Logistic (RLOGIST) Example #2

SUDAAN Statements and Results Illustrated

- Zeger and Liang's SE method
- Naïve SE method
- Conditional marginals
- REFLEVEL
- SETENV

Input Data Set(s): BRFWGT.SAS7bdat

Example

Teratology Experiment, Clustered Binary Data: Evaluation of the Compound DEHP on Fetal Death.

This example demonstrates the GEE model-fitting techniques (Zeger and Liang, 1986; Liang and Zeger, 1986) in the context of a typical teratology experiment (cluster-correlated data).

This example also features the estimation of conditional marginals and their 95% confidence limits.

Solution

The typical teratology screening experiment involves administration of a compound to pregnant dams of a given animal species, followed by evaluation of the fetuses just prior to the end of gestation for various types of malformations. The experimental groups consist of a control group and anywhere from two to four exposed groups, representing increasing dosages of the compound under test. The data for this example have been taken from Butler (1988) and represent fetal death in CD-1 mice after administration of the compound DEHP at dosages of 0, 250, 500, 1000, or 1500 ppm during gestation. Sample sizes ranged from 24 to 30 litters per group. As reported by Butler, the average litter sizes were slightly larger in the control (13.2) vs. all other dose groups (11.5 to 12.3), but a dose-related trend was not evident for these data. ***Exhibit 1*** shows the structure of the data.

Exhibit 1. Structure of the Fetal Death Data

Dose Group 1 = Control, 2 = High Dose	**Litter ID**	**Fetus ID**	**Y = fetal death** 0 = alive, 1= dead
1	1	1	0
1	1	2	1
1	1	3	0
1	2	1	0
1	2	2	0
2	10	1	0
2	10	2	1
2	20	1	1
2	20	2	1
2 . . .	30 . . .	1 . . .	1 . . .

N = 1,619 records on the file
(1,619 fetuses clustered within 131 litters)

In this example, the observations on fetuses are clustered within litters, and the variance estimation techniques in SUDAAN are directly applicable for accounting for the intralitter correlation. The SUDAAN DESCRIPT and RLOGIST programs are used to:

1) estimate and compare dose-specific descriptive statistics (via PROC DESCRIPT) and

2) fit logistic dose-response models (via PROC RLOGIST) based on the teratology experiment. The logistic models are fit using the GEE methodology of Zeger and Liang (1986), comparing independent vs. exchangeable working correlations.

This example was run in SAS-Callable SUDAAN, and the SAS program and *.LST files are provided.

The sample design option WR (with replacement sampling) on the RLOGIST and DESCRIPT procedure statements invokes the robust variance estimator appropriate for these experimental data. The NEST statement in SUDAAN indicates that litters (represented by DAM) are the clusters.

The variable DEAD (0 vs 1) appears on the VAR statement, and the CATLEVEL statement indicates that we want to estimate totals and percentages for DEAD=1.

DOSE_5 is specified on the SUBGROUP statement in DESCRIPT. Since there is no TABLES statement, DESCRIPT will produce a 1-way table defined by DOSE_5.

The SETENV and PRINT statements are optional. SETENV defines default formats for printed results, and the PRINT statement further customizes the output by requesting specific statistics with user-defined labels and formats. The RFORMAT statement associates SAS formats with variables.

Exhibit 2. SAS-Callable SUDAAN Code (1st Call to DESCRIPT)

```
libname in v604 "c:\11winbetatest\CIs for Marginals\Logistic\Teratology Manual
                 Example";

proc format;
  value dead 1="1=Yes"
             0="0=No";
  value dose 1="1=Control"
             2="2=250 ppm"
             3="3=500 ppm"
             4="4=1000 ppm"
             5="5=1500 ppm";

data one; set in.terata;
proc sort data=one; by dam;

PROC DESCRIPT DATA=one FILETYPE=SAS NOMARG DESIGN=WR ATLEVEL1=2;
  NEST _ONE_ DAM;
  WEIGHT _ONE_;

  VAR DEAD;
  CATLEVEL 1;

  SUBGROUP DOSE_5;
  LEVELS   5;

  SETENV LABWIDTH=16 COLWIDTH=8 DECWIDTH=2;
  PRINT ATLEV1="LITTERS"
        NSUM="FETUSES"
        TOTAL="DEAD"
        PERCENT="PCT DEAD"
        SEPERCENT="SE"
        DEFFPCT="DESIGN EFFECT"/
        STYLE=NCHS ATLEV1FMT=F7.0 NSUMFMT=F7.0 DEFFPCTFMT=F6.2 TOTALFMT=F5.0;
  RFORMAT DOSE_5 dose.;
  RFORMAT DEAD dead.;
  RTITLE "Group Statistics for Teratology Data";
  RFOOTNOTE "Fetal Death in CD-1 Mice";
```

