SUDAAN

Software for the Statistical Analysis of Correlated Data

Analyzing Repeated Measures and Cluster-Correlated Data Using SUDAAN® Release 7.5

by

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Prepared for:
Joint Statistical Meetings
Continuing Education Workshop
August, 1997

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Analyzing Repeated Measures and Cluster-Correlated Data Using SUDAAN® Release 7.5

ABSTRACT

Researchers often encounter data which are observed in clusters. Individual responses may represent multiple outcomes from the same patient or animal, or multiple units within a larger cluster, such as a physician clinic or an animal litter. Failure to account for the cluster effect in the statistical analysis can result in underestimated standard errors and false positive test results. In addition, cross-over clinical trials will not yield the associated increase in statistical power if the design is ignored in the analysis.

This seminar will describe many of the new features in SUDAAN Release 7.5, including**:** **1)** ***Jackknife variance estimation*** for descriptive statistics and regression modelling; **2)** ***GEE capabilities*** in linear, logistic, and multinomial logistic regression, with robust and model-based variance estimation; **3)** ***User-friendly contrast statements*** in all regression procedures, **4)** ***Reference level statement*** for specifying the reference cells of categorical covariates in all regression procedures; **5)** ***Least squares means*** estimation for linear regression, and **5)** ***R-square*** based on the log-likelihood for logistic regression.

SUDAAN fits marginal or population-averaged regression models via Generalized Estimating Equations (***GEEs***), treating the intracluster correlation as a nuisance parameter. Robust variance estimators ensure consistent variance estimates and valid inferences even when the correlation structure has been misspecified.

Clustered Data Applications

Pharmaceutical Research

Toxicology / Preclinical Studies

- ***Developmental toxicity***
  Presence of malformations and death recorded on fetuses clustered within litters *(Cluster = litter)*

- ***Neurobehavioral toxicity***
  Recurrent failure times recorded over a series of trials on each animal *(Cluster = animal)*

Clinical Trials

- ***Periodontal / Dental trials***
  Multiple teeth per patient *(Cluster = patient)*

- ***Ophthalmology trials***
  Pairs of eyes per patient *(Cluster = patient)*

- ***Repeated measures studies***
  Recurrent events per patient, such as illnesses or adverse events *(Cluster = patient)*

  Example
  Repeated ordinal responses of pain relief over an 8-hour period in a randomized clinical trial of acute pain relief comparing placebo with 2 analgesics (Gansky, *et al*, 1994, *Journal of Biopharmaceutical Statistics)*

Clustered Data Applications

Pharmaceutical Research

Clinical Trials *(continued)*

- ***Cross-Over Studies***
  Patients receive each treatment in sequence
  (Cluster = patient)

  Example:
  3-period, 3 treatment cross-over study (Snapinn and Small,1986, *Biometrics*):

  Investigational drug, aspirin, and placebo administered in sequence to headache sufferers;
  Patients rated each drug on scale of 1-4 according to amount of pain relief.

Why Did We Bother Developing SUDAAN?

Intra-Cluster Correlation

- Potential for clustermates to respond similarly (genetic and environmental influences)

- Experimental units from the same cluster are not statistically independent

- Usually results in ***overdispersion***, or extra-variation in the responses beyond what would be expected under independence

- Negative correlations have the opposite effect
  i.e., ***underdispersion***, or reduction in variance below what would be expected under independence

- Other standard statistical packages (*e.g.*, SAS®, SPSS®) do not uniformly address the correlated data problem in all analytical procedures

  SAS mainly uses correlated data methods for discrete (GENMOD) and continuous (MIXED, GENMOD) outcomes in regression models, but not for descriptive data analysis

  SUDAAN uses correlated data methods for:

  - Regression modelling
  - Estimating and analyzing:
    Means, medians, percentages, percentiles, odds ratios and relative risks, and ratios of random variables
  - Chi-square tests in contingency tables
  - Cochran-Mantel-Haenszel tests in contingency tables

Impact on Statistical Analysis

Failure to account for the cluster effect ***usually*** leads to:

- Underestimated standard errors for parameters of interest (means, proportions, regression coefficients)
- Test statistics with inflated Type I error rates (false positive tests of treatment effects)

Implications for Safety and Efficacy

Safety

- False positives
- Erroneously declaring compounds unsafe

Efficacy

- False positives
- Erroneously declaring new drugs efficaceous
- Reverse effects for cross-over designs:
  - Loss of Power
  - Failure to detect effective treatments

Multivariate Responses (Clustered Data)

Notation

i = *cluster*

= $1, \ldots, n$

j = *observation within the cluster*

= $1, \ldots, m_i$

Data

$(y_{ij}, \boldsymbol{x}_{ij})$, $j = 1, \ldots, m_i$

$i = 1, \ldots, n$

$N = \sum_i m_i$ = *total sample size*

Responses

$\boldsymbol{y_i} = (y_{i1}, y_{i2}, \ldots, y_{im_i})$

Covariates

$\boldsymbol{x}_{ij} = (x_{ij1}, x_{ij2}, \ldots, x_{ijp})$

This is the clustered data situation covered by SUDAAN

Assumptions: Independence Vs. Clustered Data

Independence

$$\boldsymbol{Y} = \begin{bmatrix} y_1 \\ \cdot \\ \cdot \\ \cdot \\ y_N \end{bmatrix} \qquad \boldsymbol{V}(\boldsymbol{Y}) = \sigma^2 \boldsymbol{I}_{\boldsymbol{N}} = \begin{bmatrix} \sigma^2 & 0 & 0 & \ldots & 0 \\ 0 & \sigma^2 & 0 & \ldots & 0 \\ 0 & 0 & \sigma^2 & \ldots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \ldots & \sigma^2 \end{bmatrix}$$

Observations independent, constant variance

Clustered Data (SUDAAN):

$$\boldsymbol{Y} = \begin{bmatrix} y_{11} \\ \vdots \\ y_{1m_1} \\ \vdots \\ y_{n1} \\ \vdots \\ y_{nm_n} \end{bmatrix}$$

n clusters of m_i observations $\left(N = \sum_{i=1}^{n} m_i\right)$

Unequal observations per cluster $= m_i$

Example: n litters with m_i pups per litter

Assumptions: Independence Vs. Clustered Data

Clustered Data (SUDAAN):

$$\boldsymbol{V}(\boldsymbol{Y}) = \begin{bmatrix} V_1 & 0 & 0 & \cdots & 0 \\ 0 & V_2 & 0 & \cdots & 0 \\ 0 & 0 & V_3 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & V_n \end{bmatrix}$$

Cluster–Correlated Data

Block–Diagonal by Cluster

V_i is an m_i x m_i matrix

$$\boldsymbol{V_i} = \begin{bmatrix} \sigma^2_{(i)1} & \sigma_{(i)12} & \sigma_{(i)13} & \cdots & \sigma_{(i)1m} \\ \sigma_{(i)21} & \sigma^2_{(i)2} & \sigma_{(i)23} & \cdots & \sigma_{(i)2m} \\ \vdots & & \ddots & & \vdots \\ \vdots & & & \ddots & \vdots \\ \sigma_{(i)m1} & \sigma_{(i)m2} & \sigma_{(i)m3} & \cdots & \sigma^2_{(i)m} \end{bmatrix}$$

- V_i is an m_i x m_i variance covariance matrix of observations in the *i*-th cluster
- ***No assumptions on structure*** of V_i (could be unstructured, multi-level, AR(1), exchangeable, etc.)
- Observations independent between clusters, completely arbitrary correlation structure within clusters

Independence Vs. Clustered Data: Fitting Linear Regression Models

Standard Situation: Linear Regression

$$\boldsymbol{Y} = \begin{bmatrix} y_1 \\ . \\ . \\ . \\ y_N \end{bmatrix}$$

$$E(\boldsymbol{Y}) = \boldsymbol{X}\beta$$

$$\boldsymbol{V}(\boldsymbol{Y}) = \sigma^2 \boldsymbol{I}_N$$

Independent obs, constant variance

Standard Solution to Normal Equations:

$$\boldsymbol{b} = (\boldsymbol{X}'\boldsymbol{X})^{-1}\boldsymbol{X}'\boldsymbol{Y}$$

$$Var(\boldsymbol{b}) = \hat{\sigma}^2 (\boldsymbol{X}'\boldsymbol{X})^{-1} \qquad \hat{\sigma}^2 = \text{Mean Square Error}$$

This variance formula only holds when: $V(\boldsymbol{Y}) = \sigma^2 \boldsymbol{I}_N$

Independence Vs. Clustered Data: Fitting Linear Regression Models

How is SUDAAN different?

$$\boldsymbol{V}(\boldsymbol{Y}) = \boldsymbol{V}_{\boldsymbol{Y}} = \begin{bmatrix} V_1 & 0 & 0 & \cdots & 0 \\ 0 & V_2 & 0 & \cdots & 0 \\ 0 & 0 & V_3 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & V_n \end{bmatrix}$$

Cluster-Correlated Data

Block-Diagonal by Cluster

V_i is an m_i x m_i matrix

$$\boldsymbol{b} = (\boldsymbol{X}'\boldsymbol{X})^{-1}\boldsymbol{X}'\boldsymbol{Y}$$

Use ***between-cluster (robust) variance formula*** to estimate:

$Var(\boldsymbol{b}) = \boldsymbol{V}_{\boldsymbol{b}}$ Estimates each element separately

KEY POINT:

$V_{\boldsymbol{b}} \neq \hat{\sigma}^2 (X'X)^{-1}$ due to cluster-correlated data

Independence Vs. Clustered Data
Fitting Linear Regression Models

Null Hypothesis:

$$H_0: \boldsymbol{C}\beta = \mathbf{0}$$

C is a contrast matrix of rank r

General Form for Test Statistic:

$$Q = (\boldsymbol{Cb})' \left[\boldsymbol{C}\ Var(\boldsymbol{b})\, \boldsymbol{C}'\right]^{-1} (\boldsymbol{Cb})$$

Standard Situation

$$Q = (\boldsymbol{Cb})' \left[\hat{\sigma}^2\, \boldsymbol{C}(\boldsymbol{X}'\boldsymbol{X})^{-1}\boldsymbol{C}'\right]^{-1} (\boldsymbol{Cb})$$

$$= \frac{r \cdot MS_{H_0}}{MS_{error}} \sim r\, F_{r,\, N-r}$$

Standard computing formula used by most software packages

SUDAAN Test Statistic:

$$Q = (\boldsymbol{Cb})' \left[\boldsymbol{C}\boldsymbol{V}_{\boldsymbol{b}}\boldsymbol{C}'\right]^{-1} (\boldsymbol{Cb})$$

Does not reduce to any simple computing formula

SUDAAN Software Package

Software for Statistical Analysis of Correlated Data

- Single program, written in the *C* language, consisting of a family of statistical procedures

- As easy to use as SAS!

  - Uses a SAS-like interface
  - Accepts SAS data sets as input

- Two Modes of Operation:

  1) SAS-Callable
     (Win 95, SUN/Solaris, VAX/VMS, IBM/MVS)

  2) Stand-Alone
     (many platforms, including Windows)

- SPSS Users: Release 7.5 reads SPSS files

SUDAAN Procedures

DESCRIPTIVE PROCEDURES

CROSSTAB
Computes frequencies, percentage distributions, odds ratios, relative risks, and their standard errors (or confidence intervals) for user-specified cross-tabulations, as well as chi-square tests of independence and the Cochran-Mantel-Haenszel chi-square test for stratified two-way tables.

DESCRIPT
Computes estimates of means, totals, proportions, percentages, geometric means, quantiles, and their standard errors; also computes standardized estimates and tests of single degree-of-freedom contrasts among levels of a categorical variable.

RATIO
Computes estimates and standard errors of generalized ratios of the form $\Sigma y / \Sigma x$, where x and y are observed variables; also computes standardized estimates and tests single-degree-of-freedom contrasts among levels of a categorical variable.

REGRESSION PROCEDURES

REGRESS
Fits linear regression models and performs hypothesis tests concerning the model parameters. Uses ***GEE*** to efficiently estimate regression parameters, with robust and model-based variance estimation.

LOGISTIC
Fits logistic regression models to binary data and computes hypothesis tests for model parameters; also estimates odds ratios and their 95% confidence intervals for each model parameter.

MULTILOG
Fits logistic and multinomial logistic regression models to ordinal and nominal categorical data and computes hypothesis tests for model parameters; estimates odds ratios and their 95% confidence intervals for each model parameter; uses ***GEE*** to efficiently estimate regression parameters, with robust and model-based variance estimation.

SURVIVAL
Fits discrete and continuous proportional hazards models to failure time data; also estimates hazard ratios and their 95% confidence intervals for each model parameter.

Elements of a SUDAAN Procedure

PROC MULTILOG **DATA** = name **options...;**

NEST Strata Cluster ;

None (_ONE_) or Blocking Factor

Person (repeated) Litter (teratology) Clinic or Site

For Regression Modelling:

MODEL dependent = independent ;

Y = DOSE ;

For Descriptive Statistics:

VAR response_variables ;

TABLE categorical effects (*e.g.*, DOSE) ;

Enhancements to SUDAAN Release 7.5

Resampling Methods for Robust Variance Estimation

- Jackknife
- Balanced Repeated Replication (BRR)

Enhancements of GEE Capabilities

- Exchangeable correlations in linear regression (as already in logistic and multinomial logistic since Release 7.0)
- Robust (default) and model-based variances in GEE applications

Other Regression Enhancements

- REFLEVEL statement to change the reference level for categorical covariates
- User-friendly contrast statement (EFFECTS) for testing simultaneous regression effects, simple effects in interaction models, and more
- R-square (Cox and Snell, 1989) in logistic regression
- Least Squares Means (LSMEANS) statement in linear regression
- MULTILOG Procedure for multinomial logistic regression (7.0)

SAS-Callable Platforms

- Windows
- SUN/Solaris

Now reads SPSS files (in addition to SAS and ASCII)

Two Variance Estimation Methods in SUDAAN

Basic Concept Behind Both

1) Use ***consistent estimators*** of the parameters

   e.g., Means, Proportions, Percentages, Odds Ratios, Regression Coefficients

   Can even estimate the correlation structure to improve the efficiency of β

   Intracluster correlation treated as a nuisance parameter

2) ***Robust variance estimators*** ensure consistent variance estimates and valid inferences:

   - Taylor linearization / GEE
   - Jackknife resampling (new in Release 7.5)

   - *Without* imposing strict distributional assumptions about the response of interest

Taylor Linearization Approach

Two-Step Procedure for Variance Estimation:

1) ***Use Taylor series linearization to approximate functions of linear statistics (e.g., ratios of random variables)***

Example: Teratology
Proportion of malformed fetuses in a teratology experiment

$$\hat{p} = \frac{\sum_{i=1}^{n}\sum_{j=1}^{m_i} y_{ij}}{\sum_{i=1}^{n} m_i} = \frac{Number\ \ Malformed\ \ Fetuses}{Total\ \ Number\ \ of\ \ Fetuses}$$

Find linear approximation to this nonlinear statistic (Kendall and Stuart, 1973);
Between-cluster variance formulas available for *linear* statistics.

Woodruff (1971):

- Equivalent computational procedure using Taylor series linearized values

- Each observational unit gets a linearized value for a particular statistic.

2) ***Compute between-cluster variance of the sum of the linearized values***

Between-Cluster Variance Estimator

Goal is to estimate $Var(\hat{\theta})$:

$$Z_{ij} = \textit{Linearized Value of } \hat{\theta} \textit{ for unit}-ij$$

Proportion, $\hat{p}$: $\quad Z_{ij} = (y_{ij} - \hat{p}) \; / \; \sum_{i=1}^{n} m_i$

$$Z_i = \sum_{j=1}^{m_i} Z_{ij} \qquad \textit{Cluster Totals}$$

$$\bar{Z} = \frac{1}{n} \sum_{i=1}^{n} Z_i \qquad \textit{Mean of Cluster Totals}$$

$$\hat{Var}(\hat{\theta}) = \frac{n}{n-1} \sum_{i=1}^{n} (Z_i - \bar{Z})^2$$

For a proportion, $\hat{p}$:

$$Var(\hat{p}) = \frac{1}{\left(\sum_{i=1}^{n} m_i \right)^2} \frac{n}{n-1} \sum_{i=1}^{n} \left(y_i - \hat{p}\, m_i \right)^2$$

Jackknife Variance Estimation

Coming in Release 7.5:
Resampling Methods for Correlated Data

Quenouille (1956): Reducing bias in estimation
Tukey (1958): Approximate confidence intervals

Start With Given Point Estimator:
Descriptive statistics (*e.g.*, means, proportions)
Regression parameter vectors

Use consistent estimators of location parameters
Naively treat the correlated responses as independent

Covariance Estimates for Descriptive Statistics

Binomial proportions (Gladen, 1979 *JASA*):
Proportion of fetuses that are malformed in a teratology study

$$\hat{p} = \frac{\sum_{i=1}^{n}\sum_{j=1}^{m_i} y_{ij}}{\sum_{i=1}^{n} m_i}$$

Jackknife Variance Estimation

An estimate based on all clusters ***except the k-th*** is as follows:

$$\hat{p}_{(k)} = \frac{\sum_{i \neq k}^{n} \sum_{j=1}^{m_i} y_{ij}}{\sum_{i \neq k}^{n} m_i}$$

Jackknife Variance Estimate for $\hat{p}$:

$$\hat{\sigma}^2_{JK} = \frac{n-1}{n} \sum_{k=1}^{n} \left[\hat{p}_{(k)} - \hat{p}_{(.)} \right]^2$$

where $\hat{p}_{(.)}$ is the average of the Jackknife estimates:

$$\hat{p}_{(.)} = \frac{\sum_{k=1}^{n} \hat{p}_{(k)}}{n} \quad .$$

Jackknife Variance Estimation

Assuming

$$E(y_i \mid m_i) = m_i p$$
$$V(y_i \mid m_i) = h(m_i) \ ,$$

Then:

$$\frac{\hat{p} - p}{\hat{\sigma}_{JK}} \rightarrow Z \sim N(0,1)$$

Jackknife Variance Estimation

Covariance of Regression Parameters

- Logistic regression parameters obtained under a binomial likelihood (Carr and Portier, 1993 *Biometrics*)

- Cox model parameters obtained under a partial likelihood (Lipsitz and Parzen, 1996 *Biometrics*; Lipsitz, Dear, and Zhao, 1994 *Biometrics*)

Start With Given Point Estimator $\hat{\beta}$:

Estimated parameter vector obtained by naively assuming the observations within a cluster are independent

Solution to any score estimating equation of the form

$$\mu(\hat{\beta}) = \sum_{i=1}^{n} \mu_i(\hat{\beta}) = 0$$

where $\mu_i(\hat{\beta})$ is the contribution to the "score" vector from the *i*-th cluster.

Example

Logistic score equations under binomial likelihood

$$\boldsymbol{U}(\beta) = \frac{\partial \mathrm{Log\,L}(\beta)}{\partial \beta} = \sum_i \sum_j \boldsymbol{x}'_{ij} y_{ij} - \sum_i \sum_j \boldsymbol{x}'_{ij} p_{ij}(\beta)$$

Jackknife Variance Estimation

Regression Parameters *(continued)*

As long as the model for the marginal mean is correctly specified, the MLE $\hat{\beta}$ is asymptotically consistent and normally distributed

Jackknife Variance Estimator For $\hat{\beta}$

$$Var_{JK}(\hat{\beta}) = \left(\frac{n-p}{n}\right)\sum_{i=1}^{n}\left(\hat{\beta}_{-i} - \hat{\beta}_{.}\right)\left(\hat{\beta}_{-i} - \hat{\beta}_{.}\right)'$$

where

p = number of parameters in the model,

$\hat{\beta}_{-i}$ = estimate of β obtained by deleting the m_i observations in cluster i and solving the estimating equations via the Newton-Raphson algorithm, and

$\hat{\beta}_{.}$ = the average of the $\hat{\beta}_{-i}$.

Clusters are removed sequentially and with-replacement

JK variance estimator is consistent for estimating the asymptotic variance of $\hat{\beta}$

Jackknife Variance Estimation

Regression Parameters *(continued)*

Simulation in Small Sample Situations

Evaluating treatment effect in logistic regression models (Carr and Portier, *Biometrics*, 1993)

Jackknife Method:

- Controlled Type I error
- Estimated location parameters without bias
- Estimated variance of parameter estimates without bias
- Similar to Zeger/Liang GEE in terms of performance

Assumptions and Validity for Taylor Linearization and Jackknife

- Clusters are statistically independent
- No strict distributional assumptions for the response of interest
- Yields consistent estimates of the variance as the number of clusters tends to infinity
- Method is valid for any underlying intracluster correlation structure, as long as clusters are statistically independent
- Also valid in presence of additional sources of correlation within each clustermate (*e.g.*, multiple levels of nesting)

The MULTILOG Procedure

Multinomial Logistic Regression
(Release 7.0)

- ***Generalized Logit Models***
  - Nominal Outcomes

    e.g., Type of health plan (A, B, C, D)

- ***Cumulative Logit Models***
  - Ordinal Outcomes

    e.g., Pain Relief:
    none, mild, moderate, complete relief
  - "Proportional Odds Models"

- Binary Logistic is a special case of each
- Model-fitting Approach
  - Fits ***marginal*** or ***population-averaged*** models
  - Uses GEE to model the intracluster correlations and efficiently estimate regression coefficients

Applications in Pharmaceutical Research

Toxicology / Pre-Clinical Studies

- ***Developmental Toxicity***
  Severity of malformations recorded on fetuses clustered within litters (cluster = litter)

Clinical Trials

- ***Repeated Measures Studies***
  Multiple illness or adverse events per patient
  (cluster = patient)

  Example
  Repeated ordinal responses of pain relief over an 8-hour period in a randomized clinical trial of acute pain relief comparing placebo with 2 analgesics (Gansky, Koch, et al., 1994, Journal of Biopharmaceutical Statistics)

- ***Cross-Over Studies***
  Subjects receive each treatment in sequence
  (cluster = patient)

  Example
  3-period, 3 treatment cross-over study (Snapinn and Small, 1986, Biometrics):
  Investigational drug, aspirin, and placebo administered in sequence to headache sufferers
  Patients rated each drug on scale of 1-4 according to amount of pain relief.

