ABSTRACT

The Spearman-Karber method is a nonparametric procedure for computing an ED50 estimate (and fiducial limits) that is not currently available in the SAS® system. This paper reviews the Spearman-Karber method and presents SAS software code that can be used to generate ED50 estimates and fiducial (confidence) limits. The code was written for use with SAS software version 6.07 in VMS®. The advantages/disadvantages of the Spearman-Karber vs. probit analysis in computing ED50 estimates will be discussed.

INTRODUCTION

In drug research it is often desired to estimate the dosage of a compound that would elicit a response in half of the subjects. This is commonly known as the median effective dose, or just ED50. Use of a probit analysis (the PROBIT procedure) for ED50 estimation (e.g., quantal assays) requires assuming that the underlying tolerance distribution is normal. The nonparametric Spearman-Karber method does not require this assumption. In addition, a study by Bross (1950) found that with small sample sizes the Spearman-Karber point estimator gave closer agreement to the true ED50 than maximum likelihood even when assuming an underlying logistic distribution. It should be noted that probit and logit methods are commonly accepted as being nearly identical. Also, use of only five subjects at 3 or 4 dose levels can be small enough to cause convergence problems with probit analysis.

Under these conditions, use of the method proposed by Spearman (1908) and Karber (1931) may be more appropriate. Their procedure calculates an ED50 estimate along with 95% fiducial (confidence) limits.

In this paper the Spearman-Karber method will be reviewed. SAS software code to compute Spearman-Karber estimates will be presented. An example will be shown for illustrative purposes.

SPEARMAN-KARBER METHOD

If there are k dose levels of treatment, let \( x_1, x_2, \ldots, x_k \) represent the common logarithm of each dose level, and \( p_1, p_2, \ldots, p_k \) represent the proportion responding at each dose level. Then the Spearman-Karber estimate of the mean of the log tolerance distribution is defined as:

\[
m = \frac{\sum_{i=1}^{k} (p_i - p) (x_i + x_{i+1})}{2}
\]

The simpler formula given in most texts assumes equal spacing between doses on the log scale, which is not always common in practice. The general formula shown above allows for any type of dose spacing. Note that using the log of dosage precludes the use of control data since the log of zero (the control dosage) is undefined.

It is assumed that at dose levels below \( x_i \) the response rate would be 0% and at dose levels above \( x_i \) there would be 100% response (Finney 1978). However, a problem with the general formula is that it requires dose levels \( x_1 \) and \( x_k \), which are below and above, respectively, the actual experimental doses. The term with \( x_1 \) will be zero only if the response rate at \( x_1 \) was 0%. Similarly, the term with \( x_k \) will be zero only if the response rate at \( x_k \) was 100%. Even studies designed to ensure 0% and 100% responses at the extreme doses can observe unusual results. Therefore, when these two terms come into play, the choice of these "fake" dose levels, \( x_0 \) and \( x_{k-1} \), will determine how much weight is given to those terms. Egger (1979) proposed using

\[
x_0 = 2x_1 - x_k \quad \text{and} \quad x_{k-1} = 2x_k - x_1
\]

as the "fake" dose levels. Response rates of 0% and 100%, respectively, are assigned to these dose levels.

If \( n_1, n_2, \ldots, n_k \) represents the number of subjects tested at each of the \( k \) levels then the variance of the Spearman-Karber estimate is

\[
\text{var}(m) = \frac{0.25}{s^2} \sum_{i=1}^{k} (n_i x_i) / n_i
\]

Note that the relative sample sizes have no influence on the point estimate, but will effect the variance. Approximate 95% fiducial (confidence) limits can be computed by normal approximation, i.e.,

\[
m \pm 1.96 \text{ s}
\]

where \( s \) is the square root of \( \text{var}(m) \).