Exhibit 3. First Page of SUDAAN Output (SAS *.LST File)

```
                                S U D A A N
            Software for the Statistical Analysis of Correlated Data
           Copyright      Research Triangle Institute   February 2011
                                Release 11.0.0


DESIGN SUMMARY: Variances will be computed using the Taylor Linearization Method,
Assuming a With Replacement (WR) Design
    Sample Weight: _ONE_
    Stratification Variables(s): _ONE_
    Primary Sampling Unit: DAM


Number of observations read    :   1619    Weighted count :     1619
Denominator degrees of freedom :    130
```

Exhibit 4. Descriptive Statistics (TABLECELL Group)

```
Variance Estimation Method: Taylor Series (WR)

Group Statistics for Teratology Data

by: Variable, DOSE GROUP.

------------------------------------------------------------------------------
Variable
   DOSE GROUP                                                          DESIGN
                    LITTERS   FETUSES    DEAD   PCT DEAD         SE   EFFECT
------------------------------------------------------------------------------
DEAD: 1=Yes
   1=Control             30       396      66      16.67       4.11     4.81
   2=250 ppm             26       320      32      10.00       1.53     0.83
   3=500 ppm             26       319      42      13.17       1.84     0.94
   4=1000 ppm            24       276     139      50.36       7.44     6.09
   5=1500 ppm            25       308     258      83.77       4.65     4.88
------------------------------------------------------------------------------
Fetal Death in CD-1 Mice
```

There are 1,619 pups on the file and 130 denominator degrees of freedom (number of litters - 1) available for computing variance estimates (see ***Exhibit 3***).

The results in ***Exhibit 4*** indicate that the incidence of fetal death was lowest in the control, 250 ppm, and 500 ppm groups (17%, 10%, and 13%, respectively) and highest in the 1000 ppm and 1500 ppm groups (50% and 84%, respectively). The SEs produced by SUDAAN are adjusted for intralitter correlation.

Exhibit 4 also contains design effects for the binomial-based percentages. The design effect measures the inflation (or deflation) in variance of a sample statistic due to intracluster correlation beyond that expected if the data were independent. It is estimated as the ratio of the cluster sample variance obtained through Taylor linearization ($V_{Cluster}$) vs. that obtained under the assumption of independence (V_{Indep}).

The predicted design effect for a mean or proportion is directly proportional to the size of the intracluster correlation and the cluster size (Kish and Frankel, 1974)

$$\text{DEFF} = 1 + \rho(m\text{-}1),$$

where m is the constant cluster size, and ρ is the intracluster correlation. Neuhaus and Segal (1993) showed that this relationship also provides accurate design effect approximations for coefficients from binary response regression models with exchangeable correlations, a single cluster-level covariate, and

variable cluster sizes. In the case of unequal cluster sizes, it has been recommended that *m* be replaced by a weighted analogue

$$\tilde{m} = \frac{\sum_i \sum_j m_{mij}^2}{\sum_i \sum_j m_{ij}} \quad ,$$

where m_{ij} is the cluster size for the *j*-th litter in dose group *i*.

Observed design effects $(V_{Cluster} / V_{Indep})$ for the dose-specific percentages ranged from 0.83 to 6.09 for these data (see ***Exhibit 4***). The 250 and 500 ppm groups had design effects just under 1.0, indicating small but slightly negative intralitter correlations. Using the Pearson correlation coefficient, Butler reported intracluster correlations of -0.01 in each of these two groups. The control and higher dose groups had correlations closer to 0.3 and 0.4, and we detected substantial design effects near 5.0 and above in these groups, indicating greater than a fivefold increase in the strictly binomial variance due to intralitter correlation. The observed design effects closely corresponded to the predicted values in each group, with predictions based on the dose-specific weighted litter sizes and correlations estimated by Butler.

