:F:-1                239.92248  0.0000
lA.mridXsexXtmpstds44254401:F:1                 182.65710  0.0000
lA.mridXsexXtmpstds44254401:F:24                219.90026  0.0000
lA.mridXsexXtmpstds44254401:F:360               209.35985  0.0000
lA.mridXsexXtmpstds44472001:M:0.5               129.21209  0.0000
lA.mridXsexXtmpstds44472001:M:2                 156.31355  0.0000
lA.mridXsexXtmpstds44472001:M:3                 173.21154  0.0000
lA.mridXsexXtmpstds44472001:M:4                 189.58883  0.0000
lA.mridXsexXtmpstds44472001:F:0.5               159.68734  0.0000
lA.mridXsexXtmpstds44472001:F:2                 182.03717  0.0000
lA.mridXsexXtmpstds44472001:F:3                 180.11939  0.0000
lA.mridXsexXtmpstds44472001:F:4                 188.25562  0.0000
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  95.18208  0.0000
lA.mridXsexXtmpstdsPadilla:M:0.5                 37.84232  0.0000
lA.mridXsexXtmpstdsPadilla:M:1                   52.60521  0.0000
```

```
lA.mridXsexXtmpstdsPadilla:M:1.5                61.90530  0.0000
lA.mridXsexXtmpstdsPadilla:M:4                  76.33954  0.0000
lA.mridXsexXtmpstdsPadilla:M:24                 72.43145  0.0000
lD                                              -3.65466  0.0003
lg                                               2.21889  0.0269
lTr                                             -1.92168  0.0552
 Correlation:
                                               lA.XX44254401:M:-
lA.mridXsexXtmpstds44254401:M:1                 0.000
lA.mridXsexXtmpstds44254401:M:24                0.000
lA.mridXsexXtmpstds44254401:M:360               0.000
lA.mridXsexXtmpstds44254401:F:-1                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                                              0.000
lg                                              0.000
lTr                                             0.000
                                               lA.XX44254401:M:1
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24                0.000
lA.mridXsexXtmpstds44254401:M:360               0.000
lA.mridXsexXtmpstds44254401:F:-1                0.000
lA.mridXsexXtmpstds44254401:F:1                 0.130
lA.mridXsexXtmpstds44254401:F:24                0.000
lA.mridXsexXtmpstds44254401:F:360               0.000
lA.mridXsexXtmpstds44472001:M:0.5               0.014
lA.mridXsexXtmpstds44472001:M:2                 0.097
lA.mridXsexXtmpstds44472001:M:3                 0.071
lA.mridXsexXtmpstds44472001:M:4                 0.044
lA.mridXsexXtmpstds44472001:F:0.5               0.017
lA.mridXsexXtmpstds44472001:F:2                 0.112
lA.mridXsexXtmpstds44472001:F:3                 0.074
lA.mridXsexXtmpstds44472001:F:4                 0.045
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.071
lA.mridXsexXtmpstdsPadilla:M:0.5                0.014
lA.mridXsexXtmpstdsPadilla:M:1                  0.082
lA.mridXsexXtmpstdsPadilla:M:1.5                0.099
lA.mridXsexXtmpstdsPadilla:M:4                  0.038
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
```

```
lD                                              -0.156
lg                                              -0.151
lTr                                              0.325
                                                lA.XX44254401:M:2
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360                0.000
lA.mridXsexXtmpstds44254401:F:-1                 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                                               0.000
lg                                               0.000
lTr                                              0.000
                                                lA.XX44254401:M:3
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:-1                 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                                               0.000
lg                                               0.000
lTr                                              0.000
                                                lA.XX44254401:F:-
```

```
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:-1
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                                              0.000
lg                                              0.000
lTr                                             0.000
                                               lA.XX44254401:F:1
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:-1
lA.mridXsexXtmpstds44254401:F:1
lA.mridXsexXtmpstds44254401:F:24                0.000
lA.mridXsexXtmpstds44254401:F:360               0.000
lA.mridXsexXtmpstds44472001:M:0.5               0.014
lA.mridXsexXtmpstds44472001:M:2                 0.098
lA.mridXsexXtmpstds44472001:M:3                 0.072
lA.mridXsexXtmpstds44472001:M:4                 0.045
lA.mridXsexXtmpstds44472001:F:0.5               0.017
lA.mridXsexXtmpstds44472001:F:2                 0.113
lA.mridXsexXtmpstds44472001:F:3                 0.076
lA.mridXsexXtmpstds44472001:F:4                 0.046
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.072