Generalized Logit Model

Y is a categorical response variable with *K* categories 1,2,...,*K* (nominal scale)

$\boldsymbol{x}_i = (1, x_{i1}, \ldots, x_{ip})' =$ vector of explanatory variables for subject *i*

Model $\pi_k(\boldsymbol{x_i}) = prob(Y_i = k \mid \boldsymbol{x_i}) \qquad k = 1, \ldots, K-1$

Generalized Logits Model (Agresti, 1990):

$$\log\left[\frac{\pi_k(\boldsymbol{x}_i)}{\pi_K(\boldsymbol{x}_i)}\right] = \boldsymbol{\beta}_k' \boldsymbol{x}_i \qquad k = 1, \ldots, K-1$$

- Separate parameter vector (intercepts and slopes) for *each* of the *K-1* logit equations
- $\boldsymbol{\beta_K} = \mathbf{0}$.
- $\exp(\boldsymbol{\beta_k})$ = odds of being in category *k* vs. *K* (the last) for each 1-unit increase in *x*

Cumulative Logit Model

Y is a categorical response variable with K categories 1,2,...,K

ordinal scale: *e.g.*, none, mild, moderate, severe

$\boldsymbol{x}_i = (1, x_{i1}, \ldots, x_{ip})' =$ vector of explanatory variables for subject i

Model $F_k(\boldsymbol{x}_i) = prob(Y \le k \mid \boldsymbol{x}_i) =$ cum. prob. up to and including category k

McCullagh's (1980) Proportional Odds Model:

Cumulative Logits

$$\log\left[\frac{F_k(\boldsymbol{x}_i)}{1 - F_k(\boldsymbol{x}_i)}\right] = \alpha_k + \boldsymbol{\beta}'\boldsymbol{x}_i \qquad k = 1, \ldots, K-1$$

- Separate intercepts $\boldsymbol{\alpha_k}$, but a ***common set of slopes*** $\boldsymbol{\beta}$, for k = 1,...,K-1
- $\boldsymbol{\beta}$ measures the effect of the covariates on the severity of response

Efficient Parameter Estimation

Efficiently Weight the Data to Estimate Regression Coefficients (β)

GEE Approach

(Longitudinal Data Analysis, Zeger and Liang, 1986):

1) Assume a Covariance Structure $\boldsymbol{V}_i$ to describe the relationship among observations within clusters, i=1,...,n

   - Mean / Variance Relationship:
     $V(y_{ij}) = g(\mu_{ij})$

   - Pairwise Correlation Model:
     $Corr(y_{ij}, y_{ik})$

2) Estimate Covariance Parameters

3) Weight Data Inversely Proportional to V_i to Estimate β

   V_i inserted into the usual estimating equations in order to weight the data efficiently

Efficient Parameter Estimation

Efficiently Weight the Data to Estimate Regression Coefficients (β)

GEE Approach

(Longitudinal Data Analysis, Zeger and Liang, 1986):

$i = 1, \ldots, n$ Clusters

$j = 1, \ldots, m_i$ Observational Units

$\boldsymbol{y_i} = (y_{i1}, \ldots, y_{im_i})$ Vector of responses

$\boldsymbol{\mu_i} = E(\boldsymbol{y_i}) = \boldsymbol{\mu_i}(\boldsymbol{\beta})$ Vector of marginal means
$= (\mu_{i1}, \ldots, \mu_{im_i})$

$\boldsymbol{V_i}(\boldsymbol{\alpha}) = Cov(\boldsymbol{y_i}; \boldsymbol{\mu_i}, \alpha)$ Working Covariance matrix

"Generalized" Estimating Equations:

$$U(\boldsymbol{\beta}) = \sum_{i=1}^{n} \frac{\partial \boldsymbol{\mu}_i'}{\partial \boldsymbol{\beta}} \boldsymbol{V_i}(\boldsymbol{\alpha})^{-1} (\boldsymbol{y}_i - \boldsymbol{\mu}_i) = \mathbf{0}$$

Working Covariance Structure

$$\boldsymbol{V}_i(\alpha) = \boldsymbol{A}_i^{1/2}\, \boldsymbol{R}_i(\boldsymbol{\alpha})\, \boldsymbol{A}_i^{1/2} \cdot \phi \qquad \boldsymbol{V} \text{ is Block diagonal}$$

$\boldsymbol{A}_i$ = diagonal matrix with diagonal elements equal to the marginal variances of observational units within clusters: $g(\mu_{i1}), \ldots, g(\mu_{i m_i})$

$$= \begin{bmatrix} g(\mu_{i1}) & 0 & 0 & 0 \\ 0 & g(\mu_{i2}) & 0 & 0 \\ 0 & 0 & \ddots & \vdots \\ 0 & 0 & \cdots & g(\mu_{i m_i}) \end{bmatrix}$$

Relationship Between Variance of y_{ij} and its Mean

$$Var(y_{ij}) = g(\mu_{ij}) \cdot \phi$$

g is a known variance function, ϕ is an unknown scale parameter

Binary Responses

Marginal distribution of y_{ij} is Bernoulli

Therefore $Var(y_{ij}) = \mu_{ij}(1 - \mu_{ij})$ and $\phi = 1$.

Choices for Working Correlation Matrices

$R_i(\alpha)$ is the "Working" Correlation Matrix for y_i

$$\alpha_{jk} = corr(y_{ij}, y_{ik})$$

1) ***Independent Working Correlation Matrix***
(Identity matrix implies 0 pairwise correlation)

$$R_i(\alpha) = I = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

- Estimating equations reduce to familiar forms:

  - Normal equations for linear regression
  - Score equations for logistic regression

- Leads to standard regression coefficient estimates

- Consistent and asymptotically normal, regardless of whether or not the correlation structure is correctly specified

- This approach is offered in SUDAAN, and it is perfectly valid for estimating the ***regression parameters*****.**

Choices for Working Correlation Matrices

2) ***Exchangeable***
(equal pairwise correlations)

$$\boldsymbol{R}_i(\boldsymbol{\alpha}) = \begin{bmatrix} 1 & \rho & \rho & \rho \\ \rho & 1 & \rho & \rho \\ \rho & \rho & 1 & \rho \\ \rho & \rho & \rho & 1 \end{bmatrix}$$

- SUDAAN offers this form as well

- Can improve ***efficiency*** of parameter estimates over the independence working assumption when working correlations are close to truth.

Robust Variance Estimate for GEE

$$\mathrm{Var}(\hat{\boldsymbol{\beta}}) = M_0^{-1} M_1 M_0^{-1}$$

where

$$M_0 = \sum_{i=1}^{n} \frac{\partial \boldsymbol{\mu}_i'}{\partial \boldsymbol{\beta}} \boldsymbol{V}_i^{-1} \frac{\partial \boldsymbol{\mu}_i}{\partial \boldsymbol{\beta}}$$

$$M_1 = \sum_{i=1}^{n} \frac{\partial \boldsymbol{\mu}_i'}{\partial \boldsymbol{\beta}} \boldsymbol{V}_i^{-1} Var(\boldsymbol{y}_i) \boldsymbol{V}_i^{-1} \frac{\partial \boldsymbol{\mu}_i}{\partial \boldsymbol{\beta}}$$

- M_0^{-1} (outside term) is called the ***naive*** or ***model-based*** variance (inverse of information matrix, appropriate when working assumption about covariance structure is correct)

  Sensitive to violations of model assumptions!

- M_1 (middle term) serves as a ***variance correction*** when the covariance model is misspecified

- ***Robust variance*** is consistent even when $var(y_{ij}) \neq g(\mu_{ij}) \cdot \phi$ or $\boldsymbol{R}_i(\boldsymbol{\alpha})$ is not the true correlation matrix of $\boldsymbol{Y}_i$

- $Var(\boldsymbol{y}_i)$ empirically estimated by $(\boldsymbol{y}_i - \hat{\boldsymbol{\mu}}_i)(\boldsymbol{y}_i - \hat{\boldsymbol{\mu}}_i)'$

- SUDAAN offers the ***robust*** (default) and in Release 7.5 the ***model-based*** variance estimates (via the ***SEMETHOD=MODEL*** option)

Robust Variance Estimate for GEE

- Also referred to as ***Sandwich Estimator*** or ***Variance Correction***

- Properly accounts for intracluster correlation

- Yields ***consistent variance estimates***, even if correlation structure is misspecified (*e.g.*, by specifying "working" independence when the correlations are in fact exchangeable)

  Huber (1967)
  Royall (1986)
  Binder (1983, 1992)

SYNTAX for GEE options in REGRESS and MULTILOG

```
PROC REGRESS
     MULTILOG ... R = Independent | Exchangeable
                  RSTEPS = count
                  SEMETHOD = ZEGER | BINDER | MODEL
```

R = *Independent* | *Exchangeable*

Specifies the "working" assumption for estimating the within-cluster correlation structure. The default assumption is independent working correlations. When *R=exchangeable*, the estimated exchangeable correlation matrix is available for printing.

RSTEPS = *count*

Specifies the maximum number of steps (iterating between estimated regression coefficients and correlations) used to fit the model. The default value is 0 and the default correlation structure is independent (*R=independent*). If you specify exchangeable correlations, the default value for the RSTEPS parameter is 1.

SEMETHOD = *ZEGER* | *BINDER* | *MODEL*

Specifies the method for computing standard errors of regression coefficients. ***SEMETHOD=ZEGER*** and ***BINDER*** both specify the full ***robust*** or ***sandwich*** variance estimator. For the REGRESS procedure, *ZEGER* and *BINDER* produce identical results. For the MULTILOG procedure, *ZEGER* and *BINDER* produce different results for responses with more than 2 levels. ***SEMETHOD=MODEL*** requests the ***model-based*** or ***naive*** standard error estimator, which is simply the outside of the sandwich estimator and is appropriate when the pairwise correlations within a cluster have been correctly specified.

What Does SUDAAN Model?

Marginal Models (Population-Averaged)

- *Marginal mean* of the multivariate outcomes as a function of the covariates:

$$F\left[E(y_{ij} \mid \boldsymbol{x}_{ij})\right] = \boldsymbol{x}_{ij}^{/}\boldsymbol{\beta}$$

- Focus on how X causes Y, while acknowledging the dependence within clusters (as opposed to how one Y causes another)

- Describes relationship between covariates and response *across* clusters

- Intracluster correlation treated as nuisance parameter

References:

Zeger and Liang (1986)
Liang and Zeger (1986)
Zeger, Liang, and Albert (1988)
Binder (1983, 1992)

R-Square for Logistic Regression

Proportion of Log-Likelihood Explained by the Model
(Cox and Snell, 1989)

$$R^2 = 1 - \left(\frac{L(\mathbf{0})}{L(\hat{\boldsymbol{\beta}})} \right)^{\frac{2}{n}}$$

where:

$L(\mathbf{0})$ is the likelihood of the intercept-only model
$L(\hat{\boldsymbol{\beta}})$ is the likelihood of the specified model, and
n is the sample size.

R-Square for *Linear* Regression:
Simple correlation between observed and predicted response (based on the model).

REFLEVEL Statement

- Available in all modelling procedures
- Allows the user to change the definition of the ***reference cell*** for all categorical covariates.
- By ***default***, the reference cell is the ***last level*** of each categorical covariate.

Syntax:

```
REFLEVEL  variable_1 = reference_level_1
          variable_2 = reference_level_2

          {... variable_k = reference_level_k};
```

- Each *variable_i* must be defined on the SUBGROUP and LEVELS statements
- For SUBGROUP variables ***not*** on the REFLEVEL statement, the default reference level is still the ***last*** level.

REFLEVEL Example

The following example comes from the NHANES I Survey and its Longitudinal Follow-up Study conducted 10 years later. NHANES I (*National Health and Nutrition Examination Survey I*) was a multi-stage sample survey of over 14,000 adults in the US aged 25-74 years, with data collection taking place in 1971-1975. The epidemiologic follow-up took place in 1981-1984.

In this analysis, we wish to determine whether follow-up cancer status (***CANCER12***, 1=*yes* vs. 0=*no*) is associated with a measure of body iron stores at the initial exam (***B_TIBC***, total iron-binding capacity), while adjusting for age group at initial exam (***AGEGROUP***, 1=*20-49*, 2=*50+*) and smoking status (***SMOKE***, 1=*current*, 2=*former*, 3=*never*, 4=*unknown*).

First, we supply the results with the ***default reference cells***, the last level of each categorical covariate, *i.e.*, SMOKE=4 (*unknown*) and AGEGROUP=2 (*50+)*:

```
1   PROC MULTILOG DATA="C:\\ADVANCED\\IRONSUD" FILETYPE=SAS DESIGN=WR DEFT2;

2   NEST Q_STRATA PSU1;

3   WEIGHT B_WTIRON;

4   SUBGROUP CANCER12 AGEGROUP SMOKE;

5   LEVELS   2        2        4;

6   MODEL CANCER12 = B_TIBC AGEGROUP SMOKE / CUMLOGIT;

7   SETENV COLSPCE=1 LABWIDTH=25 COLWIDTH=8 DECWIDTH=4 LINESIZE=78 PAGESIZE=60;

8   PRINT BETA="BETA" SEBETA="S.E." DEFT="DESIGN EFFECT" T_BETA="T:BETA=0"
          P_BETA="P-VALUE" DF WALDCHI WALDCHP / T_BETAFMT=F8.2 DEFTFMT=F6.2
          WALDCHIFMT=F8.2 DFFMT=F8.0;

9   TITLE "Default Reference Cell Model";

Opened SAS data file C:\ADVANCED\IRONSUD.SSD for reading.

Number of observations read       :   3290    Weighted count: 40570323
Observations used in the analysis :   3290    Weighted count: 40570323
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :     35
Maximum number of estimable parameters for the model is  6

File C:\ADVANCED\IRONSUD.SSD contains   67 Clusters
Maximum cluster size is 111 records
Minimum cluster size is  15 records
Independence parameters have converged in 5 iterations

Sample and Population Counts for Response Variable CANCER12
  Cancer   :  Sample Count      232    Population Count   1745695
  No Cancer:  Sample Count     3058    Population Count  38824628
```

REFLEVEL Example

DEFAULT Reference Cell Parameterization

```
Date: 05-29-97            Research Triangle Institute            Page  : 1
Time: 14:16:21              The MULTILOG Procedure               Table : 1

Variance Estimation Method: Robust (Binder, 1983)
Working Correlations: Independent
Link Function: Cumulative Logit
Response variable CANCER12: Cancer Status (1/2)

Default Reference Cell Model

-------------------------------------------------------------------------
Independent Variables                          DESIGN
  and Effects                  BETA     S.E. EFFECT T:BETA=0  P-VALUE
-------------------------------------------------------------------------
Intercept                    -0.8618   0.6605   0.94    -1.30   0.2004
Total Iron Binding Capacity  -0.0024   0.0018   1.10    -1.29   0.2052
Age Cohort
  20-49 yrs.                 -2.2525   0.3343   1.89    -6.74   0.0000
  50+ yrs.                    0.0000   0.0000    .        .      .
Smoking Status
  Current                    -0.5858   0.2771   0.77    -2.11   0.0417
  Former                     -0.9418   0.2922   0.84    -3.22   0.0027
  Never                      -0.4998   0.2743   0.85    -1.82   0.0770
  Unknown                     0.0000   0.0000    .        .      .
-------------------------------------------------------------------------
```

Here, each smoking group is automatically compared to the ***unknown*** smoking status (SMOKE=4), which may not be very meaningful.

REFLEVEL Example

DEFAULT Reference Cell Parameterization

```
Date: 05-29-97            Research Triangle Institute            Page  : 2
Time: 14:16:21              The MULTILOG Procedure               Table : 1

Variance Estimation Method: Robust (Binder, 1983)
Working Correlations: Independent
Link Function: Cumulative Logit
Response variable CANCER12: Cancer Status (1/2)

Default Reference Cell Model

-----------------------------------------------------
Contrast                  Degrees           P-value
                          of       Wald     Wald
                          Freedom  ChiSq    ChiSq
-----------------------------------------------------
OVERALL MODEL                    6   708.28   0.0000
MODEL MINUS INTERCEPT            5    64.47   0.0000
B_TIBC                           1     1.67   0.1967
AGEGROUP                         1    45.39   0.0000
SMOKE                            3    10.60   0.0141
-----------------------------------------------------

MULTILOG used
  CPU time       : 12.74 seconds
  Elapsed time   : 13 seconds
  Virtual memory : 2.84 MB
```

Here we see that ***Age group*** and ***Smoking status*** are significantly associated with follow-up cancer status, but ***Total iron-binding capacity*** is not (p=0.1967).

REFLEVEL Example

Using the REFLEVEL Statement

Next, using the REFLEVEL statement, we re-define the reference cells to be the ***first level*** of each categorical variable. Note the only differences in the results are in the estimates of the regression coefficients, where the expected value of the response for each level of the categorical covariate(s) is now compared to the user-specified *first* level instead of the last. The main effects tests remain unchanged.

```
10  PROC MULTILOG DATA="C:\\ADVANCED\\IRONSUD" FILETYPE=SAS DESIGN=WR DEFT2;

11  NEST Q_STRATA PSU1;

12  WEIGHT B_WTIRON;

13  REFLEVEL AGEGROUP=1 SMOKE=1;

14  SUBGROUP CANCER12 AGEGROUP SMOKE;

15  LEVELS   2        2        4;

16  MODEL CANCER12 = B_TIBC AGEGROUP SMOKE / CUMLOGIT;

17  SETENV COLSPCE=1 LABWIDTH=25 COLWIDTH=8 DECWIDTH=4 LINESIZE=78 PAGESIZE=60;

18  PRINT BETA="BETA" SEBETA="S.E." DEFT="DESIGN EFFECT" T_BETA="T:BETA=0"
          P_BETA="P-VALUE" DF WALDCHI WALDCHP / T_BETAFMT=F8.2 DEFTFMT=F6.2
          WALDCHIFMT=F8.2 DFFMT=F8.0;

19  TITLE "Using the REFLEVEL Statement";

Opened SAS data file C:\ADVANCED\IRONSUD.SSD for reading.

Number of observations read       :   3290    Weighted count: 40570323
Observations used in the analysis :   3290    Weighted count: 40570323
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :     35

Maximum number of estimable parameters for the model is  6

File C:\ADVANCED\IRONSUD.SSD contains   67 Clusters
Maximum cluster size is 111 records
Minimum cluster size is  15 records

Independence parameters have converged in 5 iterations

Sample and Population Counts for Response Variable CANCER12
  Cancer   :  Sample Count      232    Population Count   1745695
  No Cancer:  Sample Count     3058    Population Count  38824628
```

REFLEVEL Example

Using the REFLEVEL Statement

```
Date: 05-29-97            Research Triangle Institute            Page  : 1
Time: 14:16:21              The MULTILOG Procedure               Table : 1

Variance Estimation Method: Robust (Binder, 1983)
Working Correlations: Independent
Link Function: Cumulative Logit
Response variable CANCER12: Cancer Status (1/2)

Using the REFLEVEL Statement

-------------------------------------------------------------------------
Independent Variables                          DESIGN
  and Effects                  BETA     S.E. EFFECT T:BETA=0  P-VALUE
-------------------------------------------------------------------------
Intercept                    -3.7002   0.6967   1.06    -5.31   0.0000
Total Iron-Binding Capacity  -0.0024   0.0018   1.10    -1.29   0.2052
Age Cohort
  20-49 yrs.                  0.0000   0.0000    .        .      .
  50+ yrs.                    2.2525   0.3343   1.89     6.74   0.0000
Smoking Status
  Current                     0.0000   0.0000    .        .      .
  Former                     -0.3560   0.2716   1.16    -1.31   0.1985
  Never                       0.0860   0.2500   1.26     0.34   0.7330
  Unknown                     0.5858   0.2771   0.77     2.11   0.0417
-------------------------------------------------------------------------
```

Now each smoking group is compared to the *current* smokers (SMOKE=1), and we see immediately that *current smokers* are not significantly different from *former smokers* (p=0.1985) nor from those who have *never smoked* (p=0.7330).

REFLEVEL Example

Using the REFLEVEL Statement

```
Date: 05-29-97            Research Triangle Institute            Page  : 2
Time: 14:16:21              The MULTILOG Procedure               Table : 1

Variance Estimation Method: Robust (Binder, 1983)
Working Correlations: Independent
Link Function: Cumulative Logit
Response variable CANCER12: Cancer Status (1/2)

Using the REFLEVEL Statement

-----------------------------------------------------
Contrast                  Degrees           P-value
                          of       Wald     Wald
                          Freedom  ChiSq    ChiSq
-----------------------------------------------------
OVERALL MODEL                     6   708.28   0.0000
MODEL MINUS INTERCEPT             5    64.47   0.0000
B_TIBC                            1     1.67   0.1967
AGEGROUP                          1    45.39   0.0000
SMOKE                             3    10.60   0.0141
-----------------------------------------------------

MULTILOG used
  CPU time       : 13.2 seconds
  Elapsed time   : 14 seconds
  Virtual memory : 2.88 MB
```

The tests of main effects are the same, no matter which groups are designated as the reference cells.

EFFECTS Statement

- Available in all modeling procedures

Simplifies the following hypothesis testing situations:

- Testing multiple main effects and/or interactions simultaneously (*e.g.*, testing chunk interaction effects);
- Testing general linear contrasts (*e.g.*, pairwise comparisons, trends) for a specific variable(s) in the model by only specifying contrast coefficients for the variable(s) of interest;
- Testing main effects in the presence of interactions. If the model contains factors A, B, and their interaction A*B, the user can obtain the:
  1) ***Simple effect*** of A, which is the effect of variable A tested within a given level of variable B, and
  2) ***Main effects*** of A, which are averaged over the levels of B.

Syntax:

```
EFFECTS term(s) / [ NAME = "label" ] [ DISPLAY ]
                  [ REFLEVEL | AVERAGE |
                    VARIABLE_NAME = value ] ;
```

where ***term(s)*** are name of effect(s) (single variables or/and interactions) on the MODEL statement, which may include contrast matrices.

EFFECTS Statement Options

NAME = "*label*"
Assigns a label to the contrast. Default is "*Effect_nn*", where *nn* is the *nn*-th EFFECT statement in the procedure

DISPLAY
Prints the contrast coefficients

REFLEVEL, AVERAGE , VARIABLE_NAME = *value*
Tells SUDAAN how to test the effects of covariates in the model when they are interacted with other effects in the model.

Example:

```
MODEL  Y  =  A   B  A*B;
```

To test the effect of A (which may be either continuous or categorical), the user has three options:

REFLEVEL (default)
Tests the effect of A ***when B (and all other variables A is interacted with) are set to their reference levels***.

AVERAGE
Tests the effect of A ***averaged over the interaction effect***, with proportional weighting over each level of B (Graubard and Korn, 1997). The contrast coefficient vector contains the weighted proportion of subjects in the *j*-th category of the *i*-th SUBGROUP variable.

EFFECTS Statement Options

VARIABLE_NAME = *value*

Similar to the REFLEVEL option, except here ***the user chooses the level of B within which to test the effect of A***. This option is used to carry out what are commonly known as "simple effects," in which an effect A is to be tested within a specific level of B, other than the reference cell.

EFFECTS Example 1.

Using the NHANES I Study and its longitudinal follow-up (see the REFLEVEL statement examples for details), we evaluate the effects of body iron stores at initial exam (***B_TIBC***, continuous), age group at initial exam (***AGEGROUP***, 1=*20-49*, 2=*50+*), and smoking status (***SMOKE***, 1=*current*, 2=*former*, 3=*never*, 4=*unknown*) on follow-up cancer status (***CANCER12***, 1=*yes*, 2=*no*).