Exhibit 5. SAS-Callable SUDAAN Code (2nd Call to DESCRIPT)

```
PROC DESCRIPT DATA=ONE FILETYPE=SAS NOMARG DESIGN=WR;
  NEST _ONE_ DAM;
  WEIGHT _ONE_;

  VAR DEAD;
  CATLEVEL 1;

  SUBGROUP DOSE_5;
  LEVELS   5;
  CONTRAST DOSE_5 = (-1 1 0 0 0) / NAME = "Low Dose  Vs. Control";
  CONTRAST DOSE_5 = (-1 0 1 0 0) / NAME = "500 ppm   Vs. Control";
  CONTRAST DOSE_5 = (-1 0 0 1 0) / NAME = "1000 ppm  Vs. Control";
  CONTRAST DOSE_5 = (-1 0 0 0 1) / NAME = "High Dose Vs. Control";

  SETENV LABWIDTH=25 COLWIDTH=7 DECWIDTH=2 ;
  PRINT PERCENT="DIFF"
        SEPERCENT="SE"
        T_PCT="T-STAT"
        P_PCT="P-VALUE"/
        STYLE=NCHS SEPERCENTFMT=F6.2 T_PCTFMT=F6.2 P_PCTFMT=F7.4;
  RFORMAT DOSE_5 dose.;
  RFORMAT DEAD dead.;
  RTITLE "Group Comparisons for Teratology Data";
  RFOOTNOTE "Fetal Death in CD-1 Mice";
```

Here we construct contrasts to compare the percentages of dead pups in each dose group compared to controls. We used the CATLEVEL statement to estimate differences in percentages instead of proportions (the response DEAD is a 0-1 variable). The design option and NEST statements are the same as in the previous program. There are 1,619 pups on the file and 130 denominator degrees of freedom (number of litters - 1) available for computing variance estimates (see ***Exhibit 6***).

Exhibit 6. First Page of SUDAAN Output (2nd Call to DESCRIPT)

```
                                S U D A A N
           Software for the Statistical Analysis of Correlated Data
          Copyright      Research Triangle Institute   February 2011
                                 Release 11.0


DESIGN SUMMARY: Variances will be computed using the Taylor Linearization Method,
Assuming a With Replacement (WR) Design
    Sample Weight: _ONE_
    Stratification Variables(s): _ONE_
    Primary Sampling Unit: DAM


Number of observations read    :   1619    Weighted count :     1619
Denominator degrees of freedom :    130
```

Exhibit 7. Contrast Estimates (TABLECELL Group, 2nd Call to DESCRIPT)

```
Variance Estimation Method: Taylor Series (WR)

Group Comparisons for Teratology Data

for: Variable = DEAD: 1=Yes.
-----------------------------------------------------------------
CONTRAST                        DIFF       SE   T-STAT   P-VALUE
-----------------------------------------------------------------
Low Dose  Vs. Control          -6.67     4.39    -1.52    0.1310
500 ppm   Vs. Control          -3.50     4.51    -0.78    0.4386
1000 ppm  Vs. Control          33.70     8.50     3.96    0.0001
High Dose Vs. Control          67.10     6.21    10.81    0.0000
-----------------------------------------------------------------
Fetal Death in CD-1 Mice
```

Here we see that the High Dose (1500 ppm) and 1,000 ppm groups have significantly higher fetal death rates than the control group (***Exhibit 7***).

The results of regression modeling are presented next. There are two calls to RLOGIST. In the first call, below, we implement the cluster sample methods by estimating the model parameters under a standard binomial likelihood (R=independent) and computing the Zeger-Liang robust variance estimate (SEMETHOD=Zeger). This is also known as ordinary logistic regression (OLR) with a variance correction, and it is equivalent to a GEE logistic model with independent "working" correlations (which we refer to as GEE-independent). The Wald-*F* test was used to evaluate the null hypothesis of no treatment effect.

Dose group is modeled as a five-level categorical covariate on the CLASS statement. The REFLEVEL statement is used to select dose group level 1 (controls) to be the reference level for DOSE_5 in the model. The EFFECTS statement is used to compared the high dose to controls, and the CONDMARG statement requests model-adjusted risks for each level of DOSE_5.