THE CASE OF A NONZERO NATURAL RESPONSE RATE

In the discussion above, control subjects are not included in the computations. It is assumed that the control group will have a 0% response rate, and in fact it generally does. However, on the rare occasions when there is a response in one or more control subjects, the control data cannot be ignored. In such a case Goldberg (1990) suggests the following.

First, an estimator of the natural response rate is required.

\[
c = \min \left( \frac{\sum_{i=0}^{h} n_i}{\sum_{i=0}^{k} n_i} \right), \quad \text{where } s_i \text{ is the number of subjects responding at dosage } i, \text{ and } i=0 \text{ represents the experimental control group. Also, } n_i = \sum_{i=0}^{h} n_i, \text{ where } h \text{ is the highest dosage included in } c. \text{ This will lead to "data reduction" if } h \text{ is not } x_k. \text{ Note that } n_i \text{ will not be unique if adding the next } x_i \text{ and } n_i \text{ to the summations for } c \text{ does not change its value. In the case of this rare event it is recommended to use the largest } n_i \text{ among all those with the smallest } c.

Next, the response rates should be transformed to a 0 to 1 scale (Finney 1978). Let \( p_i = c (p_i, c = 1 \text{ already from Egger above}) \). Then

\[
p_i' = (p_i - c) / (1 - c).
\]
The point estimator, $m'$, is calculated the same as $m$, but now with the transformed data. Note that we are no longer calculating an ED50 proper, but rather a dose which will elicit a response rate halfway between $c$ and 1.

The natural response rate, $c$, is often considered a constant throughout computations. But, since the transformed $p_i$'s contain the term $1/(1-c)$, and $c$ is not known before the experiment, $c$ can also be considered a random variable. Either way, it must be accounted for when calculating the variance. Writing the estimate of $m'$ from the transformed response rates as a function of the estimate of $m$ from the original response rates, we get (after a bunch of algebra)

$$m' = \frac{[m-c(x_1+x_2)]}{1-c}.$$

Here we will consider $c$ as a random variable, and $1-c$ as the "denominator" of the above ratio for $m'$, and the remainder of the term as the "numerator". Approximate $90\%$ fiducial limits for a ratio are calculated using Fieller's theorem (1940),

$$U,L = \left[ m-gv_1v_2b^2 \pm \sqrt{z_{.025}v_1v_2b^2\{2\{1+c\}\{1-c\}\{n\}}\right] / (1-g),$$

where $g=\sqrt{v_1v_2b^2}$, $z_{.025}$ is the standard normal deviate, and $b=1-c$. Also, $v_1$, $v_2$, and $v_3$ are the variances of the "numerator", "denominator", and their covariance respectively:

$$v_1=var(m)+(x_1+x_2)^2\{[(1-c)\{n\}]$$

$$v_2=c\{1(1-c)\{n\}]$$

$$v_3=2(x_1+x_2)^2\{[(1-c)\{n\}]$$

where $var(m)$ is calculated with the original untransformed data.

**PROGRAM FLOW**

The program used in this paper will print out the raw data along with the log doses and proportion of subjects responding in each group. After computation of the ED50 estimate and $95\%$ limits, a second page will print these results in both log doses and 'original' units. Both pages are formatted for inclusion into final reports.

The program, printed in the appendix, was written in SAS software version 6.07 on the VAX® under the VMS operating system.

**Input**

The data is to be entered directly into the program after the CARDS statement in the first DATA step. There are only three variables to be input, the dose level, number of subjects, and number of subjects responding at each level, in that order. All three variables must be numeric and there should be no other variables in the data set.

**Example Input Data:**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Subjects</th>
<th>Responding</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>50</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>100</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>500</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

For generation of an ED50 estimate, the data must contain at least two nonzero dose levels. Fiducial limits are always calculable when there is at least one dose level with response both greater than 0% and less than 100%. Note that these are minimums only. In an ideal experiment, there should be dosed group responses at both 0% and 100% as well as between. These conditions are at the other extreme, that of caution. This Spearman-Karber program will generate estimates based on just the minimum requirements stipulated above. However, one should be wary of Spearman-Karber estimation if there are not dosed group responses on both sides of 50%.

