A CRITICAL EVALUATION OF THE STATISTICAL COMPUTER PROGRAM SPEARMAN

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INTRODUCTION

This paper presents a critical evaluation of the statistical computer program SPEARMAN. The purpose of the program is to estimate the median effective dose (ED50) or the median lethal concentration (LC50) using the trimmed Spearman-Karber method in toxicology studies. Both of these represent the concentration at which 50% of the subjects can be expected to respond to the chemical. The response for the LC50 is mortality, whereas the response for the ED50 may be concerned only with the effect of the chemical on the nervous system of fish.

The program originated at Montana State University. Originally the program consisted of a collection of subroutines written by Dr. Martin A. Hamilton and Dr. Susan Hinkins. The work was coordinated with the Fisheries Bioassay Laboratory at Montana State University.

The programming staffs at the Duluth and Athens Environmental Research Labs for the Environmental Protection Agency modified the program to its present form.

The program is intended for use in evaluating industrial effects on water quality. Rosemarie C. Russo, an Environmental Protection Agency administrator, advocates the implementation of SPEARMAN in assessing whether the industrial effects on the water quality are within the bounds specified by the Environmental Protection Agency.

BACKGROUND

The Environmental Protection Agency is concerned with estimating the ED50 or the LC50 for certain chemicals related to water quality. The most popular techniques implemented presently are based on the logit or probit model. These techniques, however, are inappropriate whenever the data do not fit the logit or probit model. Large bias in the results may occur if the model is incorrectly specified.

It is desirable to have a single method of estimation which will suffice for a wide range of conditions. The appropriate method of estimation for the ED50 or LC50 should have the following characteristics (Hamilton, 1979):

(1) be reasonably accurate and precise,

(2) be relatively unaffected by a small fraction of anomalous responses,

(3) be calculable for all, except the obviously pathological, experimental outcomes.

The routine analyses require these properties to exist if the results are to be conclusive. In analyzing numerous sets of data the experimenter is bound to encounter data which is somewhat unusual in comparison with the bulk of the data, thereby necessitating the second condition requiring robustness of the estimator.

The program SPEARMAN implements the trimmed Spearman-Karber method to estimate the median lethal concentration. The trimmed

Spearman-Karber method is a nonparametric or model-free method and satisfies the three characteristics desired for an estimator. The method does require symmetry of the response curve. The trimmed Spearman-Karber method never fails to give a reasonable estimate of the LC50 or the ED50 if $\alpha \geq 100\breve{p}_1$ and $\alpha \geq 100(1 - \breve{p}_k)$.

DESCRIPTION OF THE TRIMMED SPEARMAN-KARBER PROCEDURE

The data of a toxicity study normally consist of the concentrations of the chemical, the number exposed to each concentration and the number of mortalities at each concentration for a specified period of time. The natural logarithms of the concentrations are often used.

Let the natural logarithms of the K concentrations of the toxin be represented by $x_1, x_2, \ldots, x_k$; $n_1, n_2, \ldots, n_k$ are the number of subjects exposed to the K concentrations, respectively; $r_1, r_2, \ldots, r_k$, are the number of mortalities for a fixed time of exposure to the K concentrations, respectively. The concentrations, x_j, and their corresponding mortalities, n_j, are arranged in order by increasing level of concentration, $x_1 < x_2 < \ldots < x_k$. The observed proportion of mortality for the K concentrations, respectively, is $p_j = r_j/n_j$. The observed proportions, p_j, and their respective concentrations, x_j, esti-

mate the true response curve for a toxin. The true response curve P(x) is the (unknown) proportion of the population of subjects that would respond to a given dose level x. P(x) is a cumulative relative frequency curve. (Hamilton, 1979) The trimmed Spearman-Karber method deviates from the other methods at this point.

The first step is the adjustment of the observed proportions if the proportions do not satisfy the condition $p_1 < p_2 < \ldots < p_k$, since the true response curve will be non-decreasing. The adjustment consists of averaging the adjacent proportions, p_j and p_{j+1}, in order to create a monotone non-decreasing function $P(x_j)$. If the proportion of mortality is less for the higher concentration of the two adjacent concentrations, then the response proportions are adjusted to be equal by calculating an average response proportion. The averaging is continued until until a monotone non-decreasing relationship is achieved. The adjusted proportions will be denoted by $\bar{p}$.