Exhibit 8. SAS-Callable SUDAAN Code (1st Call to RLOGIST)

```
PROC RLOGIST DATA=one FILETYPE=SAS DESIGN=WR R=independent SEMETHOD=Zeger;
  NEST _ONE_ DAM;
  WEIGHT _ONE_;

  CLASS DOSE 5;
  REFLEVEL DOSE_5 = 1;
  MODEL DEAD = DOSE 5;
  EFFECTS DOSE_5 = (-1 0 0 0 1) / NAME = "Control vs. High Dose";
  CONDMARG DOSE_5;

  SETENV COLSPCE=2 LABWIDTH=22 COLWIDTH=7 DECWIDTH=4 TOPMGN=0;
  PRINT / betas=default risk=default tests=default cond_mrg=default
          t_betafmt=f7.2 waldffmt=f8.2 dffmt=f7.0 orfmt=f10.3 loworfmt=f8.3
          uporfmt=f8.3 condmrgfmt=f11.4 lowcmfmt=f9.4 upcmfmt=f9.4
          t_cndmrgfmt=f8.2;
  RFORMAT DOSE_5 dose.;
  RFORMAT DEAD dead.;
  RTITLE "Dose Group Effect:  GEE-Independent";
  RFOOTNOTE "Fetal Death in CD-1 Mice";
```

Exhibit 9. First Page of SUDAAN Output (1st Call to RLOGIST)

```
                                S U D A A N
           Software for the Statistical Analysis of Correlated Data
         Copyright      Research Triangle Institute     February 2011
                               Release 11.0.0


DESIGN SUMMARY: Variances will be computed using the Taylor Linearization Method, Assuming a
With Replacement (WR) Design
    Sample Weight: _ONE_
    Stratification Variables(s): _ONE_
    Primary Sampling Unit: DAM

Number of zero responses     :  1082
Number of non-zero responses :   537

Independence parameters have converged in 7 iterations

Number of observations read       :   1619    Weighted count:     1619
Observations used in the analysis :   1619    Weighted count:     1619
Denominator degrees of freedom    :    130

Maximum number of estimable parameters for the model is  5

File ONE contains  131 Clusters
 131 clusters were used to fit the model
Maximum cluster size is  19 records
Minimum cluster size is   1 records

Sample and Population Counts for Response Variable DEAD
Based on observations used in the analysis
0:  Sample Count     1082    Population Count      1082
1:  Sample Count      537    Population Count       537

R-Square for dependent variable DEAD (Cox & Snell, 1989): 0.304579

-2 * Normalized Log-Likelihood with Intercepts Only :  2057.32
-2 * Normalized Log-Likelihood Full Model           :  1469.23
Approximate Chi-Square (-2 * Log-L Ratio)           :   588.08
Degrees of Freedom                                  :        4

Note: The approximate Chi-Square is not adjusted for clustering.
      Refer to hypothesis test table for adjusted test.
```

The *R*-square statistic is based on Cox and Snell (1989) and indicates the proportion of the log-likelihood that is explained by the model. Out of the 1,619 observations read and used in the analysis, there were 537 fetal deaths (see ***Exhibit 9***).

Exhibit 10. Frequencies and Values for CLASS Variables (DOSE_5)

Frequencies and Values for CLASS Variables
by: DOSE GROUP.

DOSE GROUP	Frequency	Value
Ordered Position: 1	396	1=Control
Ordered Position: 2	320	2=250 ppm
Ordered Position: 3	319	3=500 ppm
Ordered Position: 4	276	4=1000 ppm
Ordered Position: 5	308	5=1500 ppm

Exhibit 11. Regression Coefficients (BETAS Group, 1st Call to RLOGIST)

Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Logit
Response variable DEAD: DEAD

Dose Group Effect: GEE-Independent

by: Independent Variables and Effects.