**Execution**

The data is checked for obvious entry errors, such as missing values or negative numbers. If any are present, a warning message is printed and execution stops. The data is also checked for presence of at least two nonzero dose levels. A message is printed and execution stopped if there are not.

There are two different Spearman-Karber macros (subroutines) contained in the program. Depending on the data, the program picks which macro to use. If there is a response rate greater than 0% in the control group, then the macro NONZERO is used to compute estimates. When there is no control group or the control group has no positive responses, macro REGULAR is used.

In macro NONZERO the $95\%$ fiducial limits are computed using Fieller's theorem. Macro REGULAR uses the traditional Spearman-Karber standard error presented earlier for the $95\%$ limits.

**Output**

The program prints out the hand entered data on the first page. The variables output are dose level, log of dose level, number of subjects, number of positive responses, and response rate.

The second page contains the Spearman-Karber point estimate and $95\%$ fiducial limits in both log doses and 'original' units. In cases where a nonzero response exists in the control group, the natural response rate and the factor $g$ (from Fieller's theorem) are also displayed. The value of $g$ is a measure of how significant the natural response rate is from 100%. See Finney (1978) for details on $g$.

**EXAMPLE**

If the example data from above is input, then the program output should show a resulting ED50 point estimate of 154.625, with approximate $95\%$ fiducial limits between 96.527 and 247.689.

**DISCUSSION**

The method of Spearman-Karber is often selected to analyze studies in cases where the probit model does not converge (or is not appropriate for one of many other reasons). In recent years a change has occurred within the drug industry in general protocol design. Studies now contain fewer dose levels and fewer subjects per dose. After analyzing several of the new studies, it became increasingly clear that the probit model was rarely appropriate. Even when it does converge, "reversals" of dose response wreak havoc on the fiducial limits. Since the probit model could only be used very infrequently anyway, it was decided for the sake of simplicity to always use Spearman-Karber.

Note that the Spearman-Karber method is only applicable for estimation of the ED50. If one is interested in studying the ED10, ED95, etc., other procedures are available for such estimation.

A thorough discussion of ED50 estimation and quantal response curves is contained in Finney (1978). He discusses and compares many techniques including probit and Spearman-Karber.
Even more recently, there has been discussion of changing studies to some sort of sequential design in an effort to further reduce costs. It should be noted that the current trend in the pharmaceutical industry is to move to different methods of testing which will minimize experimental costs, as the FDA no longer requires ED50 estimates in many applications. We are now researching the literature on methods known as sequential, staircase, up & down, or stepwise. Because of this, it would not be surprising to see the method presented here fall out of favor within the drug industry in the near future.

SAS is a registered trademark or trademark of SAS Institute Inc. in the USA and other countries. ® indicates USA registration. Other brand and product names are registered trademarks or trademarks of their respective companies.

ACKNOWLEDGEMENTS

I wish to thank Ken Goldberg for his help during the past two years in understanding this subject, as well as Tom Copenhaver and Steve Bailey for their comments and for allotting time in my schedule to work on this talk.

REFERENCES


APPENDIX

---

THIS FILE: SPEARMAN_KARBER.SAS

---

**APPENDIX**

---

THIS FILE: SPEARMAN_KARBER.SAS

---

*** Options MLOGIC & SYMBOLGEN are to debug Macros ***
OPTIONS LS=80 NODATE NONUMBER /* MLOGIC SYMBOLGEN */

---

Enter study info into appropriate macro variables

---

%LET PROTOCOL=; "Enter protocol number;"
%LET MODE=; "ORAL, SUBCUTANEOUS or INTRAPERITONEAL usually;"
%LET SPECIES=; "RAT or MOUSE usually;"
%LET SEX=; "FEMALE or MALE;"
%LET STITLE1= ATSAS &PROTOCOL ACUTE &MODE TOXICITY STUDY - &SPECIES &SYSDATE &SYSTIME; %LET STITLE2= PROTOCOL &PROTOCOL; %LET TABLERAW = TABLE $.1; "Table no. for ED50 raw data;"
%LET TABLEST = TABLE S-2; "Table no. for ED50 estimates;"

---

Assign macros for intermediate prints

---

%LET PUBKRBR = }; "PROC PRINT for intermediate prints;"

---

Input data below, after the cards statement
just like the example data (incl. control data).