Table I shows an example of the trimmed Spearman-Karber calculations. The proportions p_2 and p_3 are adjusted, since $p_2 > p_3$. Note that $\bar{p}_2 = \bar{p}_3 = (r_2 + r_3)/(n_2 + n_3)$.

A plot of points $(x_j, \bar{p}_j)$ is the second step. These points are connected with straight lines forming a polygonal figure which estimates the true response curve. The polygonal figure is the estimated cumulative frequency distribution for the adjusted data. An example plot for the data in Table I is

given by Figure I located in the appendix.

Trimming is the third step. An appropriate percent of trimming is carried out in both the upper and lower tails of the distribution from step two. The percent trimmed is decided upon by the experimenter and is an attempt to alleviate the effects of extreme values on the estimation results. The well-known Spearman-Karber method corresponds to no trimming, that is 0%-trimming. As the %-trimmed is increased, the standard error is increased and the sensitivity of the estimator to extreme values is decreased. It is not possible to optimize all factors at once. Keeping in mind the relationship between the %-trimmed, the sensitivity, and the standard error of the estimate, the experimenter must decide on the appropriate percentage for trimming, 10% being the most common choice.

Let α = %-trimmed;

$\hat{p}$ = the adjusted proportions;

$_{\alpha}\hat{p}$ = the adjusted proportion after trimming;

The formula is:

$$_{\alpha}\hat{p} = (\hat{p} - \alpha/100)/(1 - 2\alpha).$$

The resulting proportions ($_{\alpha}\hat{p}$) which are less than zero or greater than one are disregarded. The plot of $_{\alpha}\hat{p}$ versus concentration is a rescaling of the middle $(100 - 2\alpha)$ percent of the dose-response curve (Hamilton, et. al., 1977). Table II shows the 0- and 5%-trimmed Spearman-Karber estimates of the median μ corresponding to the data in Table I. Figure II in

the appendix shows the new polygonal figure after trimming 5% from each tail for the data in Table II.

Table I. Example of Trimmed Spearman-Karber Calculations. Data Set 1B (Hamilton, et. al.,1977)

Tank	(j)	1	2	3	4	5
Concentration	mg/L	15.54	20.47	27.92	35.98	55.52
Log_e concn	x_j	2.7434	3.0190	3.3293	3.5830	4.0167
No. of fish	n_j	20	20	20	19	20
No. of mortalities	r_j	0	1	0	1	20
Mortality proportion	p_j	0	0.05	0	0.0526	1.00
Adjusted mortality proportion	$\breve{p}_j$	0	0.025	0.025	0.0526	1.00

Calculating the mean is the final step of the process. The mean is calculated from the polygonal figure formed at step three. There are K - 1 intervals for the natural logarithms of the concentrations, x_j: (x_1, x_2), (x_2, x_3), ..., (x_{K-1}, x_K). The value of $_{\alpha}\breve{p}_{j+1} - {}_{\alpha}\breve{p}_j$ is the estimated proportion of the population tolerance found in the interval (x_j, x_{j+1}), where j = 1, 2, 3, ..., K - 1, and $_{\alpha}\breve{p}_j$ is the proportion corresponding to the x_j. The mean is calculated by summing the product of each $_{\alpha}\breve{p}_{j+1} - {}_{\alpha}\breve{p}_j$ times the interval midpoint $(x_j + x_{j+1})/2$. The

formula is:

$$\mu = ({}_{\alpha}\bar{p}_2 - {}_{\alpha}\bar{p}_1)(x_1 + x_2)/2 + ({}_{\alpha}\bar{p}_3 - {}_{\alpha}\bar{p}_2)(x_2 + x_3)/2 + \ldots + ({}_{\alpha}\bar{p}_K - {}_{\alpha}\bar{p}_{K-1})(x_{K-1} + x_K)/2.$$