Independent Variables and Effects	Beta Coeff.	SE Beta	Lower 95% Limit Beta	Upper 95% Limit Beta	T-Test B=0	P-value T-Test B=0
Intercept	-1.6094	0.2961	-2.1951	-1.0237	-5.44	0.0000
DOSE GROUP						
1=Control	0.0000	0.0000	0.0000	0.0000	.	.
2=250 ppm	-0.5878	0.3413	-1.2629	0.0874	-1.72	0.0874
3=500 ppm	-0.2769	0.3370	-0.9437	0.3899	-0.82	0.4128
4=1000 ppm	1.6239	0.4197	0.7935	2.4543	3.87	0.0002
5=1500 ppm	3.2504	0.4523	2.3556	4.1451	7.19	0.0000

Fetal Death in CD-1 Mice

The above regression coefficients (***Exhibit 11***) and *p*-values indicate that the log-odds of fetal death is significantly increased in the two highest dose groups compared to controls. The standard errors, confidence limits, and *p*-values are all adjusted for clustering.

Exhibit 12. ANOVA Table (TESTS Group, 1st Call to RLOGIST)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Logit
Response variable DEAD: DEAD

Dose Group Effect:  GEE-Independent

by: Contrast.
-------------------------------------------------------
Contrast                 Degrees
                         of                   P-value
                         Freedom     Wald F   Wald F
-------------------------------------------------------
OVERALL MODEL                 5      71.45    0.0000
MODEL MINUS INTERCEPT         4      33.23    0.0000
INTERCEPT                     .         .         .
DOSE_5                        4      33.23    0.0000
Control vs. High Dose         1      51.65    0.0000
-------------------------------------------------------
Fetal Death in CD-1 Mice
```

Exhibit 12 indicates that the overall effect of DOSE_5 is statistically significant. The contrast on the EFFECTS statement (Control vs. High Dose) is also significant. Note that this result is also duplicated in the regression coefficient table above, since the control group is specified as the reference level.

Exhibit 13. Odds Ratios (RISK Group, 1st Call to RLOGIST)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Logit
Response variable DEAD: DEAD

Dose Group Effect:  GEE-Independent

by: Independent Variables and Effects.
-----------------------------------------------------------
Independent Variables
  and Effects                          Lower      Upper
                                       95%        95%
                         Odds Ratio    Limit OR   Limit OR
-----------------------------------------------------------
Intercept                     0.200       0.111      0.359
DOSE GROUP
  1=Control                   1.000       1.000      1.000
  2=250 ppm                   0.556       0.283      1.091
  3=500 ppm                   0.758       0.389      1.477
  4=1000 ppm                  5.073       2.211     11.639
  5=1500 ppm                 25.800      10.545     63.125
-----------------------------------------------------------
Fetal Death in CD-1 Mice
```

The odds of fetal death are increased 5-fold and 25-fold in the two highest dose groups, respectively, compared to controls (***Exhibit 13***). The confidence limits do not contain the null value of 1.0, indicating statistical significance.

Exhibit 14. Conditional Marginals (COND_MRG Group, 1st RLOGIST)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Logit
Response variable DEAD: DEAD

Dose Group Effect:  GEE-Independent

by: Conditional Marginal #1.
-------------------------------------------------------------------------------
Conditional      Conditional             Lower 95%   Upper 95%
  Marginal #1    Marginal           SE   Limit       Limit      T:Marg=0   P-value
-------------------------------------------------------------------------------
DOSE GROUP
  1=Control           0.1667    0.0411      0.1002      0.2643      4.05    0.0001
  2=250 ppm           0.1000    0.0153      0.0736      0.1345      6.55    0.0000
  3=500 ppm           0.1317    0.0184      0.0993      0.1726      7.15    0.0000
  4=1000 ppm          0.5036    0.0744      0.3603      0.6464      6.77    0.0000
  5=1500 ppm          0.8377    0.0465      0.7240      0.9103     18.02    0.0000
-------------------------------------------------------------------------------
Fetal Death in CD-1 Mice
```

Exhibit 14 displays the model-adjusted fetal death risks in each dose group (expressed as a proportion), with 95% confidence limits. Note that since there is only one covariate in the model, these values are identical to those produced in PROC DESCRIPT (expressed as percentages). Model-adjusted risks are particularly useful when there are additional covariates in the model, such as fetal body weight. Again, the standard errors and *p*-values are adjusted for clustering.

Next, we fit a logistic dose-response model (via PROC RLOGIST) using the GEE methodology with exchangeable working correlations and a model-based variance (***Exhibit 15***). The model-based variance estimator assumes that the working correlation assumption is correct. The relevant syntax is *R=exchangeable* and *SEMETHOD=model* on the PROC statement. In addition, the RHOS groups containing the estimated exchangeable correlation is requested on the PRINT statement.

Exhibit 15. SAS-Callable SUDAAN Code (2nd Call to RLOGIST)