F = # of deaths (or subjects w/ characteristic of interest)
N = # of subjects in the treatment group
DOSE = dosage in mg/kg (or IU or whatever)

Think of these 3 variables as having
subscripts i= 1, 2,..., k. The common logarithm of dose
is for later use in calculations.

---

DATA ED50;
INPUT DOSE N F;
PHAT1=F/N;
LDOSE1=LOG10(DOSE);
CARDS;
0 5 0
50 5 1
100 5 1
150 5 5
RUN;
PROC SORT;
BY DOSE;
RUN;
PROC PRINT NOOBS SPLIT='';
VAR DOSE LDOSE1 N F PHAT1;
LABEL
DOSE='Dose'
LDOSE1='Log10(Dose)'
N='Animals Treated'
F='Fatalities'
PHAT1='Observed Mortality Rate';
TITLE1='STITLE1';
TITLE2='STITLE2';
TITLE3='STITLE3';
TITLE4='';
TITLE5='SEX DATA';

---

Author

Art Carter
Wyeth-Ayerst Research
Miner Farm Road
Chazy, NY 12921

---

1122
Check data for any obvious errors.
If any are found, abort program & print warning message.

DATA _NULL;
SET ED50;
FILE PRINT;
IF (PHAT1 < 0 OR 1 < PHAT1)
OR (ROUND(N,1) NE ROUND(N,0.000001))
OR (ROUND(F,1) NE ROUND(F,0.000001))
OR N=. OR F=. OR DOSE=. THEN DO;
    PUT @10 "At least one input data value is incorrect The"
    PUT @10 "number of animals per group and the number or;
    PUT @10 "deaths per group must both be positive integers.");
    PUT @10 "Also the number of deaths in a given group"
    PUT @10 "cannot be greater than the number of animals in"
    PUT @10 "that group. Or there may be at least one missing"
    PUT @10 "value. Check your input data above. If problems"
    PUT @10 "still persist after correcting data, consult a"
    PUT @10 "statistician.");
    ABORT RETURN;
END;
RUN;

DATA _NULL;
SET ED50 END=EOF;
FILE PRINT;
IF DOSE=0 THEN LEVELS=1;
IF EOF AND LEVELS LE 1 THEN DO;
    PUT @10 "The Spearman-Karber method cannot compute an"
    PUT @10 "estimate with this data. There must be at least"
    PUT @10 "two nonzero dosed groups for generation of an"
    PUT @10 "EDSO estimate. Check your input data above";
    PUT @10 "Please consult a statistician with"
    PUT @10 "any questions.");
    ABORT RETURN;
END;
RUN;

This step checks to see if there is a death in the control
group. If not, then assign the macro variable PROGRAM to
'NONZERO' so that the code with Fieller's Theorem is used.

DATA _NULL;
SET ED50;
IF _N_=1 AND DOSE=0 AND F=0 THEN
    CALL SYMPUT('PROGRAM','NONZERO');
    ELSE
        CALL SYMPUT('PROGRAM','REGULAR');
    STOP;
RUN;

Throughout this program the following naming convention
will be used for certain (groups of) variables:
those ending in _1 represent the subscript i-1.
those ending in i represent the subscript i.
those ending in i+1 represent the subscript i+1.