Table II. Examples of Calculation of 0- and 5%-trimmed Spearman-Karber Estimates of μ for Data of Table I (Hamilton, et. al., 1977)

5%

(1) Log_e of concn interval: (x_j, x_{j+1})	(2) Relative freq: ${}_5\bar{p}_{j+1} - {}_5\bar{p}_j$	(3) Midpoint of interval: $(x_j + x_{j+1})/2$	(2) x (3)
(3.5591, 3.5830)	0.00288	3.57105	0.01028
(3.5830, 3.9938)	0.99712	3.78840	3.77749
Total:	1.00000		3.78777

The estimate of μ is 3.78777, and the estimate of LC50 is thus

$e^{3.78777} = 44.15782$ mg/L.

0%

(1) Log_e of concn interval: (x_j, x_{j+1})	(2) Relative freq: $\bar{p}_{j+1} - \bar{p}_j$	(3) Midpoint of interval: $(x_j + x_{j+1})/2$	(2) x (3)
(2.7434, 3.0190)	0.025	2.8812	0.07203
(3.0190, 3.3293)	0.0	3.1742	0.0
(3.3293, 3.5830)	0.0276	3.4562	0.09539
(3.5830, 4.0167)	0.9474	3.7999	3.60002
Total:	1.0000		3.76744

The estimate of μ is 3.76744, and the estimate of LC50 is thus

$e^{3.76744} = 43.26915$ mg/L.

Note, however, that some of the first or last terms may not be present due to their deletion in step three. The trimmed mean is the median given the assumption of symmetry for the true response curve. The trimmed mean is then the estimate of the true LC50.

A corresponding confidence interval for the LC50 is also calculated by the program SPEARMAN. The confidence interval is calculated in the usual manner: the estimate plus or minus the product of a standard normal percentile and the estimated standard deviation of the estimate. Due to the conservative estimation of the variance of the estimate, the confidence intervals calculated are generally wider than necessary to assure the degree of confidence desired. For the procedure on variance estimation see (Hamilton, et. al., 1977).

The same procedure applies for estimating the ED50, except the number of mortalities is replaced by the number of responses. The confidence interval for the ED50 can also be found using the program SPEARMAN.

EVALUATION OF SPEARMAN

Key Points for Critiquing the Program

In evaluating the usefulness of the program SPEARMAN the following issues will be addressed:

(1) How to exit the program without completing the analysis;

(2) Help facilities;

(3) Are there any defaults?

(4) What happens if erroneous information is entered;

(5) Can the information be re-entered without returning to the beginning of the analysis?

(6) Is it easily understood what response is necessary for the prompts? (ease of use);

(7) Presentation of results.

Critique

The trimmed Spearman-Karber method of estimation for the Ad or the LC50 is easily programmable. The overall presentation of the program is easy to understand. My discussion will not include the plotting subsection of the program. The program may be used interactively or by batch runs. The program is written in Fortran 77 and is intended for use on the IBM PC family of microcomputers or an IBM PC compatible system.

(1) The capability to abort the analysis is very desirable. The user's guide for the program should specify the necessary command for exiting the program before analysis is complete. SPEARMAN does have the option to exit (control C), but does not have any documentation to inform the user of such an option.

(2) The program does not have any help facilities within the interactive mode, which is not surprising due to the small size and the specific purpose of the program. Accompanying the program on the distribution diskette is a very useful document file, README.1st. This file is essentially a manual for installing and executing the program SPEARMAN.

README.1st consists of the following sections: introduction, documentation, distribution diskette, file name and contents, development system, installation, execution, modification, technical contact, and a disclaimer. For each section the the information is presented in an understandable fashion and each section can stand alone by itself. The areas of importance for my discussion are the introduction, documentation, filename and contents, and execution.

The introduction along with the paper (Hamilton, et. al., 1977) provide the necessary background material for understanding the procedure implemented by the program SPEARMAN. I found no lack of information in this section.

The filename and contents section was self-explanatory. and quite necessary. This section is the forerunner to actual execution of the analyses. A quick glance at this listing provides the user with a precheck to insure all the necessary components are available for running the program SPEARMAN.