lA.mridXsexXtmpstdsPadilla:M:0.5                0.014
lA.mridXsexXtmpstdsPadilla:M:1                  0.084
lA.mridXsexXtmpstdsPadilla:M:1.5                0.100
lA.mridXsexXtmpstdsPadilla:M:4                  0.039
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lD                                             -0.158
lg                                             -0.153
lTr                                             0.330
                                               lA.XX44254401:F:2
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:-1
```

```
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                                               0.000
lg                                               0.000
lTr                                              0.000
                                               lA.XX44254401:F:3
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:-1
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                                               0.000
lg                                               0.000
lTr                                              0.000
                                               lA.XX44472001:M:0
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:-1
lA.mridXsexXtmpstds44254401:F:1
lA.mridXsexXtmpstds44254401:F:24
lA.mridXsexXtmpstds44254401:F:360
lA.mridXsexXtmpstds44472001:M:0.5
```

```
lA.mridXsexXtmpstds44472001:M:2                -0.001
lA.mridXsexXtmpstds44472001:M:3                -0.008
lA.mridXsexXtmpstds44472001:M:4                -0.007
lA.mridXsexXtmpstds44472001:F:0.5               0.104
lA.mridXsexXtmpstds44472001:F:2                -0.002
lA.mridXsexXtmpstds44472001:F:3                -0.008
lA.mridXsexXtmpstds44472001:F:4                -0.007
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.044
lA.mridXsexXtmpstdsPadilla:M:0.5                0.085
lA.mridXsexXtmpstdsPadilla:M:1                  0.034
lA.mridXsexXtmpstdsPadilla:M:1.5                0.010
lA.mridXsexXtmpstdsPadilla:M:4                 -0.006
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lD                                             -0.024
lg                                              0.006
lTr                                            -0.083
                                               lA.XX44472001:M:2
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:-1
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                 0.056
lA.mridXsexXtmpstds44472001:M:4                 0.036
lA.mridXsexXtmpstds44472001:F:0.5              -0.002
lA.mridXsexXtmpstds44472001:F:2                 0.087
lA.mridXsexXtmpstds44472001:F:3                 0.059
lA.mridXsexXtmpstds44472001:F:4                 0.036
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.054
lA.mridXsexXtmpstdsPadilla:M:0.5               -0.001
lA.mridXsexXtmpstdsPadilla:M:1                  0.059
lA.mridXsexXtmpstdsPadilla:M:1.5                0.076
lA.mridXsexXtmpstdsPadilla:M:4                  0.030
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lD                                             -0.141
lg                                             -0.141
lTr                                             0.266
                                               lA.XX44472001:M:3
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:-1
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                 0.027
lA.mridXsexXtmpstds44472001:F:0.5              -0.009
```

```
lA.mridXsexXtmpstds44472001:F:2                 0.065
lA.mridXsexXtmpstds44472001:F:3                 0.044
lA.mridXsexXtmpstds44472001:F:4                 0.027
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.036
lA.mridXsexXtmpstdsPadilla:M:0.5               -0.007
lA.mridXsexXtmpstdsPadilla:M:1                  0.041
lA.mridXsexXtmpstdsPadilla:M:1.5                0.055
lA.mridXsexXtmpstdsPadilla:M:4                  0.023
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lD                                             -0.102
lg                                             -0.105
lTr                                             0.203
                                               lA.XX44472001:M:4
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:-1
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              -0.008
lA.mridXsexXtmpstds44472001:F:2                 0.041
lA.mridXsexXtmpstds44472001:F:3                 0.028
lA.mridXsexXtmpstds44472001:F:4                 0.017
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.022
lA.mridXsexXtmpstdsPadilla:M:0.5               -0.006
lA.mridXsexXtmpstdsPadilla:M:1                  0.025
lA.mridXsexXtmpstdsPadilla:M:1.5                0.035
lA.mridXsexXtmpstdsPadilla:M:4                  0.015
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lD                                             -0.064
lg                                             -0.067
lTr                                             0.130
                                               lA.XX44472001:F:0