The **EFFECTS statement** can be used to:

1) Test the combined effect of *Agegroup* and *Smoke*:

```
EFFECTS AGEGROUP SMOKE /
        NAME = "Combined Age, Smoke";
```

2) Compare *Smoke* Level 1 to Level 2 (the default reference level for *Smoke* is Level 4):

```
EFFECTS SMOKE = (-1 1 0 0) / NAME="Smoke 1 vs 2";
```

EFFECTS Example 1.

```
1   PROC MULTILOG DATA="C:\\ADVANCED\\IRONSUD" FILETYPE=SAS DESIGN=WR DEFT2;

2   NEST Q_STRATA PSU1;

3   WEIGHT B_WTIRON;

4   SUBGROUP CANCER12 AGEGROUP SMOKE;

5   LEVELS   2        2        4;

6   MODEL CANCER12 = B_TIBC AGEGROUP SMOKE / CUMLOGIT;

7   EFFECTS AGEGROUP SMOKE / NAME = "Combined Age, Smoke";

8   EFFECTS SMOKE=(-1 1 0 0) / NAME = "Smoke 1 vs 2";

9   SETENV COLSPCE=1 LABWIDTH=25 COLWIDTH=8 DECWIDTH=4 LINESIZE=78 PAGESIZE=60;

10  PRINT BETA="BETA" SEBETA="S.E." DEFT="DESIGN EFFECT" T_BETA="T:BETA=0"
          P_BETA="P-VALUE" DF WALDCHI WALDCHP /
          T_BETAFMT=F8.2 DEFTFMT=F6.2 DFFMT=F8.0 WALDCHIFMT=F8.2;

11  TITLE "EFFECTS Statement Example";


NOTE: Terms in the MODEL statement have been rearranged
      to follow subgroup order.

Opened SAS data file C:\ADVANCED\IRONSUD.SSD for reading.

Number of observations read       :   3290    Weighted count: 40570323
Observations used in the analysis :   3290    Weighted count: 40570323
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :     35

Maximum number of estimable parameters for the model is  6

File C:\ADVANCED\IRONSUD.SSD contains   67 Clusters
Maximum cluster size is 111 records
Minimum cluster size is  15 records

Independence parameters have converged in 5 iterations

Sample and Population Counts for Response Variable CANCER12
  Cancer   :  Sample Count      232    Population Count   1745695
  No Cancer:  Sample Count     3058    Population Count  38824628
```

EFFECTS Example 1.

```
Date: 05-29-97            Research Triangle Institute            Page  : 1
Time: 14:46:25              The MULTILOG Procedure               Table : 1

Variance Estimation Method: Robust (Binder, 1983)
Working Correlations: Independent
Link Function: Cumulative Logit
Response variable CANCER12: Cancer Status (1/2)

EFFECTS Statement Example

-------------------------------------------------------------------------
Independent Variables                          DESIGN
  and Effects                   BETA     S.E. EFFECT T:BETA=0  P-VALUE
-------------------------------------------------------------------------
Intercept                    -0.8618   0.6605   0.94    -1.30   0.2004
Age Cohort
  20-49 yrs.                 -2.2525   0.3343   1.89    -6.74   0.0000
  50+ yrs.                    0.0000   0.0000    .        .      .
Smoking Status
  Current                    -0.5858   0.2771   0.77    -2.11   0.0417
  Former                     -0.9418   0.2922   0.84    -3.22   0.0027
  Never                      -0.4998   0.2743   0.85    -1.82   0.0770
  Unknown                     0.0000   0.0000    .        .      .
Total Iron-Binding Capacity  -0.0024   0.0018   1.10    -1.29   0.2052
-------------------------------------------------------------------------
```

EFFECTS Example 1.

```
Date: 05-29-97            Research Triangle Institute            Page  : 2
Time: 14:46:25              The MULTILOG Procedure               Table : 1

Variance Estimation Method: Robust (Binder, 1983)
Working Correlations: Independent
Link Function: Cumulative Logit
Response variable CANCER12: Cancer Status (1/2)

EFFECTS Statement Example

-----------------------------------------------------
Contrast                  Degrees           P-value
                          of       Wald     Wald
                          Freedom  ChiSq    ChiSq
-----------------------------------------------------
OVERALL MODEL                    6   708.28   0.0000
MODEL MINUS INTERCEPT            5    64.47   0.0000
AGEGROUP                         1    45.39   0.0000
SMOKE                            3    10.60   0.0141
B_TIBC                           1     1.67   0.1967
Combined Age, Smoke              4    53.16   0.0000
Smoke 1 vs 2                     1     1.72   0.1899
-----------------------------------------------------

MULTILOG used
  CPU time       : 17.42 seconds
  Elapsed time   : 18 seconds
  Virtual memory : 2.88 MB
```

The combined effect of *Age* and *Smoking Status* is statistically significant (p=0.0000). However, *current smokers* (SMOKE=1) are not significantly different (p=0.1899) from *former smokers* (SMOKE=2).

EFFECTS Example 2.

In this example, we evaluate the effects of body iron stores at initial exam (***TRFSAT***, 1= *high* vs. 0=*normal* indicator), smoking status (***SMOKE***, 1=*current*, 2=*former*, 3=*never*, 4=*unknown*), age group at initial exam (***AGEGROUP,*** 1=*20-49* yrs, 2=*50+ yrs*), and various two-way interactions on a binary response, cancer status at follow-up (***CANCER1***, 1=*yes* vs. 0=*no*).

The **EFFECTS Statement** can be used to easily test simultaneous interaction effects (smoking by age group, smoking by indicator of body iron stores):

```
EFFECTS SMOKE*AGEGROUP SMOKE*TRFSAT / NAME="Chunk Interactions";
```

```
66  PROC LOGISTIC DATA="C:\\ADVANCED\\IRONSUD" FILETYPE=SAS DESIGN=WR DEFT2;

67  NEST Q_STRATA PSU1;

68  WEIGHT B_WTIRON;

69  SUBGROUP SMOKE AGEGROUP;

70  LEVELS   4     2;

71  MODEL CANCER1 = TRFSAT SMOKE AGEGROUP SMOKE*AGEGROUP SMOKE*TRFSAT;

72  EFFECTS SMOKE*AGEGROUP SMOKE*TRFSAT / NAME = "Chunk Interactions";

73  SETENV COLSPCE=1 LABWIDTH=25 COLWIDTH=8 DECWIDTH=4 LINESIZE=78 PAGESIZE=60;

74  PRINT BETA="BETA" SEBETA="S.E." DEFT="DESIGN EFFECT" T_BETA="T:BETA=0"
          P_BETA="P-VALUE" DF WALDCHI WALDCHP
          / SEBETAFMT=F8.5 DFFMT=F8.0 T_BETAFMT=F8.2 DEFTFMT=F6.2 WALDCHIFMT=F8.2;

75  TITLE "Using EFFECTS to Test Chunk Interactions";


NOTE: Terms in the MODEL statement have been rearranged
      to follow subgroup order.

Opened SAS data file C:\ADVANCED\IRONSUD.SSD for reading.
Number of zero responses     :  3058
Number of non-zero responses :   232

Parameters have converged in 5 iterations

Number of observations read       :   3290    Weighted count: 40570323
Observations used in the analysis :   3290    Weighted count: 40570323
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :     35

Maximum number of estimable parameters for the model is 12

R-Square for dependent variable CANCER1 (Cox & Snell, 1989): 0.046486
```

EFFECTS Example 2.

Using EFFECTS to Test Chunk Interactions

Date: 04-04-97 Research Triangle Institute Page : 1
Time: 15:55:41 The LOGISTIC Procedure Table : 1

Response variable CANCER1: Cancer Status (0/1)

Using Effects to Test Chunk Interactions

Independent Variables and Effects	BETA	S.E.	DESIGN EFFECT	T:BETA=0	P-VALUE
Intercept	-1.6135	0.27254	0.72	-5.92	0.0000
Smoking Status					
Current	-0.6159	0.37457	0.97	-1.64	0.1090
Former	-1.6133	0.33255	0.65	-4.85	0.0000
Never	-0.5606	0.35346	0.93	-1.59	0.1217
Unknown	0.0000	0.00000	.	.	.
Age Cohort					
20-49 yrs.	-3.8676	0.84072	0.31	-4.60	0.0001
50+ yrs.	0.0000	0.00000	.	.	.
High Transferrin					
Saturation (0/1)	0.1745	0.52386	0.72	0.33	0.7411
Smoking Status, Age Cohort					
Current, 20-49 yrs.	1.4407	1.03113	0.41	1.40	0.1711
Current, 50+ yrs.	0.0000	0.00000	.	.	.
Former, 20-49 yrs.	2.2305	1.05117	0.44	2.12	0.0410
Former, 50+ yrs.	0.0000	0.00000	.	.	.
Never, 20-49 yrs.	1.5366	1.03999	0.44	1.48	0.1485
Never, 50+ yrs.	0.0000	0.00000	.	.	.
Unknown, 20-49 yrs.	0.0000	0.00000	.	.	.
Unknown, 50+ yrs.	0.0000	0.00000	.	.	.
Smoking Status, High Transferrin Saturation					
Current	-0.1905	0.56612	0.58	-0.34	0.7385
Former	1.1955	0.69445	0.94	1.72	0.0940
Never	-0.1575	0.50445	0.52	-0.31	0.7568
Unknown	0.0000	0.00000	.	.	.

EFFECTS Example 2.

Using EFFECTS to Test Chunk Interactions

```
Date: 04-04-97            Research Triangle Institute            Page  : 2
Time: 15:55:41              The LOGISTIC Procedure               Table : 1

Response variable CANCER1: Cancer Status (0/1)

Using EFFECTS to Test Chunk Interactions

-----------------------------------------------------
Contrast                  Degrees           P-value
                          of       Wald     Wald
                          Freedom  ChiSq    ChiSq
-----------------------------------------------------
OVERALL MODEL                 12   819.25   0.0000
MODEL MINUS INTERCEPT         11   101.61   0.0000
INTERCEPT                      .      .       .
SMOKE                          .      .       .
AGEGROUP                       .      .       .
TRFSAT                         .      .       .
SMOKE * AGEGROUP               3     4.96   0.1749
TRFSAT * SMOKE                 3     6.02   0.1105
Chunk Interactions             6    21.21   0.0017
-----------------------------------------------------
```

The combined interaction effect is statistically significant (p=0.0017). To test the same hypothesis using the CONTRAST statement, we would specify the following 12-row contrast matrix. The number of rows equals the number of regression coefficients to be tested in the contrast, with 1's in the columns corresponding to those regression coefficients. All other columns for intercept and main effects are 0's.

```
CONTRAST 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0
         0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0
         0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0
         0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0
         0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0
         0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0
         0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0
         0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0
         0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0
         0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0
         0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0
         0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1
         / NAME="CHUNK INTERACTIONS";
```

EFFECTS Example 2.

Comparison to the CONTRAST Statement

```
62  PROC LOGISTIC DATA="C:\\ADVANCED\\IRONSUD" FILETYPE=SAS DESIGN=WR DEFT2;

63  NEST Q_STRATA PSU1;

64  WEIGHT B_WTIRON;

65  SUBGROUP SMOKE AGEGROUP;

66  LEVELS   4     2;

67  MODEL CANCER1=TRFSAT SMOKE AGEGROUP SMOKE*AGEGROUP SMOKE*TRFSAT;

68  CONTRAST 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0
             0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0
             0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0
             0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0
             0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0
             0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0
             0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0
             0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0
             0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0
             0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0
             0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1
             / NAME="CHUNK INTERACTIONS";

69  SETENV COLSPCE=1 LABWIDTH=25 COLWIDTH=8 DECWIDTH=4 LINESIZE=78 PAGESIZE=60;

70  PRINT BETA="BETA" SEBETA="S.E." DEFT="DESIGN EFFECT" T_BETA="T:BETA=0"
          P_BETA="P-VALUE" DF WALDCHI WALDCHP / SEBETAFMT=F8.5 T_BETAFMT=F8.2
          DEFTFMT=F6.2 WALDCHIFMT=F8.2 DFFMT=F8.0;

71  TITLE "Using CONTRAST to Test Chunk Interactions";

Opened SAS data file C:\ADVANCED\IRONSUD.SSD for reading.
Number of zero responses     :  3058
Number of non-zero responses :   232

Parameters have converged in 5 iterations
Number of observations read       :   3290    Weighted count: 40570323
Observations used in the analysis :   3290    Weighted count: 40570323
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :     35

Maximum number of estimable parameters for the model is 12

R-Square for dependent variable CANCER1 (Cox & Snell, 1989): 0.046486
```

EFFECTS Example 2.

Comparison to the CONTRAST Statement

```
Date: 03-27-97            Research Triangle Institute            Page  : 1
Time: 14:25:00              The LOGISTIC Procedure               Table : 1

Response variable CANCER1: Cancer Status (0/1)

Using CONTRAST to Test Chunk Interactions

-------------------------------------------------------------------
Independent Variables and
  Effects                                 DESIGN
                            BETA     S.E. EFFECT T:BETA=0  P-VALUE
-------------------------------------------------------------------
Intercept                -1.6135  0.27254   0.72    -5.92   0.0000
High Transferrin
  Saturation (0/1)        0.1745  0.52386   0.72     0.33   0.7411
Smoking Status
  Current                -0.6159  0.37457   0.97    -1.64   0.1090
  Former                 -1.6133  0.33255   0.65    -4.85   0.0000
  Never                  -0.5606  0.35346   0.93    -1.59   0.1217
  Unknown                 0.0000  0.00000    .        .      .
Age Cohort
  20-49 yrs.             -3.8676  0.84072   0.31    -4.60   0.0001
  50+ yrs.                0.0000  0.00000    .        .      .
Smoking Status, Age Cohort
  Current, 20-49 yrs.     1.4407  1.03113   0.41     1.40   0.1711
  Current, 50+ yrs.       0.0000  0.00000    .        .      .
  Former, 20-49 yrs.      2.2305  1.05117   0.44     2.12   0.0410
  Former, 50+ yrs.        0.0000  0.00000    .        .      .
  Never, 20-49 yrs.       1.5366  1.03999   0.44     1.48   0.1485
  Never, 50+ yrs.         0.0000  0.00000    .        .      .
  Unknown, 20-49 yrs.     0.0000  0.00000    .        .      .
  Unknown, 50+ yrs.       0.0000  0.00000    .        .      .
Smoking Status, High
  Transferrin Saturation
  (0/1)
  Current                -0.1905  0.56612   0.58    -0.34   0.7385
  Former                  1.1955  0.69445   0.94     1.72   0.0940
  Never                  -0.1575  0.50445   0.52    -0.31   0.7568
  Unknown                 0.0000  0.00000    .        .      .
-------------------------------------------------------------------
```

EFFECTS Example 2.

Comparison to the CONTRAST Statement

```
Date: 03-27-97            Research Triangle Institute            Page  : 2
Time: 14:25:00              The LOGISTIC Procedure               Table : 1

Response variable CANCER1: Cancer Status (0/1)

Using CONTRAST to Test Chunk Interactions

-----------------------------------------------------
Contrast                  Degrees           P-value
                          of       Wald     Wald
                          Freedom  ChiSq    ChiSq
-----------------------------------------------------
OVERALL MODEL                 12   819.25   0.0000
MODEL MINUS INTERCEPT         11   101.61   0.0000
INTERCEPT                      .      .      .
TRFSAT                         .      .      .
SMOKE                          .      .      .
AGEGROUP                       .      .      .
SMOKE * AGEGROUP               3     4.96   0.1749
TRFSAT * SMOKE                 3     6.02   0.1105
CHUNK INTERACTIONS             6    21.21   0.0017
-----------------------------------------------------

LOGISTIC used
  CPU time       : 29.27 seconds
  Elapsed time   : 30 seconds
  Virtual memory : 2.23 MB
```

The results are the same as for the EFFECTS statement, with the simultaneous interactions being statistically significant.

EFFECTS Example 3.

In this example, we evaluate the effect of smoking status (***SMOKE***, 1=*current*, 2=*former*, 3=*never*, 4=*unknown*) on a binary response, cancer status at follow-up (***CANCER1***, 1=*yes* vs. 0=*no*) under the following conditions:

1) When Age Group=1 (20-49 yrs),
2) When Age Group=2 (50+ yrs),
3) When Age Group is at its reference level (level 2=50+ yrs),
4) Averaged over the interaction cells with Age Group.

The **EFFECTS statement** can be used to easily test these hypotheses:

```
EFFECTS SMOKE / AGEGROUP=1  NAME = "SMOKE in AGEGROUP=1";
EFFECTS SMOKE / AGEGROUP=2  NAME = "SMOKE in AGEGROUP=2";
EFFECTS SMOKE / REFLEVEL  NAME = "SMOKE in Age Reference Level";
EFFECTS SMOKE / AVERAGE  NAME = "SMOKE Averaged Over
                                 Interaction";
```

EFFECTS Example 3.

```
76  PROC LOGISTIC DATA="C:\\ADVANCED\\IRONSUD" FILETYPE=SAS DESIGN=WR DEFT2;

77  NEST Q_STRATA PSU1;

78  WEIGHT B_WTIRON;

79  SUBGROUP AGEGROUP SMOKE;

80  LEVELS   2        4;

81  MODEL CANCER1 = TRFSAT AGEGROUP SMOKE AGEGROUP*SMOKE;

82  EFFECTS SMOKE / AGEGROUP=1 NAME="Smoke Effect in Age=20-49";

83  EFFECTS SMOKE / AGEGROUP=2 NAME="Smoke Effect in Age=50+";

84  EFFECTS SMOKE / REFLEVEL NAME="Smoke Effect at Age Reference Level";

85  EFFECTS SMOKE / AVERAGE NAME="Smoke averaged over interaction";

86  SETENV COLSPCE=1 LABWIDTH=25 COLWIDTH=8 DECWIDTH=4 LINESIZE=78 PAGESIZE=60;

87  PRINT BETA="BETA" SEBETA="S.E." DEFT="DESIGN EFFECT" T_BETA="T:BETA=0"
          P_BETA="P-VALUE" DF WALDCHI WALDCHP
          /SEBETAFMT=F8.5 DFFMT=F8.0 T_BETAFMT=F8.2 DEFTFMT=F6.2 WALDCHIFMT=F8.2;

88  TITLE "Using EFFECTS to Test Simple Effects;


NOTE: Terms in the MODEL statement have been rearranged
      to follow subgroup order.

Opened SAS data file C:\ADVANCED\IRONSUD.SSD for reading.
Number of zero responses     :  3058
Number of non-zero responses :   232

Parameters have converged in 5 iterations

Number of observations read       :   3290    Weighted count: 40570323
Observations used in the analysis :   3290    Weighted count: 40570323
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :     35

Maximum number of estimable parameters for the model is  9

R-Square for dependent variable CANCER1 (Cox & Snell, 1989): 0.043642
```

EFFECTS Example 3.

```
Date: 04-04-97            Research Triangle Institute            Page  : 1
Time: 15:55:41              The LOGISTIC Procedure               Table : 1

Response variable CANCER1: Cancer Status (0/1)

Using EFFECTS to Test Simple Effects

-----------------------------------------------------------------------
Independent Variables and
  Effects                                  DESIGN
                             BETA     S.E. EFFECT T:BETA=0  P-VALUE
-----------------------------------------------------------------------
Intercept                  -1.6762  0.25187   0.79    -6.65   0.0000
Age Cohort
  20-49 yrs.               -3.8681  0.84493   0.31    -4.58   0.0001
  50+ yrs.                  0.0000  0.00000    .        .      .
Smoking Status
  Current                  -0.6625  0.31953   0.91    -2.07   0.0455
  Former                   -1.1591  0.34790   1.05    -3.33   0.0020
  Never                    -0.6030  0.30426   0.91    -1.98   0.0554
  Unknown                   0.0000  0.00000    .        .      .
High Transferrin
  Saturation (0/1)          0.3997  0.20980   1.19     1.91   0.0650
Age Cohort, Smoking Status
  20-49 yrs., Current       1.4290  1.03443   0.41     1.38   0.1759
  20-49 yrs., Former        2.2399  1.04173   0.43     2.15   0.0385
  20-49 yrs., Never         1.5345  1.04652   0.45     1.47   0.1515
  20-49 yrs., Unknown       0.0000  0.00000    .        .      .
  50+ yrs., Current         0.0000  0.00000    .        .      .
  50+ yrs., Former          0.0000  0.00000    .        .      .
  50+ yrs., Never           0.0000  0.00000    .        .      .
  50+ yrs., Unknown         0.0000  0.00000    .        .      .
-----------------------------------------------------------------------
```

EFFECTS Example 3.

```
Date: 04-04-97            Research Triangle Institute            Page  : 2
Time: 15:55:41              The LOGISTIC Procedure               Table : 1

Response variable CANCER1: Cancer Status (0/1)

Using EFFECTS to Test Simple Effects

-----------------------------------------------------------
Contrast                        Degrees           P-value
                                of        Wald    Wald
                                Freedom   ChiSq   ChiSq
-----------------------------------------------------------
OVERALL MODEL                        9   859.59   0.0000
MODEL MINUS INTERCEPT                8    89.15   0.0000
INTERCEPT                            .       .       .
AGEGROUP                             .       .       .
SMOKE                                .       .       .
TRFSAT                               1     3.63   0.0567
AGEGROUP * SMOKE                     3     5.25   0.1547
Smoke Effect in Age=20-49            3     1.66   0.6466
Smoke Effect in Age=50+              3    11.15   0.0110
Smoke Effect at Age Reference Level  3    11.15   0.0110
Smoke averaged over interaction      3     0.36   0.9491
-----------------------------------------------------------

LOGISTIC used
  CPU time       : 25.87 seconds
  Elapsed time   : 26 seconds
  Virtual memory : 2.02 MB
```

Note that the test for *"Smoke Effect in Age=50+"* is equivalent to *"Smoke in Age Reference Level."* Here we see that:

1) There is a marginally significant interaction between age and smoking on follow-up cancer status (p=0.1547). SUDAAN computes this test automatically, without the need for the EFFECTS statement.

2) There is no significant effect of smoking on cancer status when age group=20-49 yrs. (p=0.6466), although the regression coefficients on the previous page (provided automatically by SUDAAN) and the EFFECTS statement here indicates a significant smoking effect when age is at its reference level (50+ yrs., p=0.0110).

3) There is no significant effect of smoking when smoking is averaged over its interaction with age (p=0.9302).

Now the same results via the CONTRAST statement:

EFFECTS Example 3.

Comparison to the CONTRAST Statement

```
72  PROC LOGISTIC DATA="C:\\ADVANCED\\IRONSUD" FILETYPE=SAS DESIGN=WR DEFT2;

73  NEST Q_STRATA PSU1;

74  WEIGHT B_WTIRON;

75  SUBGROUP AGEGROUP SMOKE;

76  LEVELS   2        4;

77  MODEL CANCER1 = TRFSAT AGEGROUP SMOKE AGEGROUP*SMOKE;

78  CONTRAST 0 0 0 0 -1 0 0 1 -1 0 0 1 0 0 0 0
             0 0 0 0 -1 0 1 0 -1 0 1 0 0 0 0 0
             0 0 0 0 -1 1 0 0 -1 1 0 0 0 0 0 0
             / NAME="SMOKE IN AGE=1";

79  CONTRAST 0 0 0 0 -1 0 0 1 0 0 0 0 -1 0 0 1
             0 0 0 0 -1 0 1 0 0 0 0 0 -1 0 1 0
             0 0 0 0 -1 1 0 0 0 0 0 0 -1 1 0 0
             / NAME="SMOKE IN AGE=2";

80  SETENV COLSPCE=1 LABWIDTH=25 COLWIDTH=8 DECWIDTH=4 LINESIZE=78 PAGESIZE=60;

81  PRINT BETA="BETA" SEBETA="S.E." DEFT="DESIGN EFFECT" T_BETA="T:BETA=0"
          P_BETA="P-VALUE" DF WALDCHI WALDCHP / SEBETAFMT=F8.5 DFFMT=F8.0
          T_BETAFMT=F8.2 DEFTFMT=F6.2 WALDCHIFMT=F8.2;

82  TITLE "Testing Simple Effects via the CONTRAST Statement";

Opened SAS data file C:\ADVANCED\IRONSUD.SSD for reading.
Number of zero responses     :  3058
Number of non-zero responses :   232

Parameters have converged in 5 iterations

Number of observations read       :   3290    Weighted count: 40570323
Observations used in the analysis :   3290    Weighted count: 40570323
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :     35

Maximum number of estimable parameters for the model is  9

R-Square for dependent variable CANCER1 (Cox & Snell, 1989): 0.043642
```

EFFECTS Example 3.

Comparison to the CONTRAST Statement

```
Date: 03-27-97            Research Triangle Institute            Page  : 1
Time: 14:25:00              The LOGISTIC Procedure               Table : 1

Response variable CANCER1: Cancer Status (0/1)

Testing Simple Effects Via the CONTRAST Statement
```

Independent Variables and Effects	BETA	S.E.	DESIGN EFFECT	T:BETA=0	P-VALUE
Intercept	-1.6762	0.25187	0.79	-6.65	0.0000
High Transferrin Saturation (0/1)	0.3997	0.20980	1.19	1.91	0.0650
Age Cohort					
20-49 yrs.	-3.8681	0.84493	0.31	-4.58	0.0001
50+ yrs.	0.0000	0.00000	.	.	.
Smoking Status					
Current	-0.6625	0.31953	0.91	-2.07	0.0455
Former	-1.1591	0.34790	1.05	-3.33	0.0020
Never	-0.6030	0.30426	0.91	-1.98	0.0554
Unknown	0.0000	0.00000	.	.	.
Age Cohort, Smoking Status					
20-49 yrs., Current	1.4290	1.03443	0.41	1.38	0.1759
20-49 yrs., Former	2.2399	1.04173	0.43	2.15	0.0385
20-49 yrs., Never	1.5345	1.04652	0.45	1.47	0.1515
20-49 yrs., Unknown	0.0000	0.00000	.	.	.
50+ yrs., Current	0.0000	0.00000	.	.	.
50+ yrs., Former	0.0000	0.00000	.	.	.
50+ yrs., Never	0.0000	0.00000	.	.	.
50+ yrs., Unknown	0.0000	0.00000	.	.	.