The execution section could use some revisions. The user should be made aware of a very important point -- **the caps lock key should be on when using either mode of execution.** This would save the user much frustration. The first step to the analysis cannot be carried out unless yes-no prompts are answered with a Y or N, the program will not accept y or n.

Another point should be stressed in either the execution listing or within the actual questions asked of the user, namely

whether the user is interested in using the log of the concentrations entered or the actual concentrations. I feel that it would be best if the user was prompted to consider this option within the interactive question-answer mode. It would be beneficial to have the program compute the logarithms of the concentrations if they are to be used in the analysis. This would save the analyst time and possibly some errors.

(3) The presence of defaults helps the user become acquainted with the program and get a feel for typical results. SPEARMAN does implement the idea of a default in specification of the desired %-trimmed. Some other areas of interest for implementing the idea of a default response are the prompts where the user specifies the species, the chemical, the units for concentration, the units for duration, and the duration period.

When testing the installation of the program with hypothetical data sets, I found it desirable to have the option of no response for inappropriate prompts. The option for no response does exist for the following prompts: species name, chemical name, concentration units, and duration units. It might be useful to note at each of these prompts there is the option of no response.

The default for %-trimmed is to let the program choose the appropriate percentage according to an algorithm. This algorithm is based on the relationship between the %-trimmed, the sensitivity of the estimator to anomalous data and the standard error

of the estimate. The relationship is discussed in the description of the trimming procedure.

(4) A program should be aware if obviously erroneous or conflicting information is entered at the prompts. SPEARMAN does have some error checks of this nature, but lacks some in important areas. The program will not proceed until the number of concentrations entered is at least as large as the number specified. However, there is a problem of being able to enter more concentrations than specified at the previous prompt. The program does check to insure the concentrations are entered in increasing order and will not let the user proceed until the ordering is correct. The user can specify an equal number of individuals for each of the concentration levels at one prompt and then proceed to enter varying numbers of individuals at the next prompt without receiving an error message. The program merely selects the first number entered as the number of individuals at each concentration.

There should be a step in the program where the user can verify whether the information entered at the prompts is correct. It would be useful to type out the information entered before the analysis takes place. There is merit though in seeing the raw data with the summary of the LC50 or the ED50 as a check on the information entered as SPEARMAN does.

(5) Ideally the user would like to re-enter the information as soon as he has recognized that an error has been committed;

SPEARMAN does not have this capability. This is a common feature lacking in most interactive programs.

(6) The prompts should be easily understood to enable the user to answer with the appropriate response. All the prompts are self-explanatory, except for the entering of the concentrations which I earlier cited as a problem area. All required responses are brief which aids in the interpretation of the response.

(7) The presentation of the results can make or break an entire analysis. The presentation should be labeled and organized in an orderly fashion. The final summary presented by SPEARMAN meets these qualifications. Another piece of valuable information cited by the program results is the existence of non-reliable confidence limits for the estimate.

The description of the batch mode is brief and explains the execution, but fails to specify the order of the batchfile and the necessary format. A simple additional section showing the type of necessary responses and the format should be found in the manual or in this case the README.1st file under the heading "Execution" and subheading "Batch .vs. Interactive Execution".

CONCLUSION

The program SPEARMAN is compatible with the requirements specified by the Environmental Protection Agency for toxicity studies and provides an alternative means for calculating the LC50 and the ED50. The program has no operating errors, but merely an user specification problem for the form of concentration to be used in the analysis.

There are two main areas where some adjustments should be made in the program. The most important is the implementation of some indicator at the prompt for entering the concentrations to enable the user to enter the concentration in the appropriate form. The second area deals with avoiding incompatible responses for the series of prompts. Some flag procedure should be incorporated within the program to avoid these needless errors in the execution of the program.

After these adjustments have been incorporated into the program, then SPEARMAN should be ready as a tool for use in toxicity studies performed for the Environmental Protection Agency. With the robust properties of the trimmed Spearman-Karber estimator, it promises to provide more reliable and sensible results than the usual methods incorporating the logit or probit model in the presence of anomalous responsees. The procedure implimented by SPEARMAN has applicability to a wider range of observable cases and would provide a single method for use in repeated studies.