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:-1
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                -0.002
lA.mridXsexXtmpstds44472001:F:3                -0.010
lA.mridXsexXtmpstds44472001:F:4                -0.008
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.053
```

```
lA.mridXsexXtmpstdsPadilla:M:0.5                0.102
lA.mridXsexXtmpstdsPadilla:M:1                  0.041
lA.mridXsexXtmpstdsPadilla:M:1.5                0.012
lA.mridXsexXtmpstdsPadilla:M:4                 -0.007
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lD                                             -0.029
lg                                              0.008
lTr                                            -0.100
                                               lA.XX44472001:F:2
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:-1
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                 0.068
lA.mridXsexXtmpstds44472001:F:4                 0.042
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.062
lA.mridXsexXtmpstdsPadilla:M:0.5               -0.002
lA.mridXsexXtmpstdsPadilla:M:1                  0.068
lA.mridXsexXtmpstdsPadilla:M:1.5                0.087
lA.mridXsexXtmpstdsPadilla:M:4                  0.035
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lD                                             -0.162
lg                                             -0.163
lTr                                             0.306
                                               lA.XX44472001:F:3
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:-1
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                 0.029
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.038
lA.mridXsexXtmpstdsPadilla:M:0.5               -0.008
lA.mridXsexXtmpstdsPadilla:M:1                  0.043
lA.mridXsexXtmpstdsPadilla:M:1.5                0.058
lA.mridXsexXtmpstdsPadilla:M:4                  0.024
```

```
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lD                                             -0.108
lg                                             -0.111
lTr                                             0.214
                                               lA.XX44472001:F:4 lA.XXP:M:0.6
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:-1
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  0.022
lA.mridXsexXtmpstdsPadilla:M:0.5               -0.007             0.043
lA.mridXsexXtmpstdsPadilla:M:1                  0.026             0.060
lA.mridXsexXtmpstdsPadilla:M:1.5                0.035             0.059
lA.mridXsexXtmpstdsPadilla:M:4                  0.015             0.019
lA.mridXsexXtmpstdsPadilla:M:24                 0.000             0.000
lD                                             -0.065            -0.271
lg                                             -0.068            -0.257
lTr                                             0.132             0.147
                                               lA.XXP:M:0.5 lA.mXXP:M:1
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:-1
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                  0.033
lA.mridXsexXtmpstdsPadilla:M:1.5                0.009        0.064
lA.mridXsexXtmpstdsPadilla:M:4                 -0.006        0.022
lA.mridXsexXtmpstdsPadilla:M:24                 0.000        0.000
lD                                             -0.023       -0.121
lg                                              0.006       -0.109
lTr                                            -0.081        0.176
```

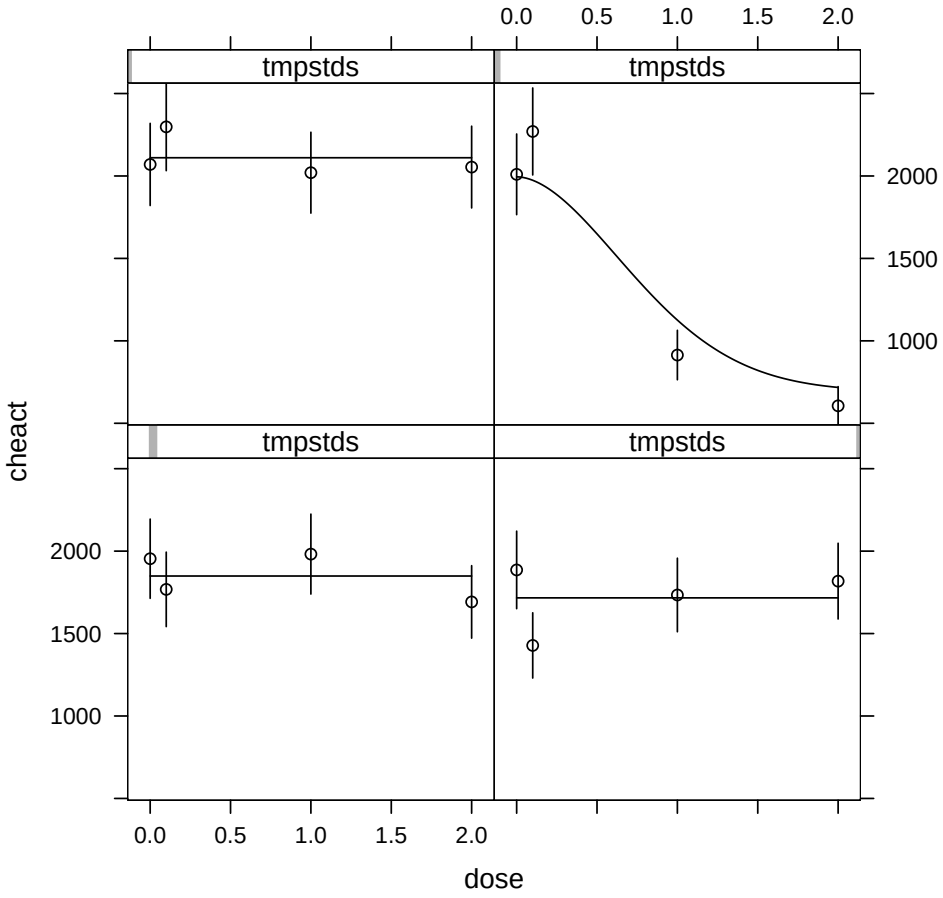
```
                                                lA.XXP:M:1. lA.XXP:M:4
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:-1
lA.mridXsexXtmpstds44254401:F:1
lA.mridXsexXtmpstds44254401:F:24
lA.mridXsexXtmpstds44254401:F:360
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                   0.030
lA.mridXsexXtmpstdsPadilla:M:24                  0.000       0.000
lD                                              -0.144      -0.055
lg                                              -0.141      -0.057
lTr                                              0.255       0.111
                                                lA.XXP:M:2 lD     lg
lA.mridXsexXtmpstds44254401:M:1
lA.mridXsexXtmpstds44254401:M:24
lA.mridXsexXtmpstds44254401:M:360
lA.mridXsexXtmpstds44254401:F:-1
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                                               0.000
lg                                               0.000      0.995
lTr                                              0.000     -0.469 -0.499

Standardized Within-Group Residuals:
        Min          Q1         Med          Q3         Max
-2.30888126 -0.71018871 -0.08127139  0.57584835  3.35409941
```

```
Number of Observations: 538
Number of Groups: 3
```

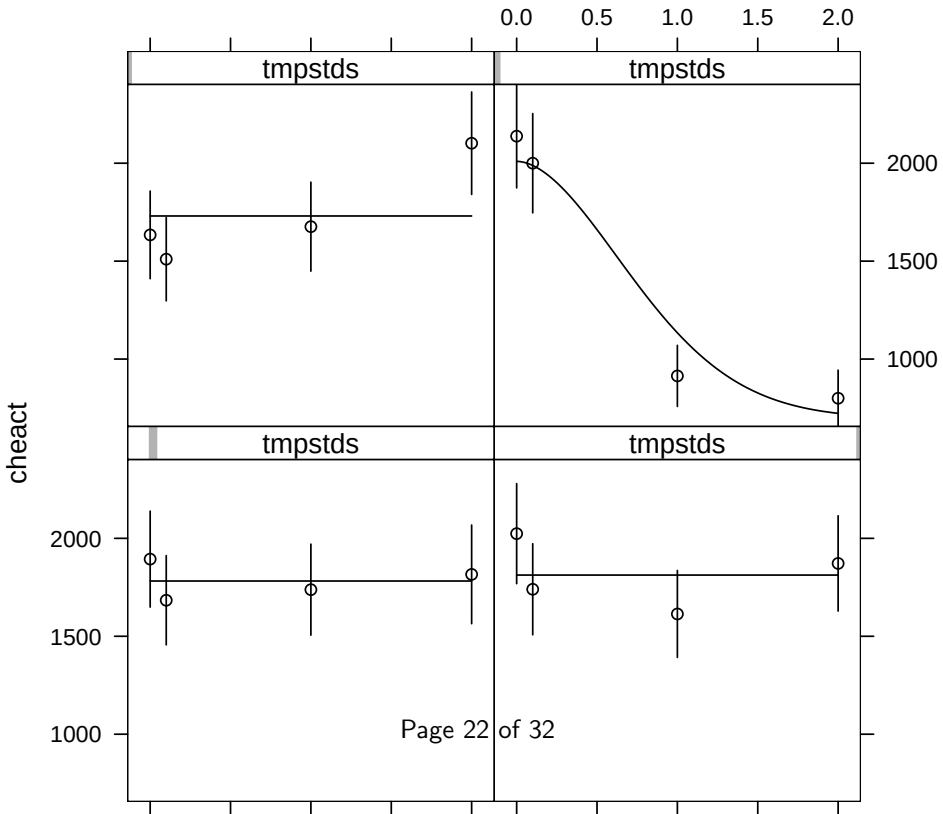
Diagnostic plots for this model: Plots of data with 95% CI and fitted curve for each combination of mrid and sex. First set up the data set and predicted values for plotting.