EFFECTS Example 3.

Comparison to the CONTRAST Statement

```
Date: 03-27-97            Research Triangle Institute            Page  : 2
Time: 14:25:00              The LOGISTIC Procedure               Table : 1

Response variable CANCER1: Cancer Status (0/1)

Testing Simple Effects Via the CONTRAST Statement

-----------------------------------------------------
Contrast                  Degrees           P-value
                          of       Wald     Wald
                          Freedom  ChiSq    ChiSq
-----------------------------------------------------
OVERALL MODEL                     9   859.59   0.0000
MODEL MINUS INTERCEPT             8    89.15   0.0000
INTERCEPT                         .      .      .
TRFSAT                            1     3.63   0.0567
AGEGROUP                          .      .      .
SMOKE                             .      .      .
AGEGROUP * SMOKE                  3     5.25   0.1547
SMOKE IN AGE=1                    3     1.66   0.6466
SMOKE IN AGE=2                    3    11.15   0.0110
-----------------------------------------------------

LOGISTIC used
  CPU time       : 23.95 seconds
  Elapsed time   : 24 seconds
  Virtual memory : 2.07 MB
```

LSMEANS Statement

- Available in the ***linear regression procedure*** (REGRESS).
- Produces “least squares” or “adjusted means” for any number of categorical covariates in the model.
- List one or more categorical effects from the right-hand-side of the MODEL statement. ***Continuous variables are not allowed*** on the LSMEANS statement.
- The keyword ***INTERCEPT*** specifies an overall least-squares mean, when the model contains an intercept.

Syntax:

```
LSMEANS [INTERCEPT] effect(s) / [ALL] [DISPLAY] ;
```

ALL

Requests least-squares means for ***all effects*** on the right-hand side of the MODEL statement.

DISPLAY

Requests least squares means ***contrast coefficients***.

LSMEANS Statement

Construction of the LSMEANS Contrast

- SUDAAN calculates ***contrast coefficients*** that are the weighted means of each covariate to be adjusted for in the model, using all observations for which there are no missing independent or dependent variable values.

- Contrast coefficients corresponding to the levels of the ***categorical covariates*** (appearing on the SUBGROUP statement) are the weighted numbers of individuals in each category of the covariate. Sample member weights are provided by the variable specified on the WEIGHT statement. If weights are all equal to one (*e.g.*, via the keyword _ONE_), unweighted means are used.

- The set of contrast coefficients are vector-multiplied by the estimated regression coefficients.

LSMEANS Example

The following example illustrates the construction of the LSMEANS contrast.

Data:
NHANES I Survey and its Longitudinal Follow-up Study.

Question:
Is smoking status at initial exam (***SMOKE***, where 1=*current* vs. 2=*former*, 3=*never*, 4=*unknown*) associated with a measure of body iron stores at the initial exam (***B_TIBC***, or total iron-binding capacity), while adjusting for age at initial exam?

LSMEANS
We request the least squares means of the response *B_TIBC*, total iron-binding capacity, within levels of *SMOKE*, adjusted for age at initial exam (first as categorical, then as a continuous covariate). The data are weighted by the variable *B_WTIRON*.

SUDAAN Programming Statements Demonstrating the Construction of the LSMEANS Contrast for Categorical Covariates

```
1   PROC REGRESS DATA="C:\\ADVANCED\\IRONSUD" FILETYPE=SAS DESIGN=WR DEFT2;

2   NEST Q_STRATA PSU1;

3   WEIGHT B_WTIRON;

4   SUBGROUP AGEGROUP SMOKE;

5   LEVELS   2        4;

6   MODEL B_TIBC = SMOKE AGEGROUP;

7   LSMEANS SMOKE / DISPLAY;

8   SETENV COLSPCE=1 LABWIDTH=25 COLWIDTH=8 DECWIDTH=4 LINESIZE=78 PAGESIZE=60;

9   PRINT BETA="BETA" SEBETA="S.E." DEFT="DESIGN EFFECT" T_BETA="T:BETA=0"
          P_BETA="P-VALUE" DF WALDCHI WALDCHP /
          LSMEANS=ALL T_BETAFMT=F8.2 DEFTFMT=F6.2 DFFMT=F8.0 WALDCHIFMT=F8.2;

10  TITLE "LSMEANS With Categorical Covariate";

NOTE: Terms in the MODEL statement have been rearranged
      to follow subgroup order.

Opened SAS data file C:\ADVANCED\IRONSUD.SSD for reading.

Number of observations read       :   3290    Weighted count: 40570323
Observations used in the analysis :   3290    Weighted count: 40570323
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :     35

Maximum number of estimable parameters for the model is  5

File C:\ADVANCED\IRONSUD.SSD contains   67 clusters
Maximum cluster size is 111 records
Minimum cluster size is  15 records
Weighted mean response is 354.580621
```

LSMEANS Example

Estimated Regression Coefficients for the Model

Date: 05-29-97 Research Triangle Institute Page : 4
Time: 15:28:17 The REGRESS Procedure Table : 1

Variance Estimation Method: Robust (Binder, 1983)
Working Correlations: Independent
Link Function: Identity
Response variable B_TIBC: TOTAL IRON BINDING CAPACITY

LSMEANS With Categorical Covariate

Independent Variables and Effects	BETA	S.E.	DESIGN EFFECT	T:BETA=0	P-VALUE
Intercept	**352.8876**	3.8547	1.09	91.55	0.0000
Age Cohort					
20-49 yrs.	**7.2210**	1.8968	1.12	3.81	0.0005
50+ yrs.	**0.0000**	0.0000	.	.	.
Smoking Status					
Current	**-7.5062**	3.7690	0.95	-1.99	0.0543
Former	**-1.6754**	4.2636	1.25	-0.39	0.6967
Never	**-0.9261**	3.8284	1.06	-0.24	0.8103
Unknown	**0.0000**	0.0000	.	.	.

LSMEANS Example

Least Squares Means Contrast Coefficients:

Smoking Status and Age Group

Since we want to estimate the least squares means of the response within each level of smoking status (a 4-level variable), SUDAAN will produce four rows of contrast coefficients. The first row of the matrix will produce the adjusted means for SMOKE=*current*, the second row is for SMOKE=*former*, and so on. The contrast coefficients for ***smoking status*** are 1's and 0's, indicating the level of interest. Since we are adjusting for ***age group*** as a categorical covariate, the age group coefficients are the weighted (weight = *b_wtiron*) proportion of people in each of the two categories.

Age Group Contrast Coefficients

```
Date: 05-29-97            Research Triangle Institute            Page  : 1
Time: 15:28:17               The REGRESS Procedure               Table : 1

Variance Estimation Method: Robust (Binder, 1983)
Working Correlations: Independent
Link Function: Identity
Response variable B_TIBC: TOTAL IRON BINDING CAPACITY

LS Means Contrast

-------------------------------------------------------------------------
                                          Age Cohort      Age Cohort
                          Intercept       20-49 yrs.        50+ yrs.
-------------------------------------------------------------------------
Smoking Status
  Current                     1.000            0.603           0.397
  Former                      1.000            0.603           0.397
  Never                       1.000            0.603           0.397
  Unknown                     1.000            0.603           0.397
-------------------------------------------------------------------------
```

LSMEANS Example

Least Squares Means Contrast Coefficients:

Smoking Status Coefficients

The contrast coefficients for ***smoking status*** are 1's and 0's, indicating the level of interest in each row.

```
Date: 05-29-97            Research Triangle Institute            Page  : 2
Time: 15:28:17               The REGRESS Procedure               Table : 1

Variance Estimation Method: Robust (Binder, 1983)
Working Correlations: Independent
Link Function: Identity
Response variable B_TIBC: TOTAL IRON BINDING CAPACITY

LS Means Contrast

-------------------------------------------------------------------------------
                  Smoking Status  Smoking Status  Smoking Status  Smoking Status
                         Current         Former           Never         Unknown
-------------------------------------------------------------------------------
Smoking Status
  Current                  1.000          0.000           0.000           0.000
  Former                   0.000          1.000           0.000           0.000
  Never                    0.000          0.000           1.000           0.000
  Unknown                  0.000          0.000           0.000           1.000
-------------------------------------------------------------------------------
```

LSMEANS Example

Least Squares Means Results

Age Group as Categorical Covariate

This table shows the ***estimated least-squares means***, with standard errors that are adjusted for clustering and stratification (via the NEST statement and DESIGN=WR option on the PROC statement).

```
Date: 05-29-97             Research Triangle Institute            Page  : 6
Time: 15:28:17                The REGRESS Procedure               Table : 1

Variance Estimation Method: Robust (Binder, 1983)
Working Correlations: Independent
Link Function: Identity
Response variable B_TIBC: TOTAL IRON BINDING CAPACITY

LSMEANS With Categorical Covariate

-------------------------------------------------------------
Least-Square Means                                   P-value
                                  SE LS   T-Test     T-Test
                          LS Mean Mean    LSM=0      LSM=0
-------------------------------------------------------------
Smoking Status
  Current                 349.7372  2.1938  159.4181   0.0000
  Former                  355.5680  2.2920  155.1367   0.0000
  Never                   356.3173  2.0476  174.0141   0.0000
  Unknown                 357.2434  3.5898   99.5154   0.0000
-------------------------------------------------------------
```

LSMEANS Example

Least Squares Means Contrast Coefficients:

Age at Exam as Continuous Covariate

Now we show how the contrast is formed when age is modelled as a ***continuous*** covariate.

```
11  PROC REGRESS DATA="C:\\ADVANCED\\IRONSUD" FILETYPE=SAS DESIGN=WR DEFT2;

12  NEST Q_STRATA PSU1;

13  WEIGHT B_WTIRON;

14  SUBGROUP SMOKE;

15  LEVELS   4;

16  MODEL B_TIBC = SMOKE AGEXAM;

17  LSMEANS SMOKE / DISPLAY;

18  SETENV COLSPCE=1 LABWIDTH=25 COLWIDTH=8 DECWIDTH=4 LINESIZE=78 PAGESIZE=60;

19  PRINT BETA="BETA" SEBETA="S.E." DEFT="DESIGN EFFECT" T_BETA="T:BETA=0"
          P_BETA="P-VALUE" DF WALDCHI WALDCHP /
          LSMEANS=ALL T_BETAFMT=F8.2 DEFTFMT=F6.2 DFFMT=F8.0 WALDCHIFMT=F8.2;

20  TITLE "LSMEANS With Continuous Covariate";

Opened SAS data file C:\ADVANCED\IRONSUD.SSD for reading.

Number of observations read       :   3290    Weighted count: 40570323
Observations used in the analysis :   3290    Weighted count: 40570323
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :     35

Maximum number of estimable parameters for the model is  5

File C:\ADVANCED\IRONSUD.SSD contains   67 clusters
Maximum cluster size is 111 records
Minimum cluster size is  15 records
Weighted mean response is 354.580621
```

LSMEANS Example

Estimated Regression Coefficients for the Model

Age at Exam as Continuous Covariate

```
Date: 05-29-97            Research Triangle Institute            Page  : 3
Time: 15:28:17               The REGRESS Procedure               Table : 1

Variance Estimation Method: Robust (Binder, 1983)
Working Correlations: Independent
Link Function: Identity
Response variable B_TIBC: TOTAL IRON BINDING CAPACITY

LSMEANS With Continuous Covariate

-------------------------------------------------------------------
Independent Variables and
  Effects                                DESIGN
                          BETA     S.E. EFFECT T:BETA=0  P-VALUE
-------------------------------------------------------------------
Intercept                370.4372  4.9483   1.19    74.86   0.0000
Smoking Status
  Current                 -8.0845  3.7812   0.95    -2.14   0.0396
  Former                  -2.0617  4.2763   1.26    -0.48   0.6327
  Never                   -1.5183  3.8930   1.09    -0.39   0.6989
  Unknown                  0.0000  0.0000    .        .      .
Age at Exam               -0.2778  0.0730   1.27    -3.81   0.0005
-------------------------------------------------------------------
```

LSMEANS Example

Least Squares Means Contrast Coefficients:

Age at Exam as Continuous Covariate

When age at initial exam is modelled as a continuous covariate, its single contrast coefficient is the weighted mean of ***AGEXAM*** (45.706 years). The contrast coefficients for Smoking status are the same as previously.

```
Date: 05-29-97            Research Triangle Institute            Page  : 2
Time: 15:28:17               The REGRESS Procedure               Table : 1

Variance Estimation Method: Robust (Binder, 1983)
Working Correlations: Independent
Link Function: Identity
Response variable B_TIBC: TOTAL IRON BINDING CAPACITY

LS Means Contrast

--------------------------------
                     Age at Exam
--------------------------------
Smoking Status
  Current                45.706
  Former                 45.706
  Never                  45.706
  Unknown                45.706
--------------------------------
```

LSMEANS Example

Least Squares Means Results with Age as Continuous Covariate

This table shows the ***estimated least-squares means***, with standard errors that are adjusted for clustering and stratification (via the NEST statement and DESIGN=WR option on the PROC statement), when Age is modelled as a continuous covariate.

```
Date: 05-29-97            Research Triangle Institute            Page  : 5
Time: 15:28:17               The REGRESS Procedure               Table : 1

Variance Estimation Method: Robust (Binder, 1983)
Working Correlations: Independent
Link Function: Identity
Response variable B_TIBC: TOTAL IRON BINDING CAPACITY

LSMEANS With Continuous Covariate

-------------------------------------------------------------
Least-Square Means                                   P-value
                                  SE LS    T-Test    T-Test
                         LS Mean  Mean     LSM=0     LSM=0
-------------------------------------------------------------
Smoking Status
  Current                349.6539  2.2333   156.5668   0.0000
  Former                 355.6767  2.2900   155.3203   0.0000
  Never                  356.2201  2.0547   173.3643   0.0000
  Unknown                357.7384  3.6201    98.8206   0.0000
-------------------------------------------------------------
```

Design Effects

Design Effect	Measures Variance Inflation Due to:	Default?
DEFT1	Stratification, Clustering, Unequal Weighting, and ***Oversampling***	No; This is the original one; Request on PROC Statement
DEFT2	Stratification, Clustering, Unequal Weighting SRS sample of same size as observed	No; Request on PROC statement
DEFT3	Stratification, Clustering	No; Request on PROC Statement
DEFT4	Stratification, Clustering (unequal weighting?): ***Model-based*** SRS variance (this is the standard software SE when no weights involved) ***Good for experimental designs***	**Yes**

Example 1

Developmental Toxicity Study (EPA, Butler 1988)

- 5 experimental groups
- 25-30 pregnant mice per group, ave 12.4 pups / litter
- Exposure to DEHP (Diethylhexyl phthalate, a plasticizing agent) daily during gestation

  0 ppm (Control group)
  250 ppm
  500 ppm
  1000 ppm
  1500 ppm

- Outcomes in Fetuses (within litters)

  Fetal Death (yes/no)
  Malformations (yes/no)
  Fetal Body Weight

- Focus here on fetal death: Clustered Binary Data

$$y_{ij} = \begin{cases} 0, & \text{if fetus alive} \\ 1, & \text{if fetus dead} \end{cases}$$

Question: Does the incidence of fetal death (and/or malformation) increase with dosage?

Example 1:

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

This example demonstrates the cluster sample or GEE model-fitting techniques (Zeger and Liang, 1986; Liang and Zeger, 1986) and the Jackknife in the context of a typical teratology experiment. For comparison, we include results based on a strictly binomial model (independence).

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 2 to 4 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.

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 program produces dose-specific descriptive statistics (via PROC DESCRIPT) and fits a logistic dose-response model (via PROC LOGISTIC) based on the teratology experiment. For demonstration purposes, we fit two logistic models, one with a single regressor (dose level) and another with indicator variables corresponding to each treatment group.

The sample design option ***WR*** (shorthand notation for "with-replacement sampling") on the LOGISTIC and DESCRIPT procedure statements invokes the robust variance estimator that is appropriate for these experimental data. The ***NEST*** statement in SUDAAN indicates that litters (represented by DAM) represent the clusters. The requested test statistics ***WALDCHI*** and ***SATADJCHI*** refer to the usual Wald chi-squared test and the Satterthwaite-adjusted chi-squared test (Rao and Scott, 1987), respectively. The latter test is a modification of the usual Wald statistic and has been shown to have superior operating characteristics for multiple-degree-of-freedom hypotheses in small samples (Thomas and Rao, 1987).

The estimated dose group percentages and their standard errors under the cluster sample vs. strictly binomial models are contained in Figure 1. 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).

Figure 1 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. 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):

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

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

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

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 0.85 to 6.32 for these data (see Figure 1). The 250 and 500 ppm groups had design effects just under 1.0 (when $V_{Cluster} \doteq V_{Indep}$), 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 5-fold increase in the strictly binomial variance due to intralitter correlation. The observed design effects closely corresponded to the predicted values (1) in each group, with predictions based on the dose-specific weighted litter sizes and correlations estimated by Butler.

To implement the cluster sample methods (via SUDAAN), we estimated the model parameters under a standard binomial likelihood and computed a robust variance estimate. This is also known as ***ordinary logistic regression with a variance correction*** and is equivalent to a GEE logistic model with independent "working" correlations (which we refer to as ***GEE-independent***). The Wald chi-square test was used to evaluate the null hypothesis of no dose-related effect.

For comparison, the same logistic models were also fit using:

1) GEE logistic regression models under exchangeable intralitter correlations ***(GEE-exchangeable)***,
2) ordinary logistic regression with ***Jackknife variance estimation***, and
3) ***ordinary logistic regression with no variance correction***.

Results for the GEE and Jackknife approaches were essentially the same. For testing that the slope parameter from a linear logistic model is equal to zero (Figure 3), the GEE-exchangeable approach yielded a *Z*-statistic of 9.17, compared to a GEE-independent *Z*-statistic of 8.63 and a Jackknife Z-statistic of 8.41. The estimated slope parameter was slightly larger using the GEE approach with exchangeable correlations (β = 0.00256 vs. 0.00249 for GEE-independent and

Jackknife), but this had no substantial impact on test statistics. Estimated standard errors for the GEE-exchangeable and GEE-independent approaches were equivalent (0.00029), and for Jackknife the estimated standard error was 0.00030. The observed design effect for the logistic model slope parameter was over 5.0 for these data, reflecting substantial intralitter correlations. The impact of this design effect is manifested in an inflated *Z*-statistic of 19.76 obtained from ordinary logistic regression with ***no*** variance correction.

Example 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)

Figure 1

Descriptive Statistics for Fetal Death in the DEHP Data

Dose Group	Number Litters	Number Fetuses	Total Dead	Percentage Dead	Standard Error		Design Effect	
					Cluster	Indep.	Obs.	Predicted
Control	30	396	66	16.67	4.11	1.87	4.82	4.79
250 ppm	26	320	32	10.00	1.53	1.68	0.83	0.88
500 ppm	26	319	42	13.17	1.84	1.89	0.95	0.88
1000 ppm	24	276	139	50.36	7.44	3.01	6.10	6.10
1500 ppm	25	308	258	83.77	4.65	2.10	4.89	4.93

SUDAAN **Standard Packages:** ***Too Small***

Cluster: SUDAAN (Descript Procedure)
Independence: Standard Statistical Packages (*e.g.,* SAS)

$$\text{Observed DEFF} = \frac{V_{CLUSTER}}{V_{INDEPENDENCE}}$$

$$\text{Predicted DEFF} = 1 + \hat{\rho}_i(\tilde{m}_i - 1)$$

$\tilde{m}_i$ = dose-specific weighted litter sizes

= (13.62, 12.85, 12.75, 13.14, 12.56)

$\hat{\rho}_i$ = dose-specific intra-cluster correlation (Butler, 1988)

= (0.30, -0.01, -0.01, 0.42, 0.34)

Source: Bieler and Williams (1995), *Biometrics* **51**, 764-776.

Figure 2

Logistic Regression for the DEHP Data

Exposed vs. Control Group Contrasts

Contrast	Model-Fitting Method	β_j	S.E.	Z	P-Value
250 Vs. Control	GEE (indep)	-0.5878	0.3413	-1.72	0.0874
	GEE (exch corr)	-0.5214	0.3307	-1.58	0.1142
	Jackknife	-0.5878	0.3619	-1.62	0.1068
	Independence	-0.5878	0.2300	-2.56	0.0104
500 Vs. Control	GEE (indep)	-0.2769	0.3370	-0.82	0.4128
	GEE (exch corr)	-0.2269	0.3310	-0.69	0.4902
	Jackknife	-0.2769	0.3562	-0.78	0.4383
	Independence	-0.2769	0.2135	-1.30	0.1947
1000 Vs. Control	GEE (indep)	1.6239	0.4197	3.87	0.0002
	GEE (exch corr)	1.6938	0.4004	4.23	0.0000
	Jackknife	1.6239	0.4430	3.67	0.0004
	Independence	1.6239	0.1808	8.98	0.0000
1500 Vs. Control	GEE (indep)	3.2504	0.4523	7.19	0.0000
	GEE (exch corr)	3.3346	0.4470	7.46	0.0000
	Jackknife	3.2504	0.4792	6.78	0.0000
	Independence	3.2504	0.2051	15.85	0.0000

GEE (indep): SUDAAN Logistic Procedure
GEE (exch): SUDAAN Multilog Procedure
Jackknife: SUDAAN Logistic Procedure
Independence: Standard Packages (*e.g.*, SAS Logistic)

Figure 3

Logistic Regression for the DEHP Data

Test for Dose-Related Trend (H_o: $\beta = 0$)

Model-Fitting Method	β	S.E.	Z	P-Value	Design Effect Observed	Design Effect Predicted
GEE independent	0.00249	0.00029	8.63	0.0000	4.64	4.11
GEE exchangeable	0.00256	0.00029	9.17	0.0000		
Jackknife	0.00249	0.00030	8.41	0.0000		
Independence	0.00249	0.00013	19.76	0.0000		

GEE independent: SUDAAN Logistic Procedure
GEE exchangeable: SUDAAN Multilog Procedure
Jackknife: SUDAAN Logistic Procedure
Independence: Standard Packages (*e.g.*, SAS Logistic)

Source: Bieler and Williams (1995), *Biometrics* **51**, 764-776.

$$\text{Observed DEFF} = \frac{V_{GEE\ Indep.}}{V_{INDEPENDENCE}}$$

$$\text{Predicted DEFF} = 1 + \hat{\rho}_y (\tilde{n} - 1)$$

$\tilde{n} = 13.01$ for the DEHP data

$\hat{\rho}_y = 0.259$ for the DEHP data

Example 1.