This step calculates 'fake' dose levels and responses 0 & k+1 needed for later calculations. (Egger 1979)

DATA _NULL_ FAKEDATA KEEP=LOOSE PHAT1;
SET ED50(WHERE=(DOSE NE 0)) END=k;
RETAIN LDOSE;
IF _N_=2 THEN DO;
    LDOSE=2*LDOSE1-LDOSE1;
    PHAT1=0;
    OUTPUT FAKEDATA;
END;
IF k THEN DO;
    LDOSE=2*LDOSE1-LDOSE;
    PHAT1=1;
    OUTPUT FAKEDATA;
END;
LDOSE=LDOSE1;
RUN;

&PSKRBR DATA=FAKEDATA;
TITLE2 "FAKE DATA";
RUN;

DATA EDSO DROP=DOSE;
SET EDSO(WHERE=(DOSE NE 0) KEEP=DOSE LDOSE1 PHAT1 N)
FAKEDATA(RENAME=(LDOSE=LOOSE1);
RUN;

PROC SORT DATA=EDSO;
BY LOOSE1;
RUN;

&PSKRBR;
TITLE2 "EDSO DATA AFTER ADDING OBSERVATIONS 0 AND k+1 (FAKEDATA) & SORTING";
RUN;

This step calculates the EDSO & 95% limits of
the log-doses & then computes the antilogs.

DATA ESTIMATE KEEP=logEDSO logLL logUL EDSO LL UL;
SET EDSO(RENAME=(N=NI) END=EOF;
RETAIN logEDSO varLED50 0 LDOSE1 LDOSE1 PHAT1 Ni;
IF _N_=1 THEN GO TO SKIP1;
    logEDSO=logEDSO+.5*(PHAT1-PHAT1)*(LDOSE1-LDOSE1);
    IF _N_=2 THEN GO TO SKIP2;
    varLED50=varLED50+(.25*(LOOSE1-LOOSE1)**2)
    *(PHAT1*(1-PHAT1)/Ni));
    SKIP2: LDOSE1=LDOSE1;
    SKIP1: LDOSE1=LDOSE1;
    PHAT1=PHAT1;
    Ni=NI;
    IF EOF THEN DO;
        STDERR=varLED50**.5;
        logLL=logEDSO-(1.96*STDError);
        logUL=logEDSO+(1.96*STDError);
RUN;

ED50=10**logED50;
LL=10**logLL;
UL=10**logUL;
OUTPUT;
END;

TITLE1 "&TABLES1.1;"
TITLE2 "&STITLE1.1;"
TITLE3 "&STITLE2.1;"
TITLE4 "&STITLE3.1;"
TITLES "&SEX DATA1;"

DATA _NULL_; 
SET ESTIMATE;
FORMAT 10gED50 JogLL logUL ED50 Ll UL 8.3;
FILE PRINT LINESLEFT=LL;
logLL=LEFT(logLL);
logUL=TRIM(logUL);
Ll=LEFT(LL);
UL=TRIM(UL);
PUT @20 " 
@20 "SPEARMAN - KARBER METHOD OF ESTIMATION" 
@20 "Log(ED50) = "logED50 
@20 "95% Fiducial Limits; " "( "logLL ", "logUL") "; 
STOP;
RUN;

%MEND REGULAR;

---

MACRO NONZERO computes the Spearman-Karber
ED50 estimate & approximate 95% fiducial
(confidence) limits for a study that has
at least one death in the control group.

DATA ED50(KEEP=LDOSE PHAT N NC C);
SET ED50;
RETAIN FLAG 0;
IF FLAG=1 THEN DO;
CALL SYMPUT('X1',LOOSEi);
FLAG=0;
END;
MIN=INPUT(SYMGET('C'),16.8);
IF ROUND(C,.001) EQ ROUND(MIN,.001) THEN DO;
CALL SYMPUT('NC',NC);
FLAG=1;
END;
IF DOSE=0 THEN DELETE;
RUN;

&PSKPBR DATA=ED50;
TITLE2 "ED50 DATA SET";
TITLE3 "MACRO VALUES; C = &C, NC = &NC, X1 = &X1";
RUN;