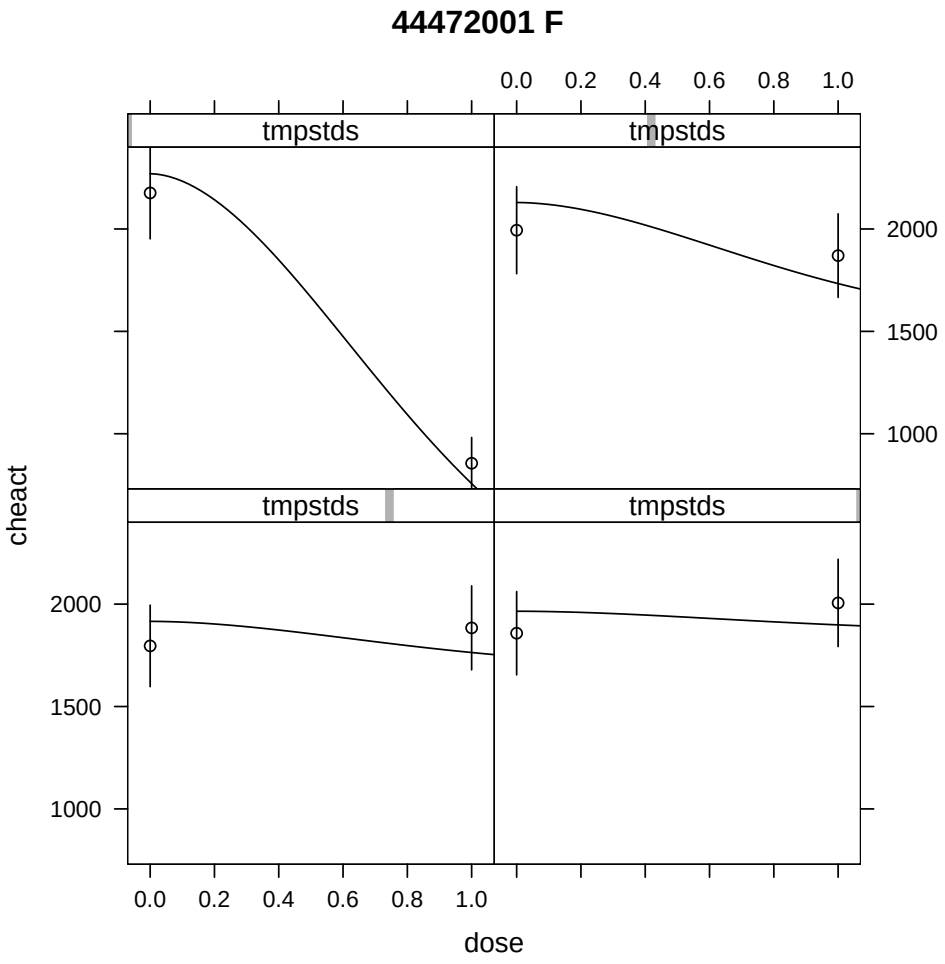
```
> tdta <- local({
+     idta <- with(dta, PhonyDF(dose, n, cheact, sd, "dose", "cheact",
+         Avals = list(mrid = mrid, sex = sex, tmpstds = tmpstds)))
+     idta$mridXsex <- with(idta, interaction(mrid, sex, drop = TRUE,
+         sep = ":"))
+     idta$mridXsexXtmpstdsXdose <- with(idta, interaction(mrid,
+         sex, tmpstds, dose, sep = ":", drop = TRUE))
+     out <- gls(cheact ~ mridXsexXtmpstdsXdose - 1, data = idta,
+         weights = varComb(varIdent(form = ~1 | mridXsex), varPower(value = 0.5)))
+     Ints <- intervals(out, which = "coef")$coef