The LEVEL.DBS File:

Contains Value Labels For Categorical Effects

```
DEAD     1      Yes
DEAD     0      No
DOSE_5   1      CONTROL
DOSE_5   2      250 ppm
DOSE_5   3      500 ppm
DOSE_5   4      1000 ppm
DOSE_5   5      1500 ppm
```

Record Layout for the LEVEL.DBS File:

Columns	Description
1-8	Variable Name
9-10	Level of the Variable
17-66	Text Label For This Level of the Variable

Note: The LEVEL.DBS file can document multiple datasets in the same directory

Example 1 Results:

Descriptive Statistics

```
1   PROC DESCRIPT DATA="TERATA" FILETYPE=SAS NOMARG ATLEVEL1=2 DESIGN=WR;

2   NEST _ONE_ DAM;

3   WEIGHT _ONE_;

4   VAR DEAD;

5   CATLEVEL 1;

6   SUBGROUP DOSE_5;

7   LEVELS   5;

8   SETENV LABWIDTH=16 COLWIDTH=10 LINESIZE=78 DECWIDTH=2 PAGESIZE=60;

9   PRINT ATLEV1=" NUMBER LITTERS"
          NSUM= " NUMBER FETUSES"
          TOTAL="TOTAL  DEAD"
          PERCENT="PERCENTAGE       DEAD"
          SEPERCENT="STANDARD    ERROR"
          DEFFPCT="DESIGN EFFECT"/
          STYLE=NCHS ATLEV1FMT=F7.0 NSUMFMT=F7.0 DEFFPCTFMT=F6.2
         SEPERCENTFMT=F8.2 TOTALFMT=F5.0;

10  TITLE "DESCRIPTIVE STATISTICS FOR TERATOLOGY DATA"
          "FETAL DEATH IN CD-1 MICE";

Opened SAS data file C:\TERA\EXAMPLES\TERATA.SSD for reading.

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

Example 1 Results:

Descriptive Statistics

```
Date: 03-19-97            Research Triangle Institute            Page  : 1
Time: 14:53:51              The DESCRIPT Procedure               Table : 1

DESCRIPTIVE STATISTICS FOR TERATOLOGY DATA

FETAL DEATH IN CD-1 MICE

-------------------------------------------------------------------------------
Variable            NUMBER    NUMBER   TOTAL   PERCENTAGE   STANDARD   DESIGN
   Dose Group      LITTERS   FETUSES    DEAD         DEAD      ERROR   EFFECT
-------------------------------------------------------------------------------
DEAD: Yes
   CONTROL              30       396      66        16.67       4.11     4.82
   250 ppm              26       320      32        10.00       1.53     0.83
   500 ppm              26       319      42        13.17       1.84     0.95
   1000 ppm             24       276     139        50.36       7.44     6.10
   1500 ppm             25       308     258        83.77       4.65     4.89
-------------------------------------------------------------------------------

DESCRIPT used
  CPU time       : 3.74 seconds
  Elapsed time   : 4 seconds
  Virtual memory : 0.84 MB
```

These results are contained in Figure 1. Note the NEST statement specification of DAM as the primary sampling unit (the cluster). With DAM as the cluster and the sample design option WR (with-replacement), the standard errors reported in this table are adjusted for clustering.

Example 1 Results:

Descriptive Statistics

```
11  PROC DESCRIPT DATA="TERATA" FILETYPE=SAS NOMARG DESIGN=WR;

12  NEST _ONE_ DAM;

13  WEIGHT _ONE_;

14  VAR DEAD;

15  CATLEVEL 1;

16  SUBGROUP DOSE_5;

17  LEVELS   5;

18  CONTRAST DOSE_5 = (-1 1 0 0 0) / NAME = "Low Dose  Vs. Control";

19  CONTRAST DOSE_5 = (-1 0 1 0 0) / NAME = "500 ppm   Vs. Control";

20  CONTRAST DOSE_5 = (-1 0 0 1 0) / NAME = "1500 ppm  Vs. Control";

21  CONTRAST DOSE_5 = (-1 0 0 0 1) / NAME = "High Dose Vs. Control";

22  SETENV LABWIDTH=25 COLWIDTH=10 LINESIZE=78 DECWIDTH=2 PAGESIZE=60;

23  PRINT PERCENT="DIFFERENCE"
          SEPERCENT="STANDARD    ERROR"
          T_PCT="T-STAT"
          P_PCT="P-VALUE"/
          STYLE=NCHS SEPERCENTFMT=F8.2 T_PCTFMT=F6.2 P_PCTFMT=F7.4;

24  TITLE "DESCRIPTIVE STATISTICS FOR TERATOLOGY DATA"
          "FETAL DEATH IN CD-1 MICE";


Opened SAS data file C:\TERA\EXAMPLES\TERATA.SSD for reading.

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

Here we construct ***contrasts*** to compare the percentages of dead pups across dose groups. We used the CATLEVEL statement to estimate percentages instead of proportions (the response DEAD is a 0-1 variable). The design option and NEST statements are equivalent to the previous run. There are 1,619 pups on the file and 130 denominator DF (#litters - 1) available for computing variance estimates.

Example 1 Results:

Descriptive Statistics

```
Date: 03-19-97            Research Triangle Institute            Page  : 1
Time: 14:53:51              The DESCRIPT Procedure               Table : 1

DESCRIPTIVE STATISTICS FOR TERATOLOGY DATA

FETAL DEATH IN CD-1 MICE

Variable = DEAD: Yes.
---------------------------------------------------------------------
Contrast                                  STANDARD
                           DIFFERENCE       ERROR   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
1500 ppm  Vs. Control           33.70        8.50     3.96    0.0001
High Dose Vs. Control           67.10        6.21    10.81    0.0000
---------------------------------------------------------------------

DESCRIPT used
  CPU time       : 4.17 seconds
  Elapsed time   : 5 seconds
  Virtual memory : 0.92 MB
```

Here we see that the 1,000 and 1,500 ppm groups have significantly higher fetal death rates than the control group.

Example 1 Results: GEE-Independent Logistic Regression Model

```
25  PROC LOGISTIC DATA="TERATA" FILETYPE=SAS DESIGN=WR;

26  NEST _ONE_ DAM;

27  WEIGHT _ONE_;

28  SUBGROUP DOSE_5;

29  LEVELS   5;

30  REFLEVEL DOSE_5 = 1;

31  MODEL DEAD = DOSE_5;

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

33  TEST SATADJCHI WALDCHI;

34  SETENV COLSPCE=1 LABWIDTH=22 COLWIDTH=8 DECWIDTH=4 LINESIZE=78 PAGESIZE=60;

35  PRINT BETA="BETA" SEBETA="S.E." DEFT="DESIGN EFFECT" T_BETA="T:BETA=0"
          P_BETA="P-VALUE" OR LOWOR UPOR
          DF="DF" SATADJDF="ADJ DF"
          WALDCHI="  CHI-SQ   (WALD)" SATADCHI="  CHI-SQ   (SAT.)"
          WALDCHP=" P-VALUE  (WALD)"  SATADCHP=" P-VALUE  (SAT.)"
          /T_BETAFMT=F8.2 DEFTFMT=F6.2 SEBETAFMT=F8.6
           ORFMT=F5.2 LOWORFMT=F6.2 UPORFMT=F6.2
           DFFMT=F7.0 SATADJDFFMT=F8.2 WALDCHIFMT=F8.2 SATADCHIFMT=F8.2;

36  TITLE "TESTING DOSE GROUP HETEROGENEITY"
          "FETAL DEATH IN CD-1 MICE";

Opened SAS data file C:\TERA\EXAMPLES\TERATA.SSD for reading.
Number of zero responses     :  1082
Number of non-zero responses :   537

Parameters have converged in 4 iterations

Number of observations read       :   1619    Weighted count:     1619
Observations used in the analysis :   1619    Weighted count:     1619
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :    130

Maximum number of estimable parameters for the model is  5
R-Square for dependent variable DEAD (Cox & Snell, 1989): 0.304579
```

Example 1 Results: GEE-Independent Logistic Regression Model

Here we fit a ***GEE logistic regresion model with independent working correlations.*** Dose group is modelled as a 5-level categorical covariate so we can compare each group to control. The REFLEVEL statement is used to select dose group level 1 (control) to be the reference level for DOSE_5 in the model. The R-square statistic is based on Cox and Snell (1989) as the proportion of the log-likelihood that is explained by the model. The EFFECTS statement requests a single degree-of-freedom contrast comparing the high dose to control.

Example 1 Results:

GEE-Independent Logistic Regression Model

```
Date: 03-19-97            Research Triangle Institute            Page  : 1
Time: 14:53:51              The LOGISTIC Procedure               Table : 1

Response variable DEAD: DEAD
TESTING DOSE GROUP HETEROGENEITY

FETAL DEATH IN CD-1 MICE

---------------------------------------------------------------------
Independent Variables
  and Effects                              DESIGN
                          BETA     S.E. EFFECT T:BETA=0  P-VALUE
---------------------------------------------------------------------
Intercept               -1.6094 0.296054   4.82    -5.44   0.0000
DOSE GROUP
  CONTROL                0.0000 0.000000    .        .      .
  250 ppm               -0.5878 0.341270   2.20    -1.72   0.0874
  500 ppm               -0.2769 0.337047   2.49    -0.82   0.4128
  1000 ppm               1.6239 0.419743   5.39     3.87   0.0002
  1500 ppm               3.2504 0.452258   4.86     7.19   0.0000
---------------------------------------------------------------------
```

```
Date: 03-19-97            Research Triangle Institute            Page  : 2
Time: 14:53:51              The LOGISTIC Procedure               Table : 1

Response variable DEAD: DEAD
TESTING DOSE GROUP HETEROGENEITY

FETAL DEATH IN CD-1 MICE

-------------------------------------------------------------------------
Contrast                                  CHI-SQ   CHI-SQ  P-VALUE  P-VALUE
                           DF   ADJ DF   (WALD)   (SAT.)  (WALD)   (SAT.)
-------------------------------------------------------------------------
OVERALL MODEL               5     3.60   357.23   107.13   0.0000   0.0000
MODEL MINUS INTERCEPT       4     3.01   132.94    94.87   0.0000   0.0000
INTERCEPT                   .      .       .        .       .        .
DOSE_5                      4     3.01   132.94    94.87   0.0000   0.0000
Control vs. High Dose       1     1.00    51.65    51.65   0.0000   0.0000
-------------------------------------------------------------------------
```

Example 1 Results:

GEE Independent Logistic Regression Model

```
Date: 03-19-97            Research Triangle Institute            Page  : 3
Time: 14:53:51              The LOGISTIC Procedure               Table : 1

Response variable DEAD: DEAD
TESTING DOSE GROUP HETEROGENEITY

FETAL DEATH IN CD-1 MICE

----------------------------------------
Independent Variables
  and Effects                 Lower  Upper
                       Odds    95%    95%
                       Ratio  Limit  Limit
----------------------------------------
Intercept               0.20   0.11   0.36
DOSE GROUP
  CONTROL               1.00   1.00   1.00
  250 ppm               0.56   0.28   1.09
  500 ppm               0.76   0.39   1.48
  1000 ppm              5.07   2.21  11.63
  1500 ppm             25.80  10.55  63.10
----------------------------------------

LOGISTIC used
  CPU time       : 7.75 seconds
  Elapsed time   : 8 seconds
  Virtual memory : 1.31 MB
```

These results indicate that the two highest dose groups have a significantly higher fetal death risk than the control group (odds ratios are 5.07 and 25.80, respectively). The treatment effect is statistically significant (p=0.0000).

Example 1 Results:

GEE-Independent Logistic Regression Model

```
37  PROC LOGISTIC DATA="TERATA" FILETYPE=SAS DESIGN=WR;

38  NEST _ONE_ DAM;

39  WEIGHT _ONE_;

40  MODEL DEAD = DOSE;

41  TEST WALDCHI SATADJCHI;

42  SETENV COLSPCE=1 LABWIDTH=22 COLWIDTH=8 DECWIDTH=4 LINESIZE=78 PAGESIZE=60;

43  PRINT BETA="BETA" SEBETA="S.E." DEFT="DESIGN EFFECT" T_BETA="T:BETA=0"
          P_BETA="P-VALUE" DF="DF" SATADJDF="ADJ DF"
          WALDCHI="  CHI-SQ   (WALD)" SATADCHI="  CHI-SQ   (SAT.)"
          WALDCHP=" P-VALUE  (WALD)"  SATADCHP=" P-VALUE  (SAT.)"
          /SEBETAFMT=F8.6 DFFMT=F7.0 T_BETAFMT=F8.2 DEFTFMT=F6.2
           SATADJDFFMT=F8.2 WALDCHIFMT=F8.2 SATADCHIFMT=F8.2;

44  TITLE "TESTING DOSE-RELATED TREND"
          "FETAL DEATH IN CD-1 MICE";

Opened SAS data file C:\TERA\EXAMPLES\TERATA.SSD for reading.
Number of zero responses     :  1082
Number of non-zero responses :   537

Parameters have converged in 4 iterations

Number of observations read       :   1619    Weighted count:     1619
Observations used in the analysis :   1619    Weighted count:     1619
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :    130

Maximum number of estimable parameters for the model is  2

R-Square for dependent variable DEAD (Cox & Snell, 1989): 0.277411
```

Now we model the treatment effect as a continuous covariate, using the actual dosage levels as the covariate values. For this reason, we do not use a SUBGROUP statement here.

Example 1 Results:

GEE Independent Logistic Regression Model

```
Date: 03-19-97            Research Triangle Institute            Page  : 1
Time: 14:53:51              The LOGISTIC Procedure               Table : 1

Response variable DEAD: DEAD
TESTING DOSE-RELATED TREND

FETAL DEATH IN CD-1 MICE

-----------------------------------------------------------------
Independent Variables
  and Effects                          DESIGN
                          BETA     S.E. EFFECT T:BETA=0  P-VALUE
-----------------------------------------------------------------
Intercept               -2.4300 0.255035   5.01    -9.53   0.0000
DOSAGE                   0.0025 0.000289   5.27     8.63   0.0000
-----------------------------------------------------------------
```

```
Date: 03-19-97            Research Triangle Institute            Page  : 2
Time: 14:53:51              The LOGISTIC Procedure               Table : 1

Response variable DEAD: DEAD
TESTING DOSE-RELATED TREND

FETAL DEATH IN CD-1 MICE

-------------------------------------------------------------------------
Contrast
                                        CHI-SQ   CHI-SQ  P-VALUE  P-VALUE
                           DF   ADJ DF  (WALD)   (SAT.)  (WALD)   (SAT.)
-------------------------------------------------------------------------
OVERALL MODEL               2     1.98   91.65    97.21   0.0000   0.0000
MODEL MINUS INTERCEPT       1     1.00   74.53    74.53   0.0000   0.0000
INTERCEPT                   1     1.00   90.78    90.78   0.0000   0.0000
DOSE                        1     1.00   74.53    74.53   0.0000   0.0000
-------------------------------------------------------------------------

LOGISTIC used
  CPU time       : 6.92 seconds
  Elapsed time   : 7 seconds
  Virtual memory : 1.24 MB
```

These results indicate there is a significant dose-related trend on the fetal death rate (p=0.0000).

Example 1 Results

Jackknife Variance Estimation

Below are the results obtained using Jackknife variance estimation. The option ***DESIGN=Jackknife*** is added to the PROC statement. All other programming statements are the same as previous. We begin with dose group modelled as a categorical covariate.

```
45  PROC LOGISTIC DATA="TERATA" FILETYPE=SAS DESIGN=JACKKNIFE;

46  NEST _ONE_ DAM;

47  WEIGHT _ONE_;

48  SUBGROUP DOSE_5;

49  LEVELS   5;

50  REFLEVEL DOSE_5=1;

51  MODEL DEAD = DOSE_5;

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

53  TEST SATADJCHI WALDCHI;

54  SETENV COLSPCE=1 LABWIDTH=22 COLWIDTH=8 DECWIDTH=4 LINESIZE=78 PAGESIZE=60;

55  PRINT BETA="BETA" SEBETA="S.E." DEFT="DESIGN EFFECT" T_BETA="T:BETA=0"
          P_BETA="P-VALUE" OR LOWOR UPOR
          DF="DF" SATADJDF="ADJ DF"
          WALDCHI="  CHI-SQ   (WALD)" SATADCHI="  CHI-SQ   (SAT.)"
          WALDCHP=" P-VALUE  (WALD)"  SATADCHP=" P-VALUE  (SAT.)"
          /T_BETAFMT=F8.2 DEFTFMT=F6.2 SEBETAFMT=F8.6
           ORFMT=F5.2 LOWORFMT=F6.2 UPORFMT=F6.2
           DFFMT=F7.0 SATADJDFFMT=F8.2 WALDCHIFMT=F8.2 SATADCHIFMT=F8.2;

56  TITLE "TESTING DOSE GROUP HETEROGENEITY VIA JACKKNIFE"
          "FETAL DEATH IN CD-1 MICE";

Opened SAS data file C:\TERA\EXAMPLES\TERATA.SSD for reading.

Number of observations read       :   1619    Weighted count:     1619
Observations used in the analysis :   1619    Weighted count:     1619
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :    130

Maximum number of estimable parameters for the model is  5
Number of zero responses     :  1082
Number of non-zero responses :   537

Parameters have converged in 4 iterations

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

Example 1 Results

Jackknife Variance Estimation

```
Date: 03-19-97            Research Triangle Institute            Page  : 1
Time: 14:53:51              The LOGISTIC Procedure               Table : 1

Response variable DEAD: DEAD

TESTING DOSE GROUP HETEROGENEITY VIA JACKKNIFE

FETAL DEATH IN CD-1 MICE

-----------------------------------------------------------------
Independent Variables
  and Effects                            DESIGN
                           BETA     S.E. EFFECT T:BETA=0  P-VALUE
-----------------------------------------------------------------
Intercept               -1.6094 0.314927   5.45    -5.11   0.0000
DOSE GROUP
  CONTROL                0.0000 0.000000    .        .      .
  250 ppm               -0.5878 0.361909   2.48    -1.62   0.1068
  500 ppm               -0.2769 0.356192   2.78    -0.78   0.4383
  1000 ppm               1.6239 0.443029   6.01     3.67   0.0004
  1500 ppm               3.2504 0.479198   5.46     6.78   0.0000
-----------------------------------------------------------------
```

```
Date: 03-19-97            Research Triangle Institute            Page  : 2
Time: 14:53:51              The LOGISTIC Procedure               Table : 1

Response variable DEAD: DEAD

TESTING DOSE GROUP HETEROGENEITY VIA JACKKNIFE

FETAL DEATH IN CD-1 MICE

-------------------------------------------------------------------------
Contrast                                 CHI-SQ   CHI-SQ  P-VALUE  P-VALUE
                           DF   ADJ DF   (WALD)   (SAT.)  (WALD)   (SAT.)
-------------------------------------------------------------------------
OVERALL MODEL               5     3.59   327.07    96.31   0.0000   0.0000
MODEL MINUS INTERCEPT       4     3.00   119.97    85.19   0.0000   0.0000
INTERCEPT                   .      .       .        .       .        .
DOSE_5                      4     3.00   119.97    85.19   0.0000   0.0000
Control vs. High Dose       1     1.00    46.01    46.01   0.0000   0.0000
-------------------------------------------------------------------------
```

Here we see that the ***estimated regression coefficients*** for the Jackknife are identical to those used for GEE-independent, but the estimated standard errors are just slightly larger.

Nevertheless, the *p*-values from the two approaches are still quite similar, and both approaches have been shown to be valid for adjusting for intracluster correlation.

Example 1 Results

Jackknife Variance Estimation

```
Date: 03-19-97             Research Triangle Institute             Page  : 3
Time: 14:53:51               The LOGISTIC Procedure                Table : 1

Response variable DEAD: DEAD

TESTING DOSE GROUP HETEROGENEITY VIA JACKKNIFE

FETAL DEATH IN CD-1 MICE

----------------------------------------
Independent Variables
  and Effects                 Lower  Upper
                       Odds    95%    95%
                       Ratio  Limit  Limit
----------------------------------------
Intercept               0.20   0.11   0.37
DOSE GROUP
  CONTROL               1.00   1.00   1.00
  250 ppm               0.56   0.27   1.14
  500 ppm               0.76   0.37   1.53
  1000 ppm              5.07   2.11  12.18
  1500 ppm             25.80  10.00  66.56
----------------------------------------

LOGISTIC used
  CPU time       : 19.99 seconds
  Elapsed time   : 20 seconds
  Virtual memory : 1.25 MB
```

Since the estimated standard errors are slightly larger for the Jackknife vs. GEE-independent approaches using these data, the ***95% confidence bands*** around the ***estimated odds ratios*** are also slightly wider using the Jackknife. Note that the odds ratios themselves are identical because the same regression coefficients are used for both approaches.

Example 1 Results

Jackknife Variance Estimation

```
57  PROC LOGISTIC DATA="TERATA" FILETYPE=SAS DESIGN=JACKKNIFE;

58  NEST _ONE_ DAM;

59  WEIGHT _ONE_;

60  MODEL DEAD = DOSE;

61  TEST WALDCHI SATADJCHI;

62  SETENV COLSPCE=1 LABWIDTH=22 COLWIDTH=8 DECWIDTH=4 LINESIZE=78 PAGESIZE=60;

63  PRINT BETA="BETA" SEBETA="S.E." DEFT="DESIGN EFFECT" T_BETA="T:BETA=0"
          P_BETA="P-VALUE" DF="DF" SATADJDF="ADJ DF"
          WALDCHI="  CHI-SQ   (WALD)" SATADCHI="  CHI-SQ   (SAT.)"
          WALDCHP=" P-VALUE  (WALD)"  SATADCHP=" P-VALUE  (SAT.)"
          /SEBETAFMT=F8.6 DFFMT=F7.0 T_BETAFMT=F8.2 DEFTFMT=F6.2
           SATADJDFFMT=F8.2 WALDCHIFMT=F8.2 SATADCHIFMT=F8.2;

64  TITLE "TESTING DOSE-RELATED TREND VIA JACKKNIFE"
          "FETAL DEATH IN CD-1 MICE";

Opened SAS data file C:\TERA\EXAMPLES\TERATA.SSD for reading.