```
PROC RLOGIST DATA=one FILETYPE=SAS DESIGN=WR R=exchangeable SEMETHOD=model;
  NEST _ONE_ DAM;
  WEIGHT _ONE_;

  CLASS DOSE 5;
  REFLEVEL DOSE_5 = 1;

  MODEL DEAD = DOSE_5;
  EFFECTS DOSE_5 = (-1 0 0 0 1) / NAME = "Control vs. High Dose";
  CONDMARG DOSE_5;

  SETENV COLSPCE=2 LABWIDTH=22 COLWIDTH=7 DECWIDTH=4 TOPMGN=0;
  PRINT / betas=default risk=default tests=default rhos=all cond_mrg=default
          t_betafmt=f7.2 waldffmt=f8.2 dffmt=f7.0 orfmt=f10.3 loworfmt=f8.3
          uporfmt=f8.3 condmrgfmt=f11.4 lowcmfmt=f9.4 upcmfmt=f9.4
          t_cndmrgfmt=f8.2;
  RFORMAT DOSE_5 dose.;
  RFORMAT DEAD dead.;
  RTITLE "Dose Group Effect:  GEE-Exchangeable";
  RFOOTNOTE "Fetal Death in CD-1 Mice";
```

Exhibit 16. First Page of SUDAAN Output (2nd Call to RLOGIST)

```
                              S U D A A N
           Software for the Statistical Analysis of Correlated Data
         Copyright      Research Triangle Institute     February 2011
                              Release 11.0.0

DESIGN SUMMARY: Variances will be computed using the Taylor Linearization Method, Assuming a With
Replacement (WR) Design
    Sample Weight: _ONE_
    Stratification Variables(s): _ONE_
    Primary Sampling Unit: DAM
    Cluster Identification Variables: _ONE_ DAM

Number of zero responses     :  1082
Number of non-zero responses :   537

Independence parameters have converged in 7 iterations

Step 1 parameters have converged in 3 iterations.

Number of observations read       :   1619    Weighted count:     1619
Observations used in the analysis :   1619    Weighted count:     1619
Denominator degrees of freedom    :    130

Maximum number of estimable parameters for the model is  5

File ONE contains  131 Clusters
 131 clusters were used to fit the model
Maximum cluster size is  19 records
Minimum cluster size is   1 records

Sample and Population Counts for Response Variable DEAD
Based on observations used in the analysis
0:  Sample Count     1082    Population Count      1082
1:  Sample Count      537    Population Count       537
```

Exhibit 17. Frequencies and Level Labels for CLASS Variable DOSE_5

Frequencies and Values for CLASS Variables
by: DOSE GROUP.

DOSE GROUP	Frequency	Value
Ordered Position: 1	396	1=Control
Ordered Position: 2	320	2=250 ppm
Ordered Position: 3	319	3=500 ppm
Ordered Position: 4	276	4=1000 ppm
Ordered Position: 5	308	5=1500 ppm

Exhibit 18. Regression Coefficients (BETAS Group, 2nd Call to RLOGIST)

Variance Estimation Method: Taylor Series (WR)
SE Method: Model-Based (Naive)
Working Correlations: Exchangeable
Link Function: Logit
Response variable DEAD: DEAD

Dose Group Effect: GEE-Exchangeable

by: Independent Variables and Effects.

Independent Variables and Effects	Beta Coeff.	SE Beta	Lower 95% Limit Beta	Upper 95% Limit Beta	T-Test B=0	P-value T-Test B=0
Intercept	-1.6271	0.2522	-2.1260	-1.1282	-6.45	0.0000
DOSE GROUP						
1=Control	0.0000	0.0000	0.0000	0.0000	.	.
2=250 ppm	-0.5222	0.4168	-1.3468	0.3025	-1.25	0.2126
3=500 ppm	-0.2274	0.3891	-0.9972	0.5424	-0.58	0.5600
4=1000 ppm	1.6919	0.3331	1.0329	2.3509	5.08	0.0000
5=1500 ppm	3.3340	0.3812	2.5799	4.0881	8.75	0.0000

Fetal Death in CD-1 Mice

Regression coefficients are estimated using the exchangeable correlation, so they are not equivalent to those from GEE-independence. Nonetheless, the results are substantively the same as GEE-independent in this example. Both approaches produce valid inferences in the presence of intralitter correlation.

Exhibit 19. ANOVA Table (TESTS Group, 2nd Call to RLOGIST)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Model-Based (Naive)
Working Correlations: Exchangeable
Link Function: Logit
Response variable DEAD: DEAD

Dose Group Effect:  GEE-Exchangeable

by: Contrast.
-----------------------------------------------------
Contrast                 Degrees
                         of                  P-value
                         Freedom     Wald F  Wald F
-----------------------------------------------------
OVERALL MODEL                  5      31.69   0.0000
MODEL MINUS INTERCEPT          4      32.67   0.0000
INTERCEPT                      .        .       .
DOSE_5                         4      32.67   0.0000
Control vs. High Dose          1      76.50   0.0000
-----------------------------------------------------
Fetal Death in CD-1 Mice
```