+     nms <- gsub("mridXsexXtmpstdsXdose", "", rownames(Ints))
+     sstr <- strsplit(nms, ":")
+     data.frame(cheact = Ints[, "est."], llim = Ints[, "lower"],
+         ulim = Ints[, "upper"], mrid = factor(sapply(sstr, function(x) x[1])),
+         sex = factor(sapply(sstr, function(x) x[2])), tmpstds = as.numeric(sapply(sstr,
+             function(x) x[3])), dose = as.numeric(sapply(sstr,
+             function(x) x[4])))
+ })
> ndta <- expand.grid(dose2 = seq(0, max(tdta$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$tmpstds <- as.numeric(sapply(sstr, function(x) x[3]))
> tmp <- drmod5
> tmp$contrasts <- NULL
> ndta$pred <- predict(tmp, newdata = ndta)
```

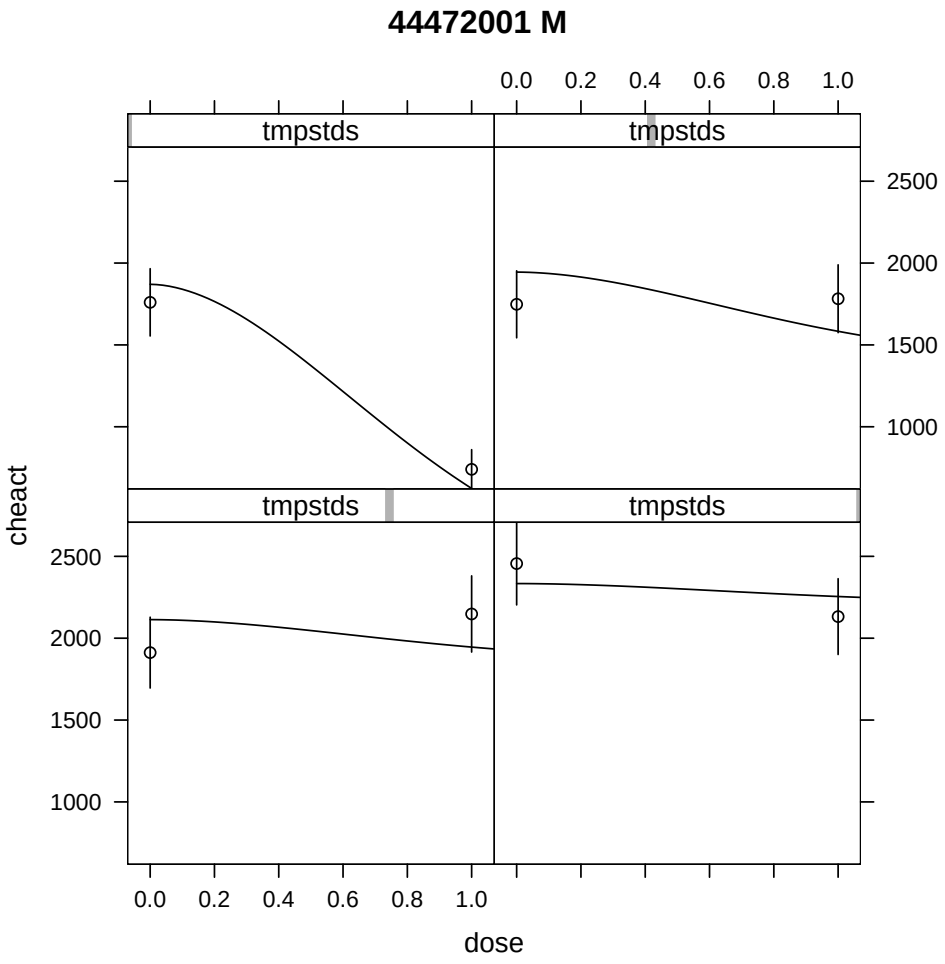
44254401 F

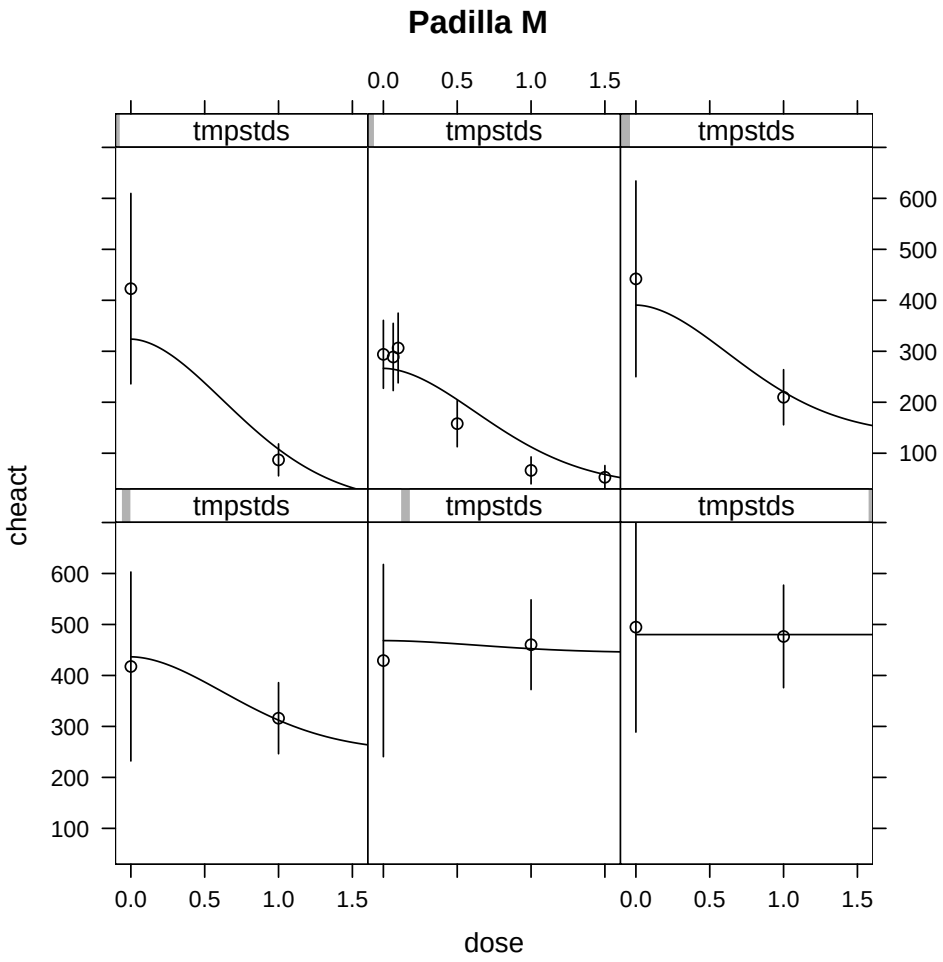


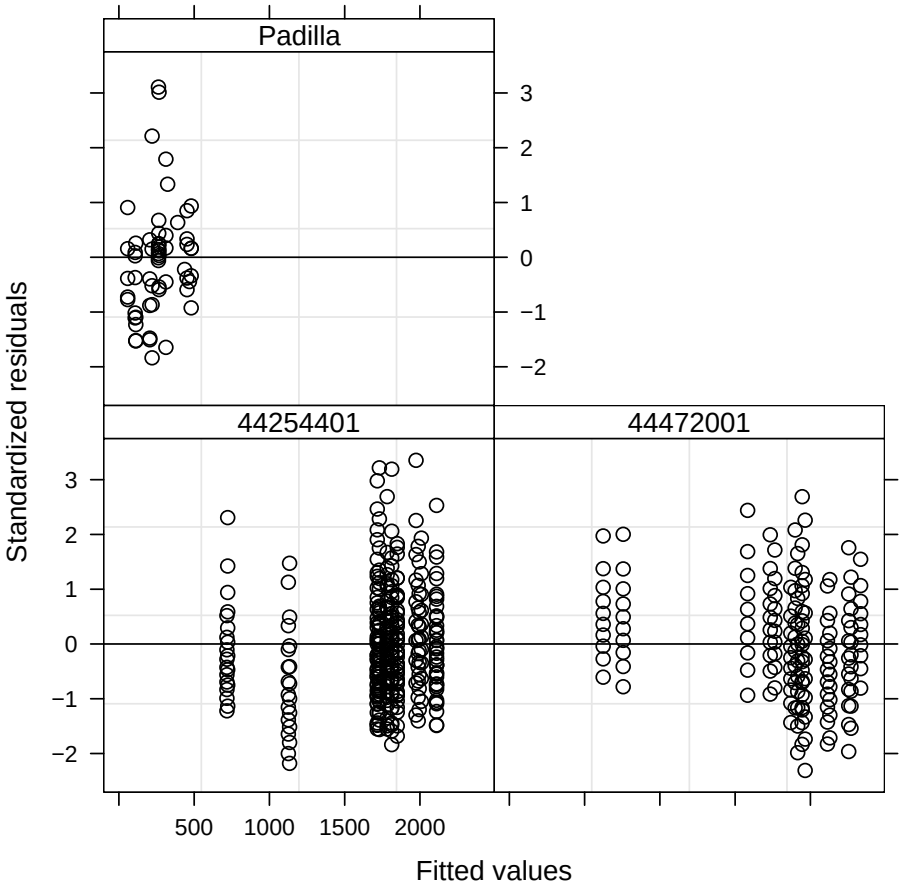
44254401 M

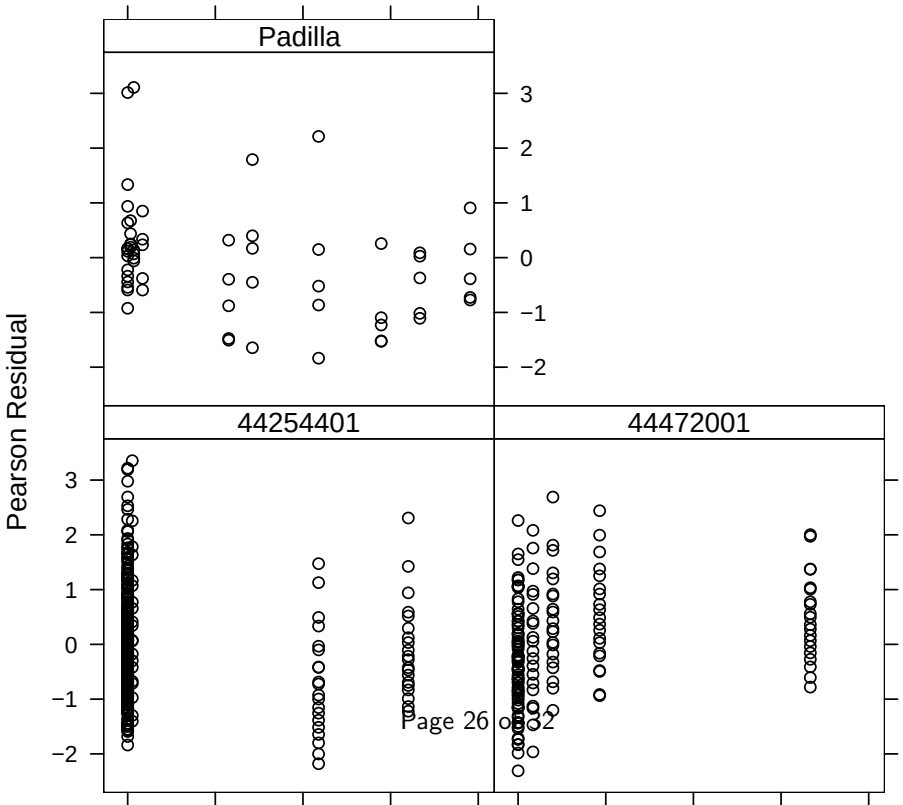


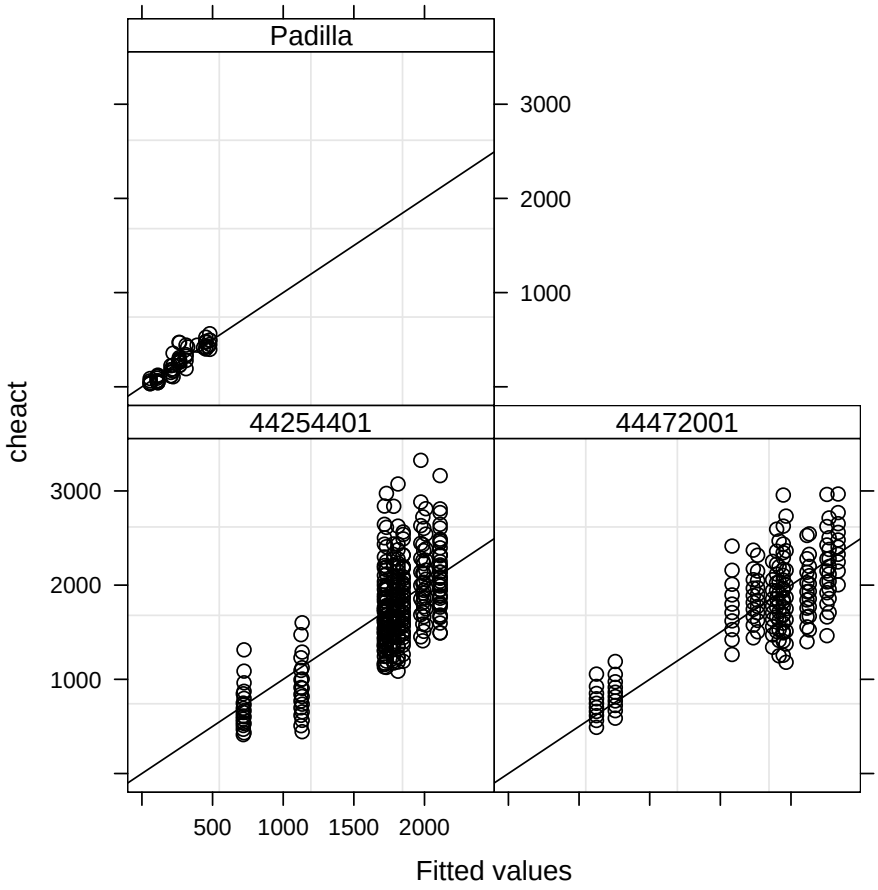

44472001 F
tmpstds
tmpstds
tmpstds
tmpstds
cheact
dose
0.0
0.2
0.4
0.6
0.8
1.0
1000
1500
2000

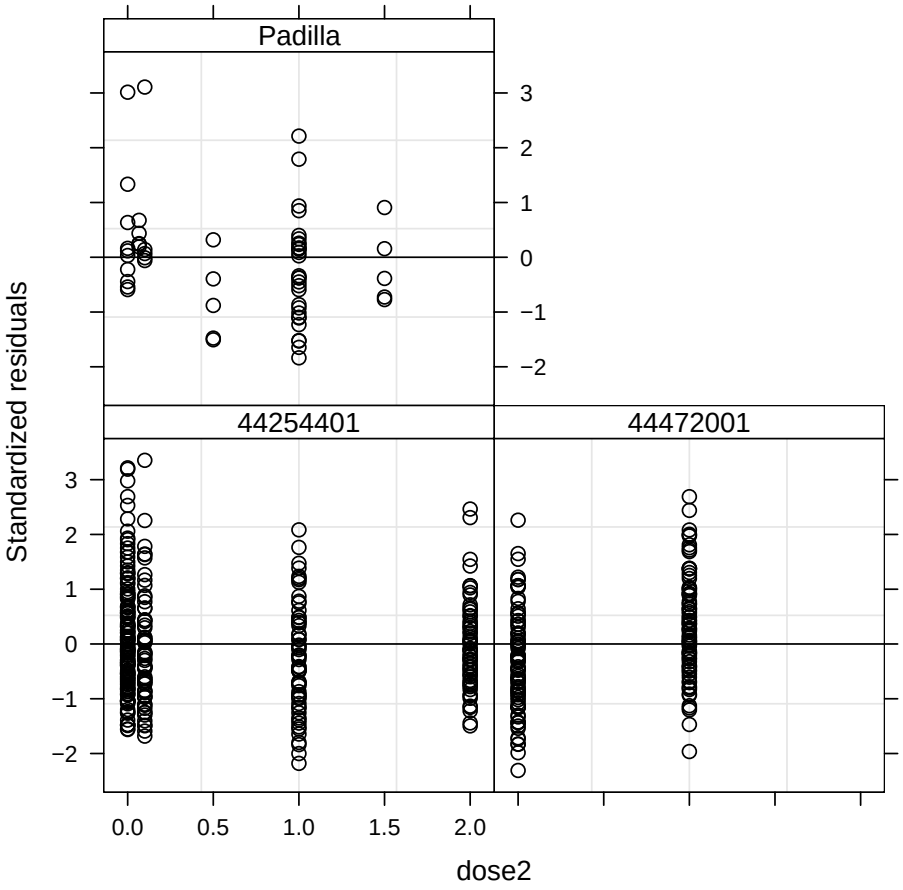

44472001 M
tmpstds
tmpstds
tmpstds
tmpstds
cheact
dose
0.0
0.2
0.4
0.6
0.8
1.0
1000
1500
2000
2500

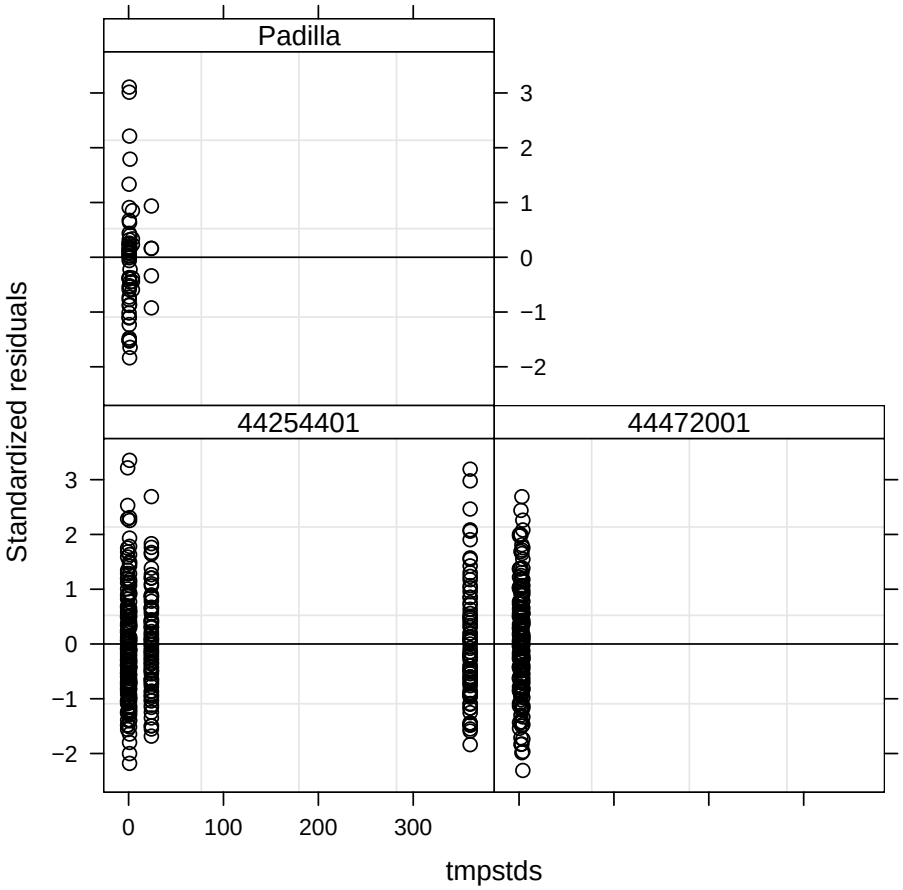

Padilla M
tmpstds
tmpstds
tmpstds
tmpstds
tmpstds
tmpstds
cheact
dose
0.0
0.5
1.0
1.5