Number of observations read       :   1619    Weighted count:     1619
Observations used in the analysis :   1619    Weighted count:     1619
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :    130

Maximum number of estimable parameters for the model is  2
Number of zero responses     :  1082
Number of non-zero responses :   537

Parameters have converged in 4 iterations

R-Square for dependent variable DEAD (Cox & Snell, 1989): 0.277411
```

Here are the Jackknife results with dosage modelled as a continuous covariate.

Example 1 Results

Jackknife Variance Estimation

```
Date: 03-19-97            Research Triangle Institute            Page  : 1
Time: 14:53:51              The LOGISTIC Procedure               Table : 1

Response variable DEAD: DEAD

TESTING DOSE-RELATED TREND VIA JACKKNIFE

FETAL DEATH IN CD-1 MICE

-------------------------------------------------------------------
Independent Variables
  and Effects                            DESIGN
                           BETA     S.E. EFFECT T:BETA=0  P-VALUE
-------------------------------------------------------------------
Intercept               -2.4300 0.262856   5.32    -9.24   0.0000
DOSAGE                   0.0025 0.000297   5.56     8.41   0.0000
-------------------------------------------------------------------
```

```
Date: 03-19-97            Research Triangle Institute            Page  : 2
Time: 14:53:51              The LOGISTIC Procedure               Table : 1

Response variable DEAD: DEAD

TESTING DOSE-RELATED TREND VIA JACKKNIFE

FETAL DEATH IN CD-1 MICE

-------------------------------------------------------------------------------
Contrast                                  CHI-SQ   CHI-SQ  P-VALUE  P-VALUE
                           DF   ADJ DF   (WALD)   (SAT.)  (WALD)   (SAT.)
-------------------------------------------------------------------------------
OVERALL MODEL               2     1.98    86.29    92.58   0.0000   0.0000
MODEL MINUS INTERCEPT       1     1.00    70.66    70.66   0.0000   0.0000
INTERCEPT                   1     1.00    85.46    85.46   0.0000   0.0000
DOSE                        1     1.00    70.66    70.66   0.0000   0.0000
-------------------------------------------------------------------------------

LOGISTIC used
  CPU time       : 16.92 seconds
  Elapsed time   : 17 seconds
  Virtual memory : 1.24 MB
```

These Jackknife results are almost identical to the GEE-independent results shown earlier.

Example 2. Multivariate Failure Time Data

Evaluation of a Coronary Heart Disease Drug on Repeated Exercise Times to Angina Pectoris

This example demonstrates SUDAAN's correlated data techniques in the context of a clinical trial. The data for this example represent repeated exercise times (in seconds) to angina pectoris in patients with coronary heart disease. We analyzed the data reported by Crouchley and Pickles (1993), in which 21 subjects were each tested four times on one day and a further four times two days later. On each day exercise time measurements were taken just before and at 1 hour, 3 hours, and 5 hours following drug administration. On one day the drug was an active treatment (an oral dose of isosorbide dinitrate) and on the other placebo. Although undertaken as a double-blind randomized cross-over design, the published data do not indicate the order of treatment, preventing any testing for carry-over effects.

The Cox proportional hazards model was used to evaluate the regression effect of treatment (or test day), after adjusting for several covariates: time since drug administration (4-level factor), and indicators for previous myocardial infarction (MI), previous coronary artery bypass surgery (CAB), and previous propranolol treatment (PP). Note that treatment day and time since drug administration are ***within-cluster*** covariates, while MI, PP, and CAB represent ***cluster-level*** covariates. For comparison, we include results based on assuming complete independence among the 8 failure times per subject.

The SUDAAN program contains code to fit the Cox proportional hazards model to the observed event times. The default sample design option ***DESIGN=WR*** (notation for "with-replacement sampling") invokes the robust variance estimator that is appropriate for the study. The ***NEST*** statement in SUDAAN indicates that the patient (PATIENT) represents the cluster or primary sampling unit, with the keyword ***_ONE_*** indicating there is a single design stratum. Additional sources of intracluster correlation, such as time within each study day, need not be specified. The requested test statistics ***WALDCHI*** and ***SATADJCHI*** refer to the Wald chi-square test and the Satterthwaite-adjusted chi-square test (Rao and Scott, 1987), respectively. The latter test is a modification of the Wald statistic and has been shown to have superior operating characteristics for multiple-degree-of-freedom hypotheses in small samples (Thomas and Rao, 1987).

Three sets of proportional hazards models were fit:

1) Model 1 was the ***main effects model***, and it included the main effects of treatment (or study day), time since drug administration (modelled as a 4-level categorical variable corresponding to pre-dosing, 1-hour, 3-hours, and 5-hours post-dosing), and the three continuous covariates MI, CAB, and PP.

2) Model 2 was the ***interaction model***, containing the main effects in Model 1 and the interaction effects between treatment and time since drug administration.

3) Finally, in Model 3 we evaluated the ***simple effects of treatment*** at each of the four times since drug administration. Model 3 required four separate runs of the proportional hazards model containing the treatment effect and the three

continuous covariates. The four runs corresponded to each of the four times since drug administration.

SUDAAN results from fitting Models 1-3 are contained in the SUDAAN output, and results from the main effects model are contained in Figure 1.

To implement the cluster sample methods using SUDAAN, we estimated the model parameters under a standard partial likelihood and applied a robust variance estimator (labelled ***Robust*** in Figure 1). The Wald chi-square test was used to evaluate the null hypothesis of no treatment effect. For comparison, the same proportional hazards model was also fit assuming complete independence of the response times (labelled ***Naive*** in Figure 1).

Figure 1 contains results for the main effects model. Note that for parameters which represent ***cluster-level covariates***, the cluster sample method results in a substantial ***increase*** in standard errors. However, for ***within-cluster covariates*** (*e.g.*, the treatment and time effects), the cluster variance estimates are substantially ***smaller*** than the independence estimates. Using the design effect results of Neuhaus and Segal (1993) and proceeding by analogy to failure time data, the large observed design effects for the cluster-level covariates (*e.g.*, previous bypass surgery) indicate large response intracluster correlations. In this situation, the variance of the regression coefficients for such covariates is increased. However, the observed design effects for within-cluster covariates whose patterns do not vary from cluster to cluster (time since drug administration and treatment day) were much less than 1 (as low as 0.30), which would be expected when the response intracluster correlation is positive and the covariate intracluster correlation is negative. In this case, variance estimates for the regression coefficients would be smaller than that expected under independence, corresponding to a gain in efficiency.

As seen in Figure 1, tests for treatment effects and time since drug administration were statistically significant under the cluster sample and independence approaches, but were slightly more significant under the cluster sample approach. Using cluster sample techniques, SUDAAN reports the estimated hazard ratio for treatment vs. control in the main effects only model to be 0.43, with a 95% confidence interval of (0.32 - 0.59). A hazard ratio less than 1.0 indicates longer exercise times in the treatment group (a protective effect against angina pectoris), and this can be seen in the predicted survival (Kaplan-Meier) functions (computed at pre-dosing, and 1-, 3-, and 5-hours post-dosing). The Kaplan-Meier functions suggest that the treatment differences are largest at 1 and 3-hours post-dosing, and in fact, SUDAAN reports a significant interaction effect between treatment day and time since drug administration (p=0.0204, Wald chi-square test). The estimated hazard ratios at 1 and 3-hours post-dosing are 0.28 and 0.34, respectively; and the hazard ratios at pre-dosing and 5-hours post-dosing are 0.56 and 0.48, respectively.

Tests for the cluster-level covariates (previous MI, bypass surgery, and propranolol treatment) became less significant under the cluster sample approach, and only previous myocardial infarction remained statistically significant in each of the three models (interaction, main effects, and time-specific treatment effects models) due to the large design effects. A user-defined general linear contrast for testing the joint effects of the three covariates is demonstrated for the main effects model (via the EFFECTS statement).

Cross-Over Clinical Trial

Repeated Exercise Times to Angina Pectoris

(Crouchley and Pickles, *Biometrics*, 1993)

- Double-blind randomized cross-over design
  (not enough info to test carry-over effects)

- 21 male patients (clusters) with coronary heart disease

- Tested 4 times on each of two consecutive days
  (Cluster size = 8)

  Just before drug administration
  1 hr post
  3 hrs post
  5 hrs post

- One day: Active treatment (isosorbide dinitrate)
  Other day: Placebo

- Outcome at each of 8 time points:

  y = exercise time to angina pectoris (in seconds)

Question: Does treatment delay the time to angina pectoris, after adjusting for time since drug administration and previous conditions?

Example 2.

Structure of the Angina Data

Patient ID	Treatment Day	Time Since Drug Admin (Hours)	Y = Exercise Time (seconds)	MI
1	1 = Placebo Day	1 = Pre	150	1
1	1	2 = 1 hr	172	1
1	1	3 = 3 hrs	118	1
1	1	4 = 5 hrs	143	1
1	2 = Treatment Day	1	136	1
1	2	2	445	1
1	2	3	393	1
1	2	4	226	1
2	1 = Placebo Day	1	205	0
2	1	2	287	0
2	1	3	211	0
2	1	4	207	0
2	2 = Treatment Day	1	250	0
2	2	2	306	0
2	2	3	206	0
2	2	4	224	0

N = 168 records (21 patients, 8 records per patient)

Example 2: Exercise Time to Angina Pectoris

Proportional Hazards Model Results

Estimated Regression Coefficient: Treatment vs. Placebo	Estimated Hazards Ratio	Standard Error of Beta		Variance Ratio
		Cluster	Independent	
-0.8395	0.43	**0.1474**	**0.1724**	**0.73 (27% reduction)**

SUDAAN **Standard Packages:** *Too Large*

- True variance ***smaller*** than under independence
- May fail to detect a treatment effect

Figure 1

Proportional Hazards Regression for Exercise Time Data

Main Effects Model

Covariate	Model-Fitting Method	β_i	S.E.	Design Effect[1]	Z	P-Value
Treatment Day (Treatment vs. Placebo)	Robust	-0.8395	0.1474	0.73	-5.70	.0000
	Naive	-0.8395	0.1724	1.00	-4.87	.0000
Time Since Drug Administration						
1 hour	Robust	-0.9295	0.2085	0.74	-4.46	.0001
	Naive	-0.9295	0.2417	1.00	-3.85	.0001
3 hours	Robust	-0.6040	0.1294	0.31	-4.67	.0001
	Naive	-0.6040	0.2311	1.00	-2.61	.0090
5 hours	Robust	-0.1827	0.1216	0.30	-1.50	.1487
	Naive	-0.1827	0.2232	1.00	-0.82	.4130
Previous MI	Robust	-1.2263	0.3636	3.29	-3.37	.0030
	Naive	-1.2263	0.2004	1.00	-6.12	.0000
Previous Bypass Surgery	Robust	0.7525	0.4025	4.17	1.87	.0762
	Naive	0.7525	0.1970	1.00	3.82	.0000
Previous Propranolol Treatment	Robust	-0.6282	0.4737	4.71	-1.33	.1998
	Naive	-0.6282	0.2182	1.00	-2.88	.0040

Number Clusters = 21; Cluster Size = 2 days X 4 times each day = 8

Estimated Hazard Ratio = 0.4319 (over 50% reduction in hazard, treatment vs. control)

Notes: Significant treatment-by-time interaction effect (via SUDAAN, p<0.05)
Largest effects occur at 1 and 3 hours post-dosing.

[1] Design Effect $= \left(\frac{SE_{Robust}}{SE_{Naive}} \right)^2$

Example 2 Results: Testing Interaction

```
14  PROC SURVIVAL DATA="EXERCISE" FILETYPE=SAS;

15  NEST _ONE_ PATIENT;

16  WEIGHT _ONE_;

17  SUBGROUP HRS SUDTRT;

18  LEVELS   4   2;

19  EVENT COMPLETE;

20  MODEL EXTIME = SUDTRT HRS SUDTRT*HRS MI CAB PP;

21  TEST WALDCHI SATADJCHI;

22  SETENV COLSPCE=1 LABWIDTH=22 COLWIDTH=8 LINESIZE=78 PAGESIZE=60;

23  PRINT BETA="BETA" SEBETA="STDERR" DEFT="DEFF" T_BETA="T:BETA=0"
          P_BETA="P-VALUE"
          DF="DF" SATADJDF="ADJ DF"
          WALDCHI="  CHI-SQ   (WALD)"
          SATADCHI="  CHI-SQ   (SAT)"
          WALDCHP=" P-VALUE  (WALDC)"
          SATADCHP=" P-VALUE  (SAT)"
          /DFFMT=F7.0 BETAFMT=F10.6 SEBETAFMT=F10.6 T_BETAFMT=F8.2 WALDCHPFMT=F8.4
           P_BETAFMT=F8.4 SATADCHPFMT=F8.4 DEFTFMT=F6.2;

24  TITLE "EXERCISE TIME TO ANGINA PECTORIS (SECONDS):  PLACEBO VS. TREATMENT"
          "PROPORTIONAL HAZARDS REGRESSION USING ROBUST VARIANCE ESTIMATOR"
          "Interaction Model";

25  FOOTNOTE "Source:  Crouchley and Pickles (1993, Biometrics 49, 1067-1076)";


Opened SAS data file C:\TERA\EXAMPLES\EXERCISE.SSD for reading.

Number of observations read       :    168    Weighted count:      168
Observations used in the analysis :    168    Weighted count:      168
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :     20

Maximum number of estimable parameters for the model is 10

Number of non-censored events:  155
Number of censored events    :   13

SURVIVAL has converged to a solution in 5 iterations.
```

Example 2 Results: Testing Interaction

Date: 03-24-97 Research Triangle Institute Page : 1
Time: 08:50:19 The SURVIVAL Procedure Table : 1

For response variable EXTIME: Exercise Time to Angina Pectoris

EXERCISE TIME TO ANGINA PECTORIS (SECONDS): PLACEBO VS. TREATMENT

PROPORTIONAL HAZARDS REGRESSION USING ROBUST VARIANCE ESTIMATOR

Interaction Model

Independent Variables and Effects	BETA	STDERR	DEFF	T:BETA=0	P-VALUE
Day					
Treatment	-0.405588	0.133014	0.18	-3.05	0.0063
Placebo	0.000000	0.000000	.	.	.
Hours Since Drug Admin					
1 hr.	-0.463372	0.201299	0.42	-2.30	0.0322
3 hrs.	-0.339857	0.132493	0.18	-2.57	0.0185
5 hrs.	-0.087686	0.113670	0.13	-0.77	0.4495
Pre-Dosing	0.000000	0.000000	.	.	.
Day, Hours Since Drug Admin					
Treatment, 1 hr.	-1.107631	0.413010	0.72	-2.68	0.0143
Treatment, 3 hrs.	-0.639324	0.251528	0.30	-2.54	0.0194
Treatment, 5 hrs.	-0.228561	0.195745	0.19	-1.17	0.2567
Treatment, Pre-Dosing	0.000000	0.000000	.	.	.
Placebo, 1 hr.	0.000000	0.000000	.	.	.
Placebo, 3 hrs.	0.000000	0.000000	.	.	.
Placebo, 5 hrs.	0.000000	0.000000	.	.	.
Placebo, Pre-Dosing	0.000000	0.000000	.	.	.
Previous MI	-1.239716	0.370078	3.38	-3.35	0.0032
Previous Bypass Surgery	0.736154	0.403746	4.18	1.82	0.0832
Previous Propranolol Trt	-0.615225	0.484650	4.91	-1.27	0.2189

Source: Crouchley and Pickles (1993, Biometrics 49, 1067-1076)

Example 2 Results: Testing Interaction

Date: 03-24-97 Research Triangle Institute Page : 2
Time: 08:50:19 The SURVIVAL Procedure Table : 1

For response variable EXTIME: Exercise Time to Angina Pectoris

EXERCISE TIME TO ANGINA PECTORIS (SECONDS): PLACEBO VS. TREATMENT

PROPORTIONAL HAZARDS REGRESSION USING ROBUST VARIANCE ESTIMATOR

Interaction Model

Contrast	DF	ADJ DF	CHI-SQ (WALD)	CHI-SQ (SAT)	P-VALUE (WALDC)	P-VALUE (SAT)
OVERALL MODEL	10	3.98	44.84	20.81	0.0000	0.0004
SUDTRT	.	.	.	.	.	.
HRS	.	.	.	.	.	.
SUDTRT * HRS	**3**	**1.80**	**9.80**	**10.35**	**0.0204**	**0.0046**
MI	1	1.00	11.22	11.22	0.0008	0.0008
CAB	1	1.00	3.32	3.32	0.0683	0.0686
PP	1	1.00	1.61	1.61	0.2043	0.2046

Source: Crouchley and Pickles (1993, Biometrics 49, 1067-1076)

SURVIVAL used
CPU time : 3.29 seconds
Elapsed time : 4 seconds
Virtual memory : 1.08 MB

Example 2 Results: Testing Main Effects

```
1   PROC SURVIVAL DATA="EXERCISE" FILETYPE=SAS;

2   NEST _ONE_ PATIENT;

3   WEIGHT _ONE_;

4   SUBGROUP HRS SUDTRT;

5   LEVELS   4   2;

6   EVENT COMPLETE;

7   MODEL EXTIME = SUDTRT HRS MI CAB PP;

8   EFFECTS MI CAB PP / NAME = "Combined Effect: MI,CAB,PP";

9   TEST WALDCHI SATADJCHI;

10  SETENV COLSPCE=1 LABWIDTH=22 COLWIDTH=8 LINESIZE=78 PAGESIZE=60;

11  PRINT BETA="BETA" SEBETA="STDERR" DEFT="DEFF" T_BETA="T:BETA=0"
          P_BETA="P-VALUE" HR LOWHR UPHR DF="DF"  SATADJDF="ADJ DF"
          WALDCHI="  CHI-SQ   (WALD)"  SATADCHI="  CHI-SQ   (SAT)"
          WALDCHP=" P-VALUE  (WALDC)"  SATADCHP=" P-VALUE  (SAT)"
          /DFFMT=F7.0 BETAFMT=F10.6 SEBETAFMT=F10.6 T_BETAFMT=F8.2 WALDCHPFMT=F8.4
           P_BETAFMT=F8.4 SATADCHPFMT=F8.4 DEFTFMT=F6.2
           HRFMT=F7.2 LOWHRFMT=F6.2 UPHRFMT=F6.2;

12  TITLE "EXERCISE TIME TO ANGINA PECTORIS (SECONDS):  PLACEBO VS. TREATMENT"
          "PROPORTIONAL HAZARDS REGRESSION USING ROBUST VARIANCE ESTIMATOR:"
          "Main Effects Model";

13  FOOTNOTE "Source:  Crouchley and Pickles (1993, Biometrics 49, 1067-1076)";

NOTE: Terms in the MODEL statement have been rearranged
      to follow subgroup order.

Opened SAS data file C:\TERA\EXAMPLES\EXERCISE.SSD for reading.

Number of observations read       :    168    Weighted count:      168
Observations used in the analysis :    168    Weighted count:      168
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :     20

Maximum number of estimable parameters for the model is  7

Number of non-censored events:  155
Number of censored events    :   13
SURVIVAL has converged to a solution in 5 iterations.
```

Example 2 Results: Testing Main Effects

```
Date: 03-24-97            Research Triangle Institute            Page  : 1
Time: 08:50:19              The SURVIVAL Procedure               Table : 1

For response variable EXTIME: Exercise Time to Angina Pectoris

EXERCISE TIME TO ANGINA PECTORIS (SECONDS):  PLACEBO VS. TREATMENT

PROPORTIONAL HAZARDS REGRESSION USING ROBUST VARIANCE ESTIMATOR:

Main Effects Model

-------------------------------------------------------------------------
Independent Variables
  and Effects                  BETA     STDERR   DEFF T:BETA=0  P-VALUE
-------------------------------------------------------------------------
Hours Since Drug Admin
  1 hr.                   -0.929513   0.208504   0.74    -4.46   0.0002
  3 hrs.                  -0.603992   0.129440   0.31    -4.67   0.0001
  5 hrs.                  -0.182658   0.121615   0.30    -1.50   0.1487
  Pre-Dosing               0.000000   0.000000    .        .      .
Day
  Treatment               -0.839508   0.147408   0.73    -5.70   0.0000
  Placebo                  0.000000   0.000000    .        .      .
Previous MI               -1.226269   0.363640   3.29    -3.37   0.0030
Previous Bypass Surgery    0.752530   0.402488   4.17     1.87   0.0762
Previous Propranolol Trt  -0.628185   0.473715   4.71    -1.33   0.1998
-------------------------------------------------------------------------
Source:  Crouchley and Pickles (1993, Biometrics 49, 1067-1076)
```

Example 2 Results: Testing Main Effects (continued)

Date: 03-24-97 Research Triangle Institute Page : 2
Time: 08:50:19 The SURVIVAL Procedure Table : 1

For response variable EXTIME: Exercise Time to Angina Pectoris

EXERCISE TIME TO ANGINA PECTORIS (SECONDS): PLACEBO VS. TREATMENT

PROPORTIONAL HAZARDS REGRESSION USING ROBUST VARIANCE ESTIMATOR:

Main Effects Model

Contrast	DF	ADJ DF	CHI-SQ (WALD)	CHI-SQ (SAT)	P-VALUE (WALDC)	P-VALUE (SAT)
OVERALL MODEL	7	3.57	49.58	20.57	0.0000	0.0003
HRS	3	2.29	31.22	30.73	0.0000	0.0000
SUDTRT	1	1.00	32.43	32.43	0.0000	0.0000
MI	1	1.00	11.37	11.37	0.0007	0.0008
CAB	1	1.00	3.50	3.50	0.0615	0.0618
PP	1	1.00	1.76	1.76	0.1848	0.1851
Combined Effect: MI,CAB,PP	3	2.86	15.43	13.17	0.0015	0.0039

Source: Crouchley and Pickles (1993, Biometrics 49, 1067-1076)

Example 2 Results: Testing Main Effects (continued)

```
Date: 03-24-97            Research Triangle Institute            Page  : 3
Time: 08:50:19              The SURVIVAL Procedure               Table : 1

For response variable EXTIME: Exercise Time to Angina Pectoris

EXERCISE TIME TO ANGINA PECTORIS (SECONDS):  PLACEBO VS. TREATMENT

PROPORTIONAL HAZARDS REGRESSION USING ROBUST VARIANCE ESTIMATOR:

Main Effects Model

-----------------------------------------------
                                    Lower  Upper
Independent Variables      Hazards   95%    95%
  and Effects              Ratio    Limit  Limit
-----------------------------------------------
Hours Since Drug Admin
  1 hr.                     0.39   0.26   0.61
  3 hrs.                    0.55   0.42   0.72
  5 hrs.                    0.83   0.65   1.07
  Pre-Dosing                1.00   1.00   1.00
Day
  Treatment                 0.43   0.32   0.59
  Placebo                   1.00   1.00   1.00
Previous MI                 0.29   0.14   0.63
Previous Bypass Surgery     2.12   0.92   4.91
Previous Propranolol Trt    0.53   0.20   1.43
-----------------------------------------------
Source:  Crouchley and Pickles (1993, Biometrics 49, 1067-1076)

SURVIVAL used
  CPU time       : 3.0 seconds
  Elapsed time   : 3 seconds
  Virtual memory : 1.08 MB
```

Example 2 Results: 1-Hour Post-Dosing Treatment Effect

```
39  PROC SURVIVAL DATA="EXERCISE" FILETYPE=SAS;

40  NEST _ONE_ PATIENT;

41  WEIGHT _ONE_;

42  SUBPOPN HOURS = 2 / NAME = "TREATMENT EFFECT @ 1 HR. POST-DOSING";

43  SUBGROUP SUDTRT;

44  LEVELS   2;

45  EVENT COMPLETE;

46  MODEL EXTIME = SUDTRT MI CAB PP;

47  TEST WALDCHI SATADJCHI;

48  SETENV COLSPCE=1 LABWIDTH=22 COLWIDTH=8 LINESIZE=78 PAGESIZE=60;

49  PRINT BETA="BETA" SEBETA="STDERR" DEFT="DEFF" T_BETA="T:BETA=0"
          P_BETA="P-VALUE" HR LOWHR UPHR
          DF="DF" SATADJDF="ADJ DF"
          WALDCHI="  CHI-SQ   (WALD)"
          SATADCHI="  CHI-SQ   (SAT)"
          WALDCHP=" P-VALUE  (WALDC)"
          SATADCHP=" P-VALUE  (SAT)"
          /DFFMT=F7.0 BETAFMT=F10.6 SEBETAFMT=F10.6 T_BETAFMT=F8.2 WALDCHPFMT=F8.4
           P_BETAFMT=F8.4 SATADCHPFMT=F8.4 DEFTFMT=F6.2
           HRFMT=F7.2 LOWHRFMT=F7.2 UPHRFMT=F7.2;

50  TITLE "EXERCISE TIME TO ANGINA PECTORIS (SECONDS):  PLACEBO VS. TREATMENT"
          "PROPORTIONAL HAZARDS REGRESSION USING CLUSTER SAMPLE TECHNIQUE" ;

51  FOOTNOTE "Source:  Crouchley and Pickles (1993, Biometrics 49, 1067-1076)";

Opened SAS data file C:\TERA\EXAMPLES\EXERCISE.SSD for reading.