REFERENCES

Hamilton, Martin A. (1979), "Robust Estimates of the ED50," Journal of the American Statistical Association, 74, 344-354.

Hamilton, Martin A., Russo, Rosemarie C., and Thurston, Robert V. (1977), "Trimmed Spearman-Karber Method for Estimating Median Lethal Concentrations in Toxicity Bioassays," Environmental Science & Technology, 11, 714-719.

APPENDIX

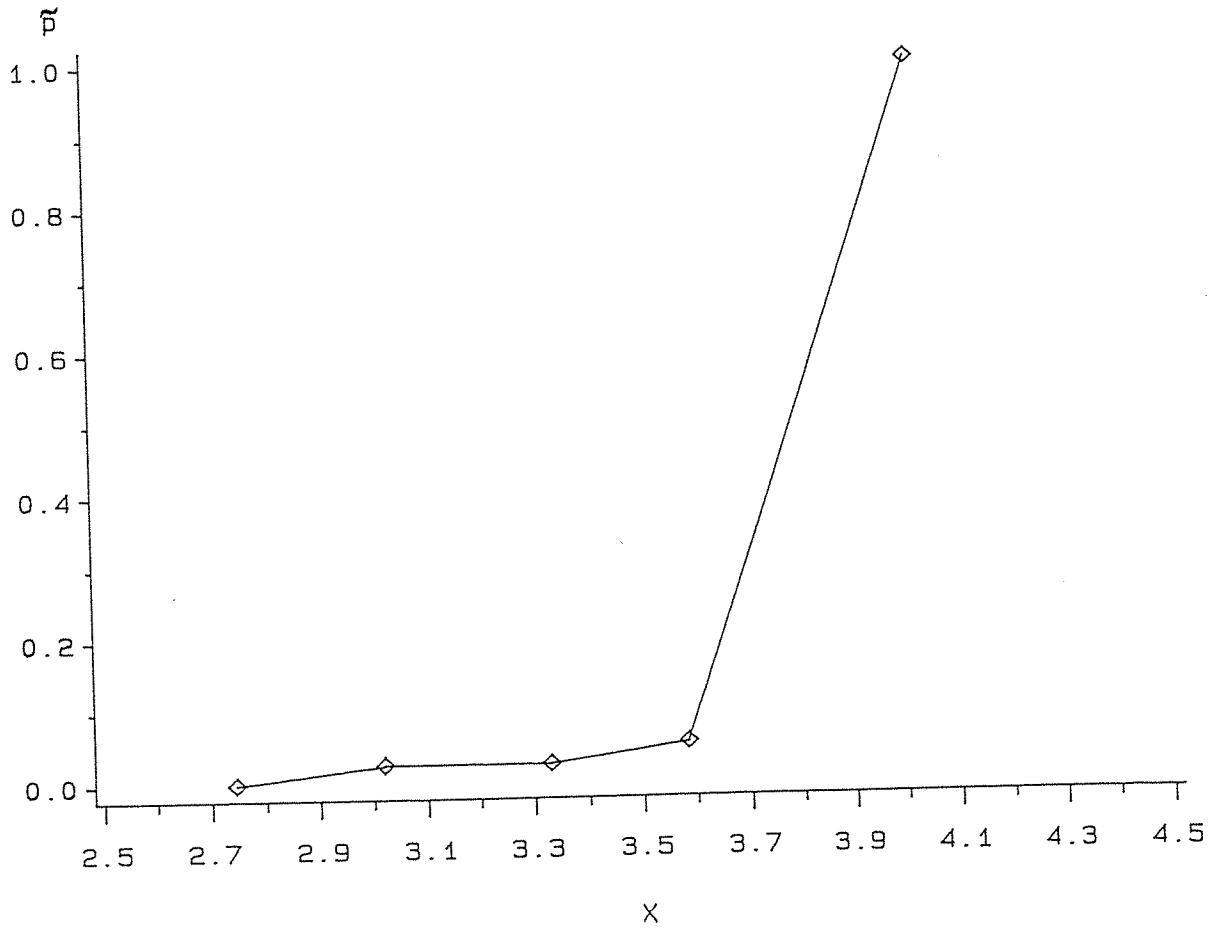

FIGURE I. Estimated cumulative relative frequency polygon for adjusted data from Table I.