---

This step calculates 'fake' dose levels and responses
0 & k+1 needed for calculations later on. (Egger 1979)

DATA _NULL_; FAKEDATA(KEEP=LDOSE PHAT);
SET ED50 END=k;
RETAIN LOOSEi;
IF N =2 THEN DO;
- - LDOSE=2'LDOSEi-LDOSEi1;
PHATi=INPUT(SYMGET('C'),16.8);
OUTPUT FAKEDATA;
END;
LDOSE=2'LDOSEi-LDOSEi1;
PHATi=1;
OUTPUT FAKEDATA;
END;
LDOSE1=LDOSE1;
RUN;

&PSKPBR DATA=FAKEDATA;
TITLE2 "FAKE DATA";
RUN;

---

DATA _NULL_; 
SET MINPROP END=END;
IF END THEN CALL SYMPUT('C',C);
RUN;

---

Create macro variable NC to be the cumulative sample
size at the dose where C is minimum. Then assign the
next highest log(dose) to macro variable X1. Delete
the control group.

DATA ED50(KEEP=LDOSE1 PHAT1 N);
SET ED50;
RETAIN FLAG 0;
IF FLAG=1 THEN DO;
CALL SYMPUT('X1',LDOSE1);
FLAG=0;
END;
MIN=INPUT(SYMGET('C'),16.8);
IF ROUND(C,.001) EQ ROUND(MIN,.001) THEN DO;
CALL SYMPUT('NC',NC);
FLAG=1;
END;
IF DOSE=0 THEN DELETE;
RUN;

&PSKPBR DATA=ED50;
TITLE2 "ED50 DATA SET";
TITLE3 "MACRO VALUES; C = &C, NC = &NC, X1 = &X1";
RUN;

---

This step calculates 'fake' dose levels and responses
0 & k+1 needed for calculations later on. (Egger 1979)

DATA _NULL_; 
FAKEDATA(KEEP=LDOSE PHAT1);
SET ED50 END=k;
RETAIN LDOSE;
IF _N_=2 THEN DO;
LDOSE=2'LDOSE1-LDOSE1;
PHAT1=INPUT(SYMGET('C'),16.8);
OUTPUT FAKEDATA;
END;
IF k THEN DO;
LDOSE=2'LDOSE1-LDOSE;
PHAT1=1;
OUTPUT FAKEDATA;
END;
LDOSE1=LDOSE1;
RUN;

&PSKPBR DATA=FAKEDATA;
TITLE2 "FAKE DATA";
RUN;

---

PROC MEANS DATA=ED50 NOPRINT MIN;
VAR C;
OUTPUT OUT=MINPROP MIN=C;
RUN;

&PSKPBR DATA=MINPROP;
TITLE2 "MINPROP DATA SET";

---

RUN;
This step merges 'fake' data with data set ED50 & orders
by increasing dose. Create macro variable H1 to be an
identifier associated with dose level X1, which is the
smallest dose level not used in finding C.

DATA ED50;
SET ED50;
IF ROUND(LDOSE1,.0001)=ROUND(SYMGET('X1'),.0001)
THEN CALL SYMPUT('H1',_N_);
RUN;
&SPPKRBR DATA=ED50;
TITLE2 "ED50 DATA AFTER ADDING OBSERVATIONS 0 AND
 k+1 (FAKEDATA) & SORTING";
TITLE3 "MACRO H1 = &H1";
RUN;

This step deletes all observations whose dose levels
are less than the largest dose used in computing C,
the natural response rate. Make the sample size, N,
for the observation representing the natural response
rate, C, to be equal to NC. Create macro variable XO
to be equal to the dose level now associated with C.