Again, ***Exhibit 19*** indicates that the results for GEE-exchangeable are substantively similar to GEE-independent in this example.

Exhibit 20. Odds Ratios (RISK Group, 2nd Call to RLOGIST)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Model-Based (Naive)
Working Correlations: Exchangeable
Link Function: Logit
Response variable DEAD: DEAD

Dose Group Effect:  GEE-Exchangeable

by: Independent Variables and Effects.
-----------------------------------------------------------
Independent Variables
  and Effects                          Lower      Upper
                                       95%        95%
                         Odds Ratio    Limit OR   Limit OR
-----------------------------------------------------------
Intercept                     0.196       0.119      0.324
DOSE GROUP
  1=Control                   1.000       1.000      1.000
  2=250 ppm                   0.593       0.260      1.353
  3=500 ppm                   0.797       0.369      1.720
  4=1000 ppm                  5.430       2.809     10.495
  5=1500 ppm                 28.050      13.195     59.628
-----------------------------------------------------------
Fetal Death in CD-1 Mice
```

Again, ***Exhibit 20*** suggests that the results for GEE-exchangeable are substantively similar to GEE-independent in this example.

Exhibit 21. Exchangeable Correlation (RHOS Group, 2nd Call to RLOGIST)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Model-Based (Naive)
Working Correlations: Exchangeable
Link Function: Logit
Response variable DEAD: DEAD

Dose Group Effect:  GEE-Exchangeable

by: DEAD.
--------------------------------
DEAD                     Correl-
                         ation
                         Matrix
--------------------------------
1                         0.1996
--------------------------------
Fetal Death in CD-1 Mice
```

The estimated exchangeable correlation is 0.1996 in this example (***Exhibit 21***). Coupled with the cluster sizes typically greater than 10, this is large enough to have a substantial impact on variance estimation and statistical inference.

Exhibit 22. Conditional Marginals (COND_MRG Group, 2nd RLOGIST)

```
Variance Estimation Method: Taylor Series (WR)
SE Method: Model-Based (Naive)
Working Correlations: Exchangeable
Link Function: Logit
Response variable DEAD: DEAD

Dose Group Effect:  GEE-Exchangeable

by: Conditional Marginal #1.
-------------------------------------------------------------------------------
Conditional     Conditional             Lower 95%   Upper 95%
  Marginal #1   Marginal           SE   Limit       Limit       T:Marg=0  P-value
-------------------------------------------------------------------------------
DOSE GROUP
  1=Control          0.1642    0.0346      0.1066      0.2445       4.74   0.0000
  2=250 ppm          0.1044    0.0310      0.0570      0.1835       3.36   0.0010
  3=500 ppm          0.1353    0.0347      0.0801      0.2196       3.90   0.0002
  4=1000 ppm         0.5162    0.0544      0.4096      0.6214       9.50   0.0000
  5=1500 ppm         0.8464    0.0372      0.7579      0.9066      22.78   0.0000
-------------------------------------------------------------------------------
Fetal Death in CD-1 Mice
```

The estimated marginals are slightly different from those under GEE-independent and from DESCRIPT, since the exchangeable correlation is used to estimate the regression coefficients. Nonetheless, the results are still substantively the same for GEE-exchangeable as GEE-independent.