Number of observations read       :    168    Weighted count:      168
Observations in subpopulation     :     42    Weighted count:       42
Observations used in the analysis :     42    Weighted count:       42
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :     20

Maximum number of estimable parameters for the model is  4

Number of non-censored events:   35
Number of censored events    :    7

SURVIVAL has converged to a solution in 5 iterations.
```

Example 2 Results: 1-Hour Post-Dosing Treatment Effect

```
Date: 03-24-97            Research Triangle Institute            Page  : 1
Time: 08:50:19              The SURVIVAL Procedure               Table : 1

For response variable EXTIME: Exercise Time to Angina Pectoris
For Subpopulation: TREATMENT EFFECT @ 1 HR. POST-DOSING

EXERCISE TIME TO ANGINA PECTORIS (SECONDS):  PLACEBO VS. TREATMENT

PROPORTIONAL HAZARDS REGRESSION USING CLUSTER SAMPLE TECHNIQUE

-------------------------------------------------------------------------
Independent Variables
  and Effects                  BETA     STDERR   DEFF T:BETA=0  P-VALUE
-------------------------------------------------------------------------
Day
  Treatment               -1.276868   0.290823   0.57    -4.39   0.0003
  Placebo                  0.000000   0.000000    .        .      .
Previous MI               -0.955064   0.437032   1.19    -2.19   0.0409
Previous Bypass Surgery    1.160058   0.443047   1.06     2.62   0.0165
Previous Propranolol Trt  -0.415035   0.436418   0.87    -0.95   0.3530
-------------------------------------------------------------------------
Source:  Crouchley and Pickles (1993, Biometrics 49, 1067-1076)
```

```
Date: 03-24-97            Research Triangle Institute            Page  : 2
Time: 08:50:19              The SURVIVAL Procedure               Table : 1

For response variable EXTIME: Exercise Time to Angina Pectoris
For Subpopulation: TREATMENT EFFECT @ 1 HR. POST-DOSING

EXERCISE TIME TO ANGINA PECTORIS (SECONDS):  PLACEBO VS. TREATMENT

PROPORTIONAL HAZARDS REGRESSION USING CLUSTER SAMPLE TECHNIQUE

-------------------------------------------------------------------------
                                       CHI-SQ   CHI-SQ  P-VALUE  P-VALUE
Contrast                 DF   ADJ DF   (WALD)   (SAT)   (WALDC)  (SAT)
-------------------------------------------------------------------------
OVERALL MODEL             4     3.13    28.50    17.68   0.0000   0.0006
SUDTRT                    1     1.00    19.28    19.28   0.0000   0.0000
MI                        1     1.00     4.78     4.78   0.0289   0.0291
CAB                       1     1.00     6.86     6.86   0.0088   0.0090
PP                        1     1.00     0.90     0.90   0.3416   0.3418
-------------------------------------------------------------------------
Source:  Crouchley and Pickles (1993, Biometrics 49, 1067-1076)
```

Example 2 Results: 1-Hour Post-Dosing Treatment Effect

```
Date: 03-24-97            Research Triangle Institute            Page  : 3
Time: 08:50:19              The SURVIVAL Procedure               Table : 1

For response variable EXTIME: Exercise Time to Angina Pectoris
For Subpopulation: TREATMENT EFFECT @ 1 HR. POST-DOSING

EXERCISE TIME TO ANGINA PECTORIS (SECONDS):  PLACEBO VS. TREATMENT

PROPORTIONAL HAZARDS REGRESSION USING CLUSTER SAMPLE TECHNIQUE

-----------------------------------------------
Independent Variables            Lower   Upper
  and Effects           Hazards  95%     95%
                        Ratio    Limit   Limit
-----------------------------------------------
Day
  Treatment              0.28    0.15    0.51
  Placebo                1.00    1.00    1.00
Previous MI              0.38    0.15    0.96
Previous Bypass Surgery  3.19    1.27    8.04
Previous Propranolol Trt 0.66    0.27    1.64
-----------------------------------------------
Source:  Crouchley and Pickles (1993, Biometrics 49, 1067-1076)

SURVIVAL used
  CPU time       : 2.85 seconds
  Elapsed time   : 3 seconds
  Virtual memory : 1.06 MB
```

Example 3

Cross-Over Clinical Trial (Ezzett and Whitehead, 1991)

- Two-treatment, 2-period cross-over design
- Comparing two Inhaler Devices in Asthma patients: New inhaler vs. a standard (delivering salbutamol).
- Patients randomized to either:

  Group 1: Device A for 1 week, B the next
  Group 2: Device B the first week, A the next

  No wash-out period

- Outcome of interest: Clarity of leaflet instructions
- Ordinal Scale:

$$y_{ij} = \begin{cases} 1, & \text{Easy} \\ 2, & \text{Only clear after rereading} \\ 3, & \text{Not very clear} \\ 4, & \text{Confusing} \end{cases}$$

Question: Is there a difference between the 2 inhaler devices with respect to clarity of leaflet instructions?

Example 3.

Cross-Over Clinical Trial With Ordinal Outcomes:

Evaluation of a New Inhaler Device via a Cross-Over Clinical Trial

Qualitative responses in a cross-over clinical trial are often ordinal. Such responses might be, for example, relief, slight relief, or no relief in studies of painkiller effectiveness. Due to the nature of cross-over studies, repeated measurements on the same subject are likely to be correlated. The intra-subject correlation must be taken into account in order to make valid inferences about the treatment effect.

Data for this example are from a two-treatment two-period crossover study conducted by 3M Health Care Ltd (Ezzet and Whitehead, 1991) to compare the suitability of two inhalation devices (A and B) in patients who are currently using a standard inhaler device delivering salbutamol. The first sequence of patients were randomized to Device A for one week (period 1) followed by Device B for another week (period 2). The second sequence of patients received the treatments in the opposite order (Device B in period 1, Device A in period 2). Patients gave their assessment on clarity of leaflet instructions accompanying the devices, recorded on an ordinal scale of: 1 = *easy*, 2 = *clear only after re-reading*, 3 = *not very clear*, and 4 = *confusing*.

Variables in the regression models included:

TREATMENT: A or B

PERIOD: 1 or 2.

The accompanying output contains results from the following SUDAAN procedures:

1)	PROC RECORDS	-	contents of the data set
2)	PROC CROSSTAB	-	descriptive statistics: distribution of the 4-level ordinal outcome across treatment group
3)	PROC MULTILOG	-	proportional odds and multinomial logit regression of treatment and period effects on leaflet clarity

Example 3

Frequency Distribution of Leaflet Clarity in the Cross-Over Clinical Trial

Inhaler Device	Total	Clarity of Leaflet Instructions			
		Easy	Requires Rereading	Not Clear	Confusing
A	286	211	71	2	2
B	286	147	118	15	6

Note: There are 286 patients (clusters) in the study

Source: Ezzet and Whitehead (1991), *Statistics in Medicine* **10**, 901-907.

Example 3

Proportional Odds Model Results

Estimated Regression Coefficient: Inhaler A vs. B	Estimated Odds Ratio	Standard Error of Beta		Variance Ratio
		Cluster	Independent	
1.0137	2.76	**0.1566**	**0.1733**	**0.78 (22% reduction)**

SUDAAN **Standard Packages:** Too Large

- True variance (via SUDAAN) ***smaller*** than under independence (*e.g.*, via SAS)
- May fail to detect a treatment effect

Example 3

Proportional Odds Model Results

Treatment Effect

Working Correlations	Variance Estimation Method	Regression Coefficient	Standard Error	Odds Ratio	T-statistic
Independent	Robust	1.0137	.1566	2.76	6.47
Exchangeable	Robust	1.0140	.1562	2.76	6.49
Exchangeable	Model-Based (Naive)	1.0140	.1577	2.76	6.43
Independent	Model-Based (Naive)	1.0137	**.1733**	2.76	5.85

Example 3.

Structure of the Clarity Data

Patient	Period	Treatment	Y = Clarity
1	1	1 = New	1 = Easy
1	2	2 = Standard	1 = Easy
2	1	1	1 = Easy
2	2	2	2 = Rereading
3	1	2	3 = Not Clear
3	2	1	2 = Rereading
4	1	2	4 = Confusing
4	2	1	1 = Easy

N = 572 records on the file

(286 clusters, 2 records per cluster)

Example 3 Results:

File Contents

```
1   PROC RECORDS DATA="C:\\TERA\\GEEORD\\CROSS" FILETYPE=SAS
                 CONTENTS COUNTREC NOPRINT;

SAS Record File C:\TERA\GEEORD\CROSS.SSD
Variables
Name       Type       Format     Description
------------------------------------------------------------------------------
PERSON     Numeric    F15.3      PERSON
TREAT      Numeric    F15.3      TREAT
SEQUENCE   Numeric    F15.3      SEQUENCE
PERIOD     Numeric    F15.3      PERIOD
CLARITY    Numeric    F15.3      CLARITY

Codes and Labels for Variable TREAT:
Code    Label
-------------
1       Inhaler A
2       Inhaler B


Codes and Labels for Variable PERIOD:
Code    Label
-------------
1       1=AB
2       2=BA


Codes and Labels for Variable CLARITY:
Code    Label
-------------
1       Easy
2       Rereading
3       Not Clear
4       Confusing

Number of records on file :    572

RECORDS used
  CPU time       : 0.55 seconds
  Elapsed time   : 1 second
  Virtual memory : 0.75 MB
```

There are 572 records (one record for each person and treatment occasion) on the SAS data set. The outcome of interest is CLARITY of leaflet instructions, coded 1=*easy*, *2=rereading required,* 3=*not clear,* and 4=*confusing.* SUDAAN picks up the labels for dependent and independent variables from the user-defined LEVEL.DBS file.

In the proportional odds model, we will model the probability of increasing clarity across treatment group and period (1 vs. 2). In the multinomial logit model, we will model the probability of being in each of the first 3 levels of CLARITY vs. the last.

The LEVEL.DBS file for Example 3:

Value labels for categorical variables:

```
CLARITY   1     Easy
CLARITY   2     Rereading
CLARITY   3     Not Clear
CLARITY   4     Confusing
TREAT     1     Inhaler A
TREAT     2     Inhaler B
SEQUENCE  1     1=AB
SEQUENCE  2     2=BA
```

Example 3 Results:

```
2   PROC CROSSTAB DATA="C:\\TERA\\NCHS\\CROSS" FILETYPE=SAS;

3   NEST _ONE_ PERSON;

4   WEIGHT _ONE_;

5   SUBGROUP TREAT CLARITY;

6   LEVELS   2     4;

7   TABLES TREAT*CLARITY;

8   SETENV DECWIDTH=0 COLWIDTH=10 LABWIDTH=15 COLSPCE=2;

9   PRINT NSUM/STYLE=NCHS;

10  TITLE "FREQUENCY DISTRIBUTION FOR INHALER DEVICE CROSS-OVER STUDY"
          "Ezzett and Whitehead, 1991" ;


Number of observations read    :    572    Weighted count :      572
Number of observations skipped :      0
(WEIGHT variable nonpositive)
Denominator degrees of freedom :    285
```

```
Date: 03-18-97            Research Triangle Institute             Page  : 1
Time: 11:18:22               The CROSSTAB Procedure               Table : 1


FREQUENCY DISTRIBUTION FOR INHALER DEVICE CROSS-OVER STUDY

Ezzett and Whitehead, 1991

Sample Size
-------------------------------------------------------------------------
TREAT            CLARITY
                      Total        Easy   Rereading   Not Clear   Confusing
-------------------------------------------------------------------------
Total                   572         358         189          17           8
Inhaler A               286         211          71           2           2
Inhaler B               286         147         118          15           6
-------------------------------------------------------------------------
```

The CROSSTAB procedure was used to obtain the ***frequency distribution*** of CLARITY across treatment. It appears that the Inhaler B leaflet is less easy to read than that for Inhaler A.

MULTILOG Programming Statements and Options

The first set of MULTILOG programming statements fits the proportional odds model in SUDAAN PROC MULTILOG. The ***DATA*** option on the ***PROC*** statement specifies a SAS data set as input. Since there is no *DESIGN* option specified, SUDAAN is using the default ***DESIGN=WR*** (with-replacement) option for variance estimation.

We will fit the following types of models:

1) ***SEMETHOD=ZEGER*** and ***R=INDEPENDENT***
Implements the GEE model-fitting technique under an independent "working" assumption and a robust variance estimator.

2) ***SEMETHOD=ZEGER*** and ***R=EXCHANGEABLE***
Implements the GEE model-fitting technique under exchangeable "working" correlations and a robust variance estimator.

3) ***SEMETHOD=MODEL*** and ***R=EXCHANGEABLE***
We compare the results using the robust variance estimator (*SEMETHOD=ZEGER*) to the model-based, or naive, variance assumption (*SEMETHOD=MODEL*). When *R=exchangeable* is specified in conjunction with *SEMETHOD=MODEL*, variances are then computed as if the exchangeable "working" correlation assumption were correct.

The ***NEST*** statement indicates that PERSON is the cluster variable. The ***WEIGHT*** statement indicates equal sampling weights of 1.0 for each person and measurement occasion.

In MULTILOG, the ***SUBGROUP*** statement contains the dependent variable and all covariates that are to be modelled as categorical covariates (with level values of 1,2,...,*k*), where the maximum number of levels (*K*) appears on the ***LEVELS*** statement.

The ***MODEL*** statement specifies the categorical dependent variable CLARITY on the left of the "=" sign (with levels 1, 2, 3, and 4), and regressors on the right. The ***CUMLOGIT*** (cumulative logit) link specifies the proportional odds model (the GENLOGIT link comes later in the output). The CUMLOGIT link will model the log-odds that CLARITY $\leq k$, where k=1,...,K-1 (or the tendency for CLARITY to be less than confusing). The ***GENLOGIT*** link will model the log-odds that CLARITY=k vs. K (or the log-odds that CLARITY is easy, requires re-reading, or not clear vs. confusing). The CUMLOGIT option produces common slopes but separate intercepts for each of the K-1 = 3 cutpoints, while the GENLOGIT option produces a separate logit equation (intercepts and slopes) for each of the 3 cutpoints.

The ***TEST*** statement specifies that we want the Wald chi-square statistic to be the default for testing main effects, interactions, and user-defined contrasts. This statement is optional. If omitted, the Wald F statistic becomes the default. However, any default statistic can be overridden on the ***PRINT*** statement.

The ***SETENV*** and ***PRINT*** statements are both optional, and control the printing of results (which statistics get printed, as well as their labels, formats, and layout).

MULTILOG Programming Statements for the Proportional Odds Model: CUMLOGIT Link

GEE with Independent Working Correlations and Robust Variance Estimates

```
11  PROC MULTILOG DATA="C:\\TERA\\GEEORD\\CROSS" FILETYPE=SAS
                  SEMETHOD=ZEGER  R=INDEPENDENT;

12  NEST _ONE_ PERSON;

13  WEIGHT _ONE_;

14  SUBGROUP CLARITY TREAT PERIOD;

15  LEVELS   4       2     2;

16  MODEL CLARITY = TREAT PERIOD / CUMLOGIT;

17  TEST WALDCHI;

18  SETENV LABWIDTH=28 MAXIND=4 LINESIZE=78 PAGESIZE=60 COLSPCE=2;

19  PRINT   BETA="BETA" SEBETA="STDERR" DEFT="DESIGN EFFECT"
            T_BETA="T:BETA=0" P_BETA="P-Value"/
            RISK=ALL TESTS=DEFAULT
            BETAFMT=F7.4 SEBETAFMT=F6.4 T_BETAFMT=F8.2 P_BETAFMT=F7.4
            DEFTFMT=F6.2 WALDCHIFMT=F6.2 WALDCHPFMT=F7.4
            ORFMT=F5.2 LOWORFMT=F6.2 UPORFMT=F6.2 DFFMT=F7.0;

20  TITLE "PROPORTIONAL ODDS MODEL FOR INHALER DEVICE CROSS-OVER STUDY"
          "Ezzett and Whitehead, 1991";


Opened SAS data file C:\TERA\GEEORD\CROSS.SSD for reading.

Independence parameters have converged in 3 iterations

Number of observations read       :    572    Weighted count:      572
Observations used in the analysis :    572    Weighted count:      572
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :    285

Maximum number of estimable parameters for the model is  5

File C:\TERA\GEEORD\CROSS.SSD contains  286 Clusters
Maximum cluster size is   2 records
Minimum cluster size is   2 records

Sample and Population Counts for Response Variable CLARITY
  Easy     :  Sample Count      358    Population Count       358
  Rereading:  Sample Count      189    Population Count       189
  Not Clear:  Sample Count       17    Population Count        17
  Confusing:  Sample Count        8    Population Count         8
```

CLARITY is the outcome variable in the model, while TREAT and PERIOD are covariates. There are 572 records on the file, corresponding to 286 clusters, with a minimum and maximum cluster size of 2 (since this is a 2-period crossover design). There are no missing values in the the data set and no SUBPOPN statement to subset the analysis, so all observations on the file are used in fitting the model. SUDAAN displays the frequency distribution of the response in the data and the number of iterations needed to estimate the regression coefficients.

Example 3 Results:

Proportional Odds Model: CUMLOGIT Link
GEE with Independent Working Correlations and Robust Variance Estimates

```
Date: 03-18-97            Research Triangle Institute            Page  : 1
Time: 11:18:22              The MULTILOG Procedure               Table : 1

Variance Estimation Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

PROPORTIONAL ODDS MODEL FOR INHALER DEVICE CROSS-OVER STUDY

Ezzett and Whitehead, 1991
```

Independent Variables and Effects	BETA	STDERR	DESIGN EFFECT	T:BETA=0	P-Value
CLARITY (cum-logit)					
Intercept 1: Easy	0.1110	0.1383	0.88	0.80	0.4229
Intercept 2: Rereading	2.7656	0.2357	1.03	11.74	0.0000
Intercept 3: Not Clear	3.9464	0.3638	0.95	10.85	0.0000
TREAT					
Inhaler A	1.0137	0.1566	0.78	6.47	0.0000
Inhaler B	0.0000	0.0000	.	.	.
PERIOD					
1=AB	-0.1512	0.1565	0.80	-0.97	0.3347
2=BA	0.0000	0.0000	.	.	.

The ***estimated regression coefficients*** for the proportional odds model indicate that Inhaler A is significantly clearer in its leaflet instructions than Inhaler B (p=0.0000, *t*-test). This is reflected in the positive regression coefficient estimate (1.0137) and in the estimated odds ratio on the next page (2.76). In other words, the odds of being $\leq$ any response level *k* are increased almost 3-fold over Inhaler B. The 3 intercept terms in the model are non-decreasing because they are cumulative over the categories of the response (*i.e.*, intercept 1 = *easy*; 2 = *easy or rereading required*; 3 = *easy, rereading, or not clear*). The fitted proportional odds model is as follows:

$$\log\left[\frac{prob(Y \leq k)}{prob(Y > k)}\right] = 0.11_{k=1} + 2.77_{k=2} + 3.95_{k=3} + 1.01 \cdot TREAT - 0.1512 \cdot PERIOD$$

where TREAT and PERIOD are converted to 0-1 indicator variables because of their appearance on the SUBGROUP statement.

Note the ***design effect*** of 0.78 for the treatment parameter. We expect design effects less than 1.0 for variables nested within the cluster, as occurs in many repeated measures designs. An improvement in precision was obtained because of the cross-over design and SUDAAN was able to recognize this gain.

Proportional Odds Model: CUMLOGIT Link
GEE with Independent Working Correlations and Robust Variance Estimates

```
Date: 03-18-97            Research Triangle Institute            Page  : 2
Time: 11:18:22              The MULTILOG Procedure               Table : 1

Variance Estimation Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

PROPORTIONAL ODDS MODEL FOR INHALER DEVICE CROSS-OVER STUDY

Ezzett and Whitehead, 1991

-----------------------------------------------------
Contrast                     Degrees          P-value
                             of       Wald    Wald
                             Freedom  ChiSq   ChiSq
-----------------------------------------------------
OVERALL MODEL                      5  272.62   0.0000
MODEL MINUS INTERCEPT              2   42.13   0.0000
TREAT                              1   41.88   0.0000
PERIOD                             1    0.93   0.3338
-----------------------------------------------------
```

Example 3 Results:

Proportional Odds Model: CUMLOGIT Link
GEE with Independent Working Correlations and Robust Variance Estimates

```
Date: 03-18-97            Research Triangle Institute            Page  : 3
Time: 11:18:22              The MULTILOG Procedure               Table : 1

Variance Estimation Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

PROPORTIONAL ODDS MODEL FOR INHALER DEVICE CROSS-OVER STUDY

Ezzett and Whitehead, 1991

-------------------------------------------------
Independent Variables and             Lower   Upper
  Effects                    Odds       95%     95%
                             Ratio    Limit   Limit
-------------------------------------------------
CLARITY (cum-logit)
  Intercept 1: Easy           1.12     0.85    1.47
  Intercept 2: Rereading     15.89     9.99   25.26
  Intercept 3: Not Clear     51.75    25.30  105.86
TREAT
  Inhaler A                   2.76     2.03    3.75
  Inhaler B                   1.00     1.00    1.00
PERIOD
  1=AB                        0.86     0.63    1.17
  2=BA                        1.00     1.00    1.00
-------------------------------------------------

MULTILOG used
  CPU time       : 4.44 seconds
  Elapsed time   : 5 seconds
  Virtual memory : 1.11 MB
```

This output contains the ***main effects tests*** for the proportional odds model, in addition to the ***estimated odds ratios*** and their ***95% confidence limits***.

Example 3 Results:

MULTILOG Programming Statements for the Proportional Odds Model: Exchangeable Correlations and Robust Variance Estimates

```
31  PROC MULTILOG DATA="C:\\TERA\\GEEORD\\CROSS" FILETYPE=SAS
                 SEMETHOD=ZEGER R=EXCHANGE;

32  NEST _ONE_ PERSON;

33  WEIGHT _ONE_;

34  SUBGROUP CLARITY TREAT PERIOD;

35  LEVELS   4       2     2;

36  MODEL CLARITY = TREAT PERIOD / CUMLOGIT;

37  TEST WALDCHI;

38  SETENV LABWIDTH=15 LINESIZE=78 PAGESIZE=60;

39  PRINT RHO / RHOFMT=F10.4;

40  SETENV LABWIDTH=28 MAXIND=4 LINESIZE=78 PAGESIZE=60 COLSPCE=2;

41  PRINT   BETA="BETA" SEBETA="STDERR" DEFT="DESIGN EFFECT"
            T_BETA="T:BETA=0" P_BETA="P-Value"/
            RISK=ALL TESTS=DEFAULT
            BETAFMT=F7.4 SEBETAFMT=F6.4 T_BETAFMT=F8.2 P_BETAFMT=F7.4
            DEFTFMT=F6.2 WALDCHIFMT=F6.2 WALDCHPFMT=F7.4
            ORFMT=F5.2 LOWORFMT=F6.2 UPORFMT=F6.2 DFFMT=F7.0;

42  TITLE "PROPORTIONAL ODDS MODEL FOR INHALER DEVICE CROSS-OVER STUDY"
          "Ezzett and Whitehead, 1991";
```

Continued on next page...

Example 3 Results:

MULTILOG Programming Statements for the Proportional Odds Model: Exchangeable Correlations and Robust Variance Estimates

continued from previous page...

```
Opened SAS data file C:\TERA\GEEORD\CROSS.SSD for reading.

Independence parameters have converged in 3 iterations

Step 1 parameters have converged in 5 iterations.