DATA ED50;
SET ED50;
IF _N_ LT SYMGET('H1')-1 THEN DELETE;
IF _N_ EQ SYMGET('H1')-1 THEN DO;
RUN;
CALL SYMPUT('XO',LDOSE1);
N=SYMGET('NC');
PHA Ti 1=INPUT(SYMGET('C'),16.8);
END;
&SPPKRBR DATA=ED50;
TITLE2 "ED50 DATA AFTER DELETING DOSES SMALLER
THAN H, XO = &XO";
RUN;

This step calculates the ED50 & traditional variance.

DATA ESTIMATE(KEEP=logEDSO varLEDSO C);
SET ED50 (RENAME=(N=Nil» END=EOF;
RETAIN logEDSO varLEDSO 0 LDOSE1 LDOSEU PHATI PHATIP Ni;
C=INPUT(SYMGET('C'),16.8);
PHA TiP=PHATI;
PHATI=(PHATI-1)/(1.0-C);
IF _N_ =1 THEN GO TO SKIP1;
logED50=logED50+.5*(PHATI-PHATI')(LDOSE1-LDOSE1);
IF _N_ =2 THEN GO TO SKIP2;
varED50=varED50+.25*((LDOSE1-LDOSE1)'**2)
*(PHATI'(1-PHATI)/Ni));
SKIP2: LDOSE1=LDOSE1;
SKIP1: LDOSE1=LDOSE1;
PHATI-PHATI';
PHATIP=PHATI';
Ni=Ni';
IF EOF THEN OUTPUT;
RUN;
&SPPKRBR;
TITLE2 "DATA SET ESTIMATE W/ log(EDSO) EST. & VAR";
RUN;

The next step estimates the variance in the presence of
nonzero natural response rate, using Feiler's theorem.

DATA VARNATCH (KEEP=ED50 logEDSO LL UL IogLL logUL C
AV SE g);
SET ESTIMATE;
ED50=10**logED50;
X0=SYMGET('X0');
X1=SYMGET('X1');
NC=SYMGET('NC');
varV=C*(1-C)/NC;
covUV=(X0+X1)/2*varV;
varU=varED50+(covUV**2*varV);
m=logED50;
g=(1.96**2*varV)((1-C)**2);
AV=(varU-2*m*varUV+m**2*varV)(1-C)**2;
SE=AV**.5;
logLL=(m-g* covUV/varV-1.96/(1-C)(varU-2*m* varUV+m**2* varV
-g* varU-covUV**2*varV)**.5)(1-g);
logUL=(m-g* covUV/varV+1.96/(1-C)(varU-2*m* varUV+m**2* varV
-g* varU-covUV**2*varV)**.5)(1-g);
LL=10**logLL;
UL=10**logUL;
RUN;
&SPPKRBR;
TITLE2 "DATA SET VARNATCH W/ED50 EST. & VARIANCE";
RUN;
TITLE1 " & TABLEST.";
TITLE2 " & STITLE1.";
TITLE3 " & STITLE2.";
TITLE4 " ";
TITLE5 " & SEX DATA.

DATA _NULL_;
SET VARNATCH;
FORMAT logEDSO logLL logUL EDSO LL UL 8.3 9 C 8.5;
FILE PRINT UNESLEFT=LL;
logLL=LEFT(logLL);
logUL=TRIM(logUL);
LL=LEFT(LL);
UL=TRIM(UL);
PUT @20 
"SPEARMAN-KARBER METHOD OF ESTIMATION"
@20 "Natural Response Rate = " C
@20 "g = " g
@20 "Log(ED50) = " logED50
@20 "95% Fiducial Limits : " ( " logLL ", " logUL ")
@20 "ED50 = " ED50
@20 "95% Fiducial Limits : " ( " LL ", " UL")
STOP;
RUN;
%MEND NONZERO;
%MACRO PICK;
%IF %INDEX(&PROGRAM,REGULAR)=1 %THEN %REGULAR;
%ELSE %NONZERO;
%MEND PICK;
%PICK;

The next step estimates the variance in the presence of
nonzero natural response rate, using Feiler's theorem.