100
200
300
400
500
600


Padilla
44254401
44472001
Standardized residuals
Fitted values
500
1000
1500
2000
3
2
1
0
−1
−2


Padilla
44254401
44472001
Pearson Residual
3
2
1
0
−1
−2

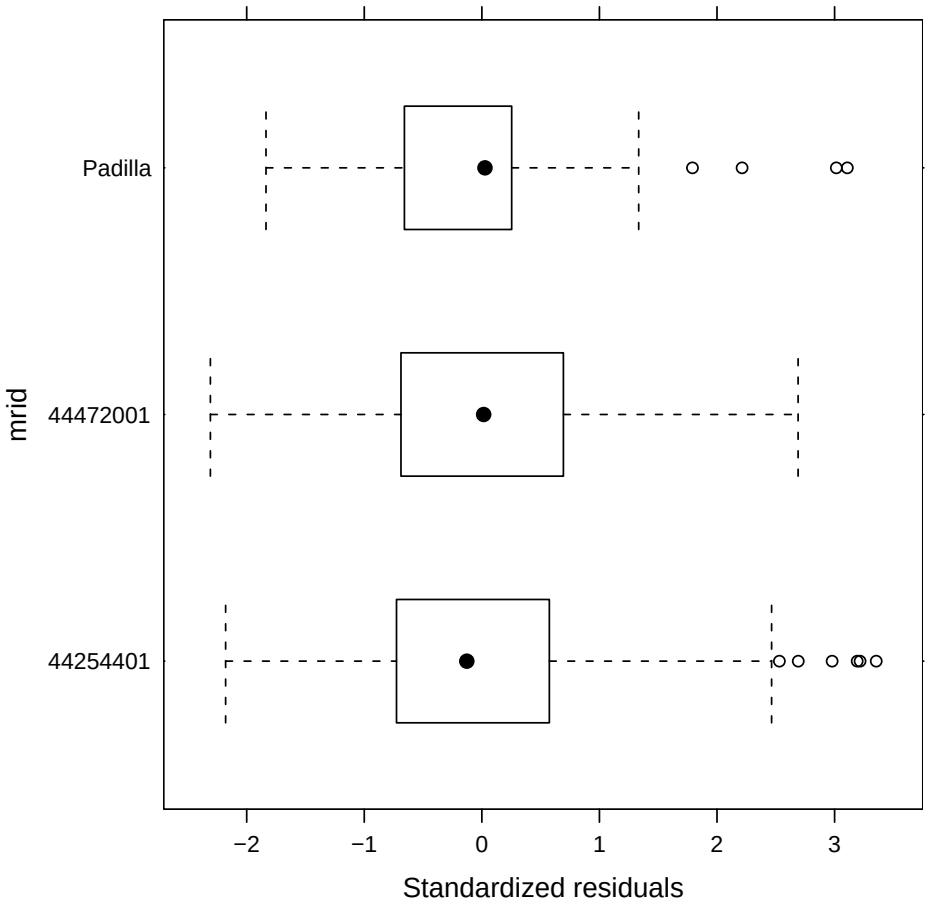

Padilla
44254401
44472001
cheact
3000
2000
1000
500
1000
1500
2000
Fitted values

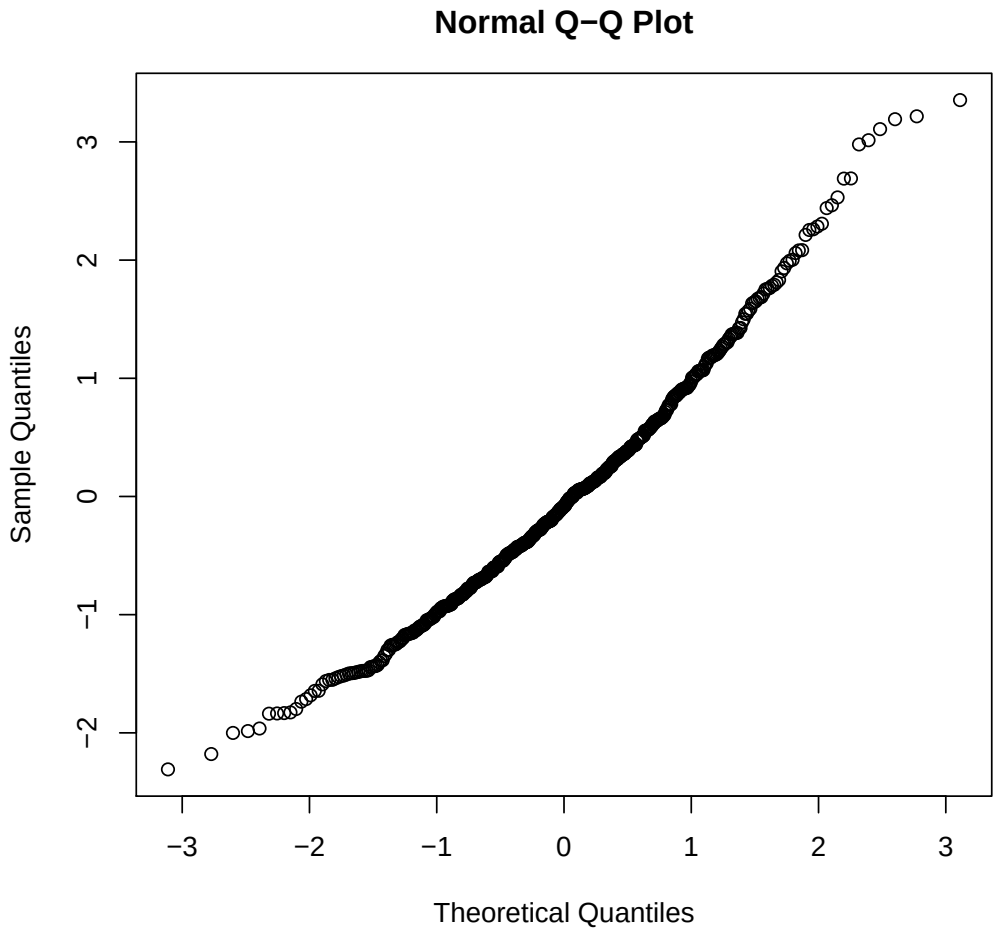

Padilla
44254401
44472001
Standardized residuals
dose2
3
2
1
0
−1
−2
0.0
0.5
1.0
1.5
2.0



Some more graphs:

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


Padilla
44472001
44254401
mrid
−2
−1
0
1
2
3
Standardized residuals



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. In these data, the BMD does not differ 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" "44472001" "Padilla"`

`lD` **(se)** -1.27997919150442 (0.350231860007029)

BMD (95% CI) 0.278043086051326 (0.142007731123985, 0.544392598128677)

BMDL, the one-sided lower 95% CL 0.158256674891678

`lTr (standard error)` -0.20532182636547 (0.106845209931516)

Recovery Half-life (95% CI) 0.81438518360932 (0.663453399067728, 0.999653070154337)

Save the results:

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

Save the results for incorporating into a database:

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