Number of observations read       :    572    Weighted count:      572
Observations used in the analysis :    572    Weighted count:      572
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :    285

Maximum number of estimable parameters for the model is  5

File C:\TERA\GEEORD\CROSS.SSD contains  286 Clusters
Maximum cluster size is   2 records
Minimum cluster size is   2 records

Sample and Population Counts for Response Variable CLARITY
  Easy     :  Sample Count      358    Population Count       358
  Rereading:  Sample Count      189    Population Count       189
  Not Clear:  Sample Count       17    Population Count        17
  Confusing:  Sample Count        8    Population Count         8
```

In the above programming statements, we request ***SEMETHOD=ZEGER*** and ***R=exchangeable*** to implement GEE under exchangeable working correlations. All other statements remain as previously for the proportional odds model (CUMLOGIT link). The starting parameter estimates, computed in the usual way under the naive assumption of independence, converged to a solution in 4 iterations. The Step 1 GEE estimates, which update the independence estimates with the estimated correlation structure, converged in 5 iterations.

Example 3 Results:

Proportional Odds Model: CUMLOGIT Link
GEE with Exchangeable Working Correlations and Robust Variance Estimates

```
Date: 03-18-97            Research Triangle Institute            Page  : 1
Time: 11:18:22              The MULTILOG Procedure               Table : 1

Variance Estimation Method: Robust (Zeger-Liang, 1986)
Working Correlations: Exchangeable
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

PROPORTIONAL ODDS MODEL FOR INHALER DEVICE CROSS-OVER STUDY

Ezzett and Whitehead, 1991

Correlation Matrix
-------------------------------------------------------
CLARITY           CLARITY
                       Easy    Rereading    Not Clear
-------------------------------------------------------
Easy                 0.2156
Rereading           -0.1975       0.2069
Not Clear           -0.0564      -0.0168       0.1427
-------------------------------------------------------
```

The ***estimated correlation structure*** is contained in the above table. Note that for a 4-level response variable, a cluster size of 2, and an exchangeable correlation model, there are exactly 6 unique correlation estimates. SUDAAN prints the lower portion of the symmetric 3-by-3 matrix. These estimates indicate that the correlation between the "*Easy to Read*" categories on both treatments (Y_{i1s}, Y_{i1t}) was 0.2156, and the correlation between the "*Rereading Required*" categories on both treatments (Y_{i2s}, Y_{i2t}) was 0.2069. Therefore, the most frequently occuring pairs are identical outcomes. The smaller negative correlations indicate that crossing response categories from Inhaler A to B is not as likely as remaining in the same response category on each treatment.

Example 3 Results:

Proportional Odds Model: CUMLOGIT Link
GEE with Exchangeable Working Correlations and Robust Variance Estimates

Date: 03-18-97 Research Triangle Institute Page : 2
Time: 11:18:22 The MULTILOG Procedure Table : 1

Variance Estimation Method: **Robust (Zeger-Liang, 1986)**
Working Correlations: **Exchangeable**
Link Function: **Cumulative Logit**
Response variable CLARITY: CLARITY

PROPORTIONAL ODDS MODEL FOR INHALER DEVICE CROSS-OVER STUDY

Ezzett and Whitehead, 1991

Independent Variables and Effects	BETA	STDERR	T:BETA=0	P-Value
CLARITY (cum-logit)				
Intercept 1: Easy	0.1085	0.1379	0.79	0.4320
Intercept 2: Rereading	2.7424	0.2344	11.70	0.0000
Intercept 3: Not Clear	3.9568	0.3639	10.87	0.0000
TREAT				
Inhaler A	1.0140	0.1562	6.49	0.0000
Inhaler B	0.0000	0.0000	.	.
PERIOD				
1=AB	-0.1531	0.1556	-0.98	0.3258
2=BA	0.0000	0.0000	.	.

This table contains the ***regression coefficient estimates*** under the exchangeable correlation structure. We see that the regression estimates are slightly larger and the variance estimates are slightly smaller compared to the independence working assumption shown previously. However, the results are qualitatively the same. Inhaler A is significantly clearer in its leaflet instructions than Inhaler B. Both working assumptions are valid no matter what the true correlation structure since SUDAAN is using the ***robust variance estimates*** (SEMETHOD=ZEGER) for computing variance and testing hypotheses.

Example 3 Results:

Proportional Odds Model: CUMLOGIT Link
GEE with Exchangeable Working Correlations and Robust Variance Estimates

```
Date: 03-18-97            Research Triangle Institute            Page  : 3
Time: 11:18:22              The MULTILOG Procedure               Table : 1

Variance Estimation Method: Robust (Zeger-Liang, 1986)
Working Correlations: Exchangeable
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

PROPORTIONAL ODDS MODEL FOR INHALER DEVICE CROSS-OVER STUDY

Ezzett and Whitehead, 1991

-----------------------------------------------------
Contrast                     Degrees          P-value
                             of       Wald    Wald
                             Freedom  ChiSq   ChiSq
-----------------------------------------------------
OVERALL MODEL                      5  272.33   0.0000
MODEL MINUS INTERCEPT              2   42.39   0.0000
TREAT                              1   42.16   0.0000
PERIOD                             1    0.97   0.3250
-----------------------------------------------------
```

This table summarizes the ***main effects tests*** under the exchangeable correlation "working" assumption. Again, these results are qualitatively similar to the "working" independence model with robust variance estimates.

Example 3 Results:

Proportional Odds Model: CUMLOGIT Link
GEE with Exchangeable Working Correlations and Robust Variance Estimates

```
Date: 03-18-97            Research Triangle Institute            Page  : 4
Time: 11:18:22              The MULTILOG Procedure               Table : 1

Variance Estimation Method: Robust (Zeger-Liang, 1986)
Working Correlations: Exchangeable
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

PROPORTIONAL ODDS MODEL FOR INHALER DEVICE CROSS-OVER STUDY

Ezzett and Whitehead, 1991

--------------------------------------------------
CLARITY (cum-logit),
  Independent Variables and          Lower   Upper
  Effects                     Odds   95%     95%
                              Ratio  Limit   Limit
--------------------------------------------------
CLARITY (cum-logit)
  Intercept 1: Easy            1.11    0.85    1.46
  Intercept 2: Rereading      15.52    9.79   24.62
  Intercept 3: Not Clear      52.29   25.56  106.99
TREAT
  Inhaler A                    2.76    2.03    3.75
  Inhaler B                    1.00    1.00    1.00
PERIOD
  1=AB                         0.86    0.63    1.17
  2=BA                         1.00    1.00    1.00
--------------------------------------------------

MULTILOG used
  CPU time       : 11.91 seconds
  Elapsed time   : 12 seconds
  Virtual memory : 1.14 MB
```

These ***odds ratios and 95% confidence limits*** for the exchangeable "working" assumption are identical to the independence "working" model. Modelling the correlations under exchangeability did not significantly improve the efficiency of the parameter estimates in this example.

Example 3 Results:

GEE Under Exchangeable Working Correlations Model-Based (Naive) Variance Estimation

Below are results from the exchangeable correlation model using the ***model-based*** or ***naive variance-covariance matrix*** of the estimated regression coefficients. The model-based variance is the M_0^{-1} matrix, or the outside portion of the robust variance estimate: $M_0^{-1} = [\boldsymbol{D}'\boldsymbol{V}^{-1}\boldsymbol{D}]^{-1}$, where $\boldsymbol{D} = \partial\pi_i / \partial\beta$ is the vector of first partial derivatives of the response probabilities π_i with respect to the regression coefficients β. In this case, the naive variance estimate is computed ***as if the exchangeable "working" correlation assumption were correct***. Since this is close to truth for litter data, we will see that results are essentially the same as with the robust variance estimator. To obtain the model-based results, we specify ***SEMETHOD=MODEL*** on the PROC statement.

```
43  PROC MULTILOG DATA="C:\\TERA\\GEEORD\\CROSS" FILETYPE=SAS
                  SEMETHOD=MODEL R=EXCHANGE;

44  NEST _ONE_ PERSON;

45  WEIGHT _ONE_;

46  SUBGROUP CLARITY TREAT PERIOD;

47  LEVELS   4       2     2;

48  MODEL CLARITY = TREAT PERIOD / CUMLOGIT;

49  TEST WALDCHI;

50  SETENV LABWIDTH=15 LINESIZE=78 PAGESIZE=60;

51  PRINT RHO / RHOFMT=F10.4;

52  SETENV LABWIDTH=28 MAXIND=4 LINESIZE=78 PAGESIZE=60 COLSPCE=2;

53  PRINT   BETA="BETA" SEBETA="STDERR" DEFT="DESIGN EFFECT"
            T_BETA="T:BETA=0" P_BETA="P-Value"/
            RISK=ALL TESTS=DEFAULT
            BETAFMT=F7.4 SEBETAFMT=F6.4 T_BETAFMT=F8.2 P_BETAFMT=F7.4
            DEFTFMT=F6.2 WALDCHIFMT=F6.2 WALDCHPFMT=F7.4
            ORFMT=F5.2 LOWORFMT=F6.2 UPORFMT=F6.2 DFFMT=F7.0;

54  TITLE "PROPORTIONAL ODDS MODEL FOR INHALER DEVICE CROSS-OVER STUDY"
          "Ezzett and Whitehead, 1991"  "Model-Based Variance Estimation";
```

...continued next page

Example 3 Results:

GEE Under Exchangeable Working Correlations
Model-Based (Naive) Variance Estimation

...continued from previous page

```
Opened SAS data file C:\TERA\GEEORD\CROSS.SSD for reading.

Number of observations read       :    572    Weighted count:      572
Observations used in the analysis :    572    Weighted count:      572
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :    285

Maximum number of estimable parameters for the model is  5

File C:\TERA\GEEORD\CROSS.SSD contains  286 Clusters

Maximum cluster size is   2 records
Minimum cluster size is   2 records

Independence parameters have converged in 3 iterations

Step 1 parameters have converged in 5 iterations.

Sample and Population Counts for Response Variable CLARITY
  Easy     :  Sample Count      358    Population Count       358
  Rereading:  Sample Count      189    Population Count       189
  Not Clear:  Sample Count       17    Population Count        17
  Confusing:  Sample Count        8    Population Count         8
```

Example 3 Results:

GEE Under Exchangeable Working Correlations Model-Based (Naive) Variance Estimation

```
Date: 03-18-97            Research Triangle Institute            Page  : 1
Time: 11:18:22              The MULTILOG Procedure               Table : 1

Variance Estimation Method: Model-Based (Naive)
Working Correlations: Exchangeable
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

PROPORTIONAL ODDS MODEL FOR INHALER DEVICE CROSS-OVER STUDY

Ezzett and Whitehead, 1991
Model-Based Variance Estimation

Correlation Matrix
-----------------------------------------------------
CLARITY           CLARITY
                       Easy    Rereading    Not Clear
-----------------------------------------------------
Easy                  0.2156
Rereading            -0.1975       0.2069
Not Clear            -0.0564      -0.0168       0.1427
-----------------------------------------------------
```

The ***estimated correlation matrix*** under exchangeability is unaffected by the choice of robust vs. model-based variance estimation.

Example 3 Results:

GEE Under Exchangeable Working Correlations
Model-Based (Naive) Variance Estimation

```
Date: 03-18-97            Research Triangle Institute            Page  : 2
Time: 11:18:22              The MULTILOG Procedure               Table : 1

Variance Estimation Method: Model-Based (Naive)
Working Correlations: Exchangeable
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

PROPORTIONAL ODDS MODEL FOR INHALER DEVICE CROSS-OVER STUDY

Ezzett and Whitehead, 1991
Model-Based Variance Estimation

---------------------------------------------------------------
Independent Variables and
  Effects                        BETA  STDERR  T:BETA=0  P-Value
---------------------------------------------------------------
CLARITY (cum-logit)
  Intercept 1: Easy            0.1085  0.1415      0.77   0.4437
  Intercept 2: Rereading       2.7424  0.2363     11.61   0.0000
  Intercept 3: Not Clear       3.9568  0.3510     11.27   0.0000
TREAT
  Inhaler A                    1.0140  0.1577      6.43   0.0000
  Inhaler B                    0.0000  0.0000       .      .
PERIOD
  1=AB                        -0.1531  0.1555     -0.98   0.3256
  2=BA                         0.0000  0.0000       .      .
---------------------------------------------------------------
```

Here we have the ***estimated regression coefficients*** computed under exchangeability and the estiamted standard errors as if the exchangeable working asssumption were correct. The standard errors are roughly the same as with the robust variance estimator for these data, indicating that the exchangeable correlation assumption is close to truth.

Example 3 Results:

GEE Under Exchangeable Working Correlations Model-Based (Naive) Variance Estimation

```
Date: 03-18-97            Research Triangle Institute            Page  : 3
Time: 11:18:22              The MULTILOG Procedure               Table : 1

Variance Estimation Method: Model-Based (Naive)
Working Correlations: Exchangeable
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

PROPORTIONAL ODDS MODEL FOR INHALER DEVICE CROSS-OVER STUDY

Ezzett and Whitehead, 1991
Model-Based Variance Estimation

-----------------------------------------------------
Contrast                    Degrees          P-value
                            of       Wald    Wald
                            Freedom  ChiSq   ChiSq
-----------------------------------------------------
OVERALL MODEL                     5  271.76   0.0000
MODEL MINUS INTERCEPT             2   42.17   0.0000
TREAT                             1   41.33   0.0000
PERIOD                            1    0.97   0.3248
-----------------------------------------------------
```

Here we have the ***main effects tests*** computed under exchangeability, using the model-based variance approach. Results are essentially the same as with the robust variance estimator.

Example 3 Results:

GEE Under Exchangeable Working Correlations
Model-Based (Naive) Variance Estimation

```
Date: 03-18-97            Research Triangle Institute            Page  : 4
Time: 11:18:22              The MULTILOG Procedure               Table : 1

Variance Estimation Method: Model-Based (Naive)
Working Correlations: Exchangeable
Link Function: Cumulative Logit
Response variable CLARITY: CLARITY

PROPORTIONAL ODDS MODEL FOR INHALER DEVICE CROSS-OVER STUDY

Ezzett and Whitehead, 1991
Model-Based Variance Estimation

--------------------------------------------------
CLARITY (cum-logit),
  Independent Variables and          Lower   Upper
  Effects                    Odds     95%     95%
                             Ratio   Limit   Limit
--------------------------------------------------
CLARITY (cum-logit)
  Intercept 1: Easy           1.11    0.84    1.47
  Intercept 2: Rereading     15.52    9.75   24.71
  Intercept 3: Not Clear     52.29   26.21  104.31
TREAT
  Inhaler A                   2.76    2.02    3.76
  Inhaler B                   1.00    1.00    1.00
PERIOD
  1=AB                        0.86    0.63    1.17
  2=BA                        1.00    1.00    1.00
--------------------------------------------------

MULTILOG used
  CPU time       : 10.60 seconds
  Elapsed time   : 11 seconds
  Virtual memory : 1.14 MB
```

Here we have the ***estimated odds ratios and their 95% confidence limits*** computed under exchangeability, using the model-based variance approach. Odds ratios are unaffected by the choice of robust vs. model-based variance estimates, and estimated confidence limits are essentially the same as with the robust variance estimator.

Example 3 Results:

MULTILOG Programming Statements for the Multinomial Logit Model: GENLOGIT Link

```
55  PROC MULTILOG DATA="C:\\TERA\\GEEORD\\CROSS" FILETYPE=SAS
                  SEMETHOD=ZEGER R=INDEPENDENT;

56  NEST _ONE_ PERSON;

57  WEIGHT _ONE_;

58  SUBGROUP CLARITY TREAT PERIOD;

59  LEVELS   4       2     2;

60  MODEL CLARITY = TREAT PERIOD / GENLOGIT;

61  TEST WALDCHI;

62  SETENV LABWIDTH=15 COLWIDTH=10 DECWIDTH=4 MAXIND=4 LINESIZE=78
           PAGESIZE=60;

63  PRINT BETA="BETA" SEBETA="STDERR" DEFT="DESIGN EFFECT"
          T_BETA="T:BETA=0" P_BETA="P-Value"/
          RISK=ALL TESTS=DEFAULT T_BETAFMT=F8.2 WALDCHIFMT=F6.2
          ORFMT=F10.2 LOWORFMT=F10.2 UPORFMT=F10.2 DFFMT=F7.0;

64  TITLE "GENERALIZED LOGIT MODEL FOR INHALER DEVICE CROSS-OVER STUDY"
          "Ezzett and Whitehead, 1991";

Opened SAS data file C:\TERA\GEEORD\CROSS.SSD for reading.

Independence parameters have converged in 5 iterations

Number of observations read       :    572    Weighted count:      572
Observations used in the analysis :    572    Weighted count:      572
Observations with missing values  :      0    Weighted count:        0
Denominator degrees of freedom    :    285

Maximum number of estimable parameters for the model is  9
File C:\TERA\GEEORD\CROSS.SSD contains  286 Clusters
Maximum cluster size is   2 records
Minimum cluster size is   2 records

Sample and Population Counts for Response Variable CLARITY
  Easy     :  Sample Count      358    Population Count       358
  Rereading:  Sample Count      189    Population Count       189
  Not Clear:  Sample Count       17    Population Count        17
  Confusing:  Sample Count        8    Population Count         8
```

The **GENLOGIT option** invokes the multinomial logit model based on the generalized logit link function. All other options remain the same as for the proportional odds model.

Example 3 Results:

Multinomial Logit Model: GENLOGIT Link

GEE with Independent Working Correlations and Robust Variance Estimates

Date: 03-18-97 Research Triangle Institute Page : 1
Time: 11:18:22 The MULTILOG Procedure Table : 1

Variance Estimation Method: **Robust (Zeger-Liang, 1986)**
Working Correlations: **Independent**
Link Function: **Generalized Logit**
Response variable CLARITY: CLARITY

GENERALIZED LOGIT MODEL FOR INHALER DEVICE CROSS-OVER STUDY

Ezzett and Whitehead, 1991

CLARITY (log-odds)		Independent Variables and Effects		
		Intercept	TREAT = Inhaler A	TREAT = Inhaler B
Easy vs Confusing	BETA	3.5099	1.4615	0.0000
	STDERR	0.6858	0.8254	0.0000
	DESIGN EFFECT	1.2232	1.0037	.
	T:BETA=0	5.12	1.77	.
	P-Value	0.0000	0.0777	.
Rereading vs Confusing	BETA	3.2510	0.5919	0.0000
	STDERR	0.6908	0.8311	0.0000
	DESIGN EFFECT	1.2281	1.0015	.
	T:BETA=0	4.71	0.71	.
	P-Value	0.0000	0.4769	.
Not Clear vs Confusing	BETA	1.0089	-0.9159	0.0000
	STDERR	0.7634	1.1557	0.0000
	DESIGN EFFECT	1.1092	1.0830	.
	T:BETA=0	1.32	-0.79	.
	P-Value	0.1874	0.4287	.

-continued-

Example 3 Results:

Multinomial Logit Model: GENLOGIT Link

GEE with Independent Working Correlations and Robust Variance Estimates

```
Date: 03-18-97            Research Triangle Institute           Page  : 2
Time: 11:18:22              The MULTILOG Procedure              Table : 1

Variance Estimation Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Generalized Logit
Response variable CLARITY: CLARITY

GENERALIZED LOGIT MODEL FOR INHALER DEVICE CROSS-OVER STUDY

Ezzett and Whitehead, 1991
```

CLARITY (log-odds)		Independent Variables and Effects	
		PERIOD = 1=AB	PERIOD = 2=BA
Easy vs Confusing	BETA	-0.5593	0.0000
	STDERR	0.7401	0.0000
	DESIGN EFFECT	0.9995	.
	T:BETA=0	-0.76	.
	P-Value	0.4505	.
Rereading vs Confusing	BETA	-0.4805	0.0000
	STDERR	0.7456	0.0000
	DESIGN EFFECT	1.0016	.
	T:BETA=0	-0.64	.
	P-Value	0.5198	.
Not Clear vs Confusing	BETA	-0.1527	0.0000
	STDERR	0.8992	0.0000
	DESIGN EFFECT	1.0411	.
	T:BETA=0	-0.17	.
	P-Value	0.8653	.

In this and the previous box we have the ***estimated regression coefficient vector*** and related statistics. Note that we now have 3 separate logit equations. So, for example, the logit equation for CLARITY = *Easy* vs. CLARITY = *Confusing* is as follows:

$$\log\left[\frac{\hat{\pi}_{EASY}}{\hat{\pi}_{CONFUSING}}\right] = 3.51 + 1.46 \cdot TREAT - 0.5593 \cdot PERIOD$$

where TREAT and PERIOD are converted to 0-1 indicator variables because of their appearance on the SUBGROUP statement. The treatment effect appears to be largest when comparing the *Easy* vs. *Confusing* categories.

Example 3 Results:

Multinomial Logit Model: GENLOGIT Link

GEE with Independent Working Correlations and Robust Variance Estimates

```
Date: 03-18-97            Research Triangle Institute            Page  : 3
Time: 11:18:22              The MULTILOG Procedure               Table : 1

Variance Estimation Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Generalized Logit
Response variable CLARITY: CLARITY

GENERALIZED LOGIT MODEL FOR INHALER DEVICE CROSS-OVER STUDY

Ezzett and Whitehead, 1991

---------------------------------------------
Contrast          Degrees
                  of        Wald     P-value
                  Freedom   ChiSq    Wald ChiSq
---------------------------------------------
OVERALL MODEL           9   233.14       0.0000
MODEL MINUS INTERCEPT   6    45.27       0.0000
INTERCEPT               .      .          .
TREAT                   3    39.88       0.0000
PERIOD                  3     1.44       0.6962
---------------------------------------------
```

The ***treatment effect*** (now with 3 degress of freedom in the multinomial logit model) is statistically significant, as in the proportional odds model.

Example 3 Results:

Multinomial Logit Model: GENLOGIT Link

GEE with Independent Working Correlations and Robust Variance Estimates

```
Date: 03-18-97            Research Triangle Institute           Page  : 4
Time: 11:18:22              The MULTILOG Procedure              Table : 1

Variance Estimation Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Generalized Logit
Response variable CLARITY: CLARITY

GENERALIZED LOGIT MODEL FOR INHALER DEVICE CROSS-OVER STUDY

Ezzett and Whitehead, 1991
```

CLARITY (log-odds)		Independent Variables and Effects		
		Intercept	TREAT = Inhaler A	TREAT = Inhaler B
Easy vs Confusing	Odds Ratio	33.44	4.31	1.00
	Lower 95% Limit	8.68	0.85	1.00
	Upper 95% Limit	128.91	21.87	1.00
Rereading vs Confusing	Odds Ratio	25.82	1.81	1.00
	Lower 95% Limit	6.63	0.35	1.00
	Upper 95% Limit	100.47	9.27	1.00
Not Clear vs Confusing	Odds Ratio	2.74	0.40	1.00
	Lower 95% Limit	0.61	0.04	1.00
	Upper 95% Limit	12.31	3.89	1.00

- continued -

The ***estimated odds*** of being in the *EASY* vs. *CONFUSING* categories is increased over 4-fold for Inhaler A vs. B.

Example 3 Results:

Multinomial Logit Model: GENLOGIT Link

GEE with Independent Working Correlations and Robust Variance Estimates

```
Date: 03-18-97            Research Triangle Institute           Page  : 5
Time: 11:18:22              The MULTILOG Procedure              Table : 1

Variance Estimation Method: Robust (Zeger-Liang, 1986)
Working Correlations: Independent
Link Function: Generalized Logit
Response variable CLARITY: CLARITY

GENERALIZED LOGIT MODEL FOR INHALER DEVICE CROSS-OVER STUDY

Ezzett and Whitehead, 1991
-----------------------------------------------------------------
| CLARITY (log-   |                 | Independent Variables and Effects
| odds)           |                 | PERIOD =   | PERIOD =   |
|                 |                 | 1=AB       | 2=BA       |
-----------------------------------------------------------------
|                 |                 |            |            |
| Easy vs         | Odds Ratio      |       0.57 |       1.00 |
| Confusing       | Lower 95% Limit |       0.13 |       1.00 |
|                 | Upper 95% Limit |       2.45 |       1.00 |
-----------------------------------------------------------------
|                 |                 |            |            |
| Rereading vs    | Odds Ratio      |       0.62 |       1.00 |
| Confusing       | Lower 95% Limit |       0.14 |       1.00 |
|                 | Upper 95% Limit |       2.68 |       1.00 |
-----------------------------------------------------------------
|                 |                 |            |            |
| Not Clear vs    | Odds Ratio      |       0.86 |       1.00 |
| Confusing       | Lower 95% Limit |       0.15 |       1.00 |
|                 | Upper 95% Limit |       5.03 |       1.00 |
-----------------------------------------------------------------

MULTILOG used
  CPU time       : 5.50 seconds
  Elapsed time   : 6 seconds
  Virtual memory : 1.18 MB
```

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