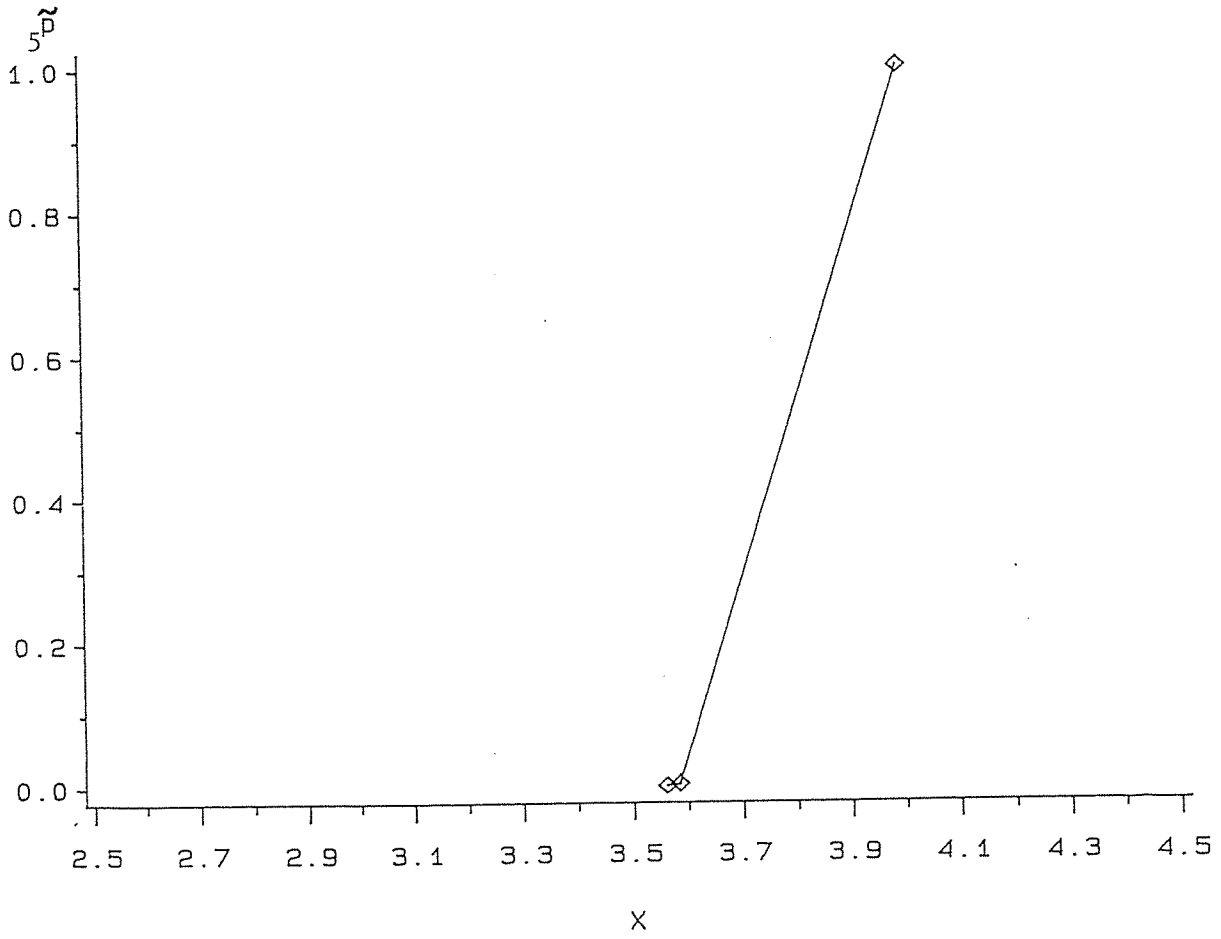

FIGURE II. Estimated cumlative relative frequency polygon of Figure I after trimming 5% from each tail