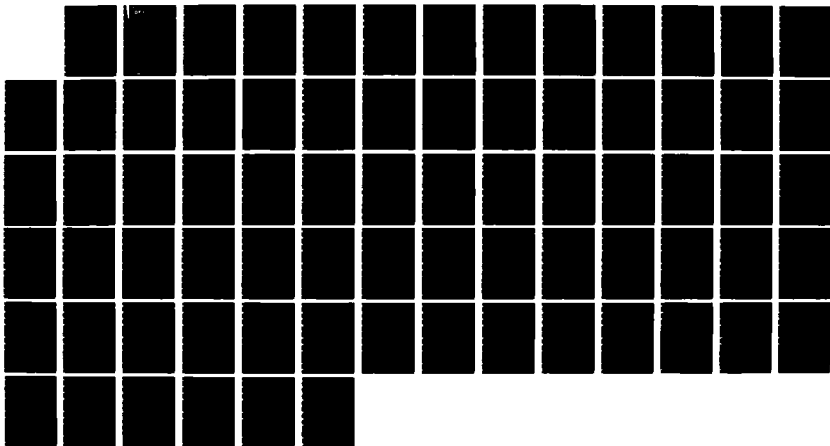
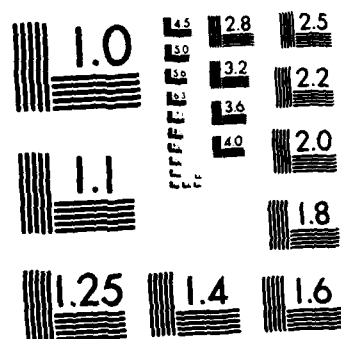


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SUFFIELD REPORT

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A PROBIT ANALYSIS PROGRAM
FOR THE DRES COMPUTER FACILITY (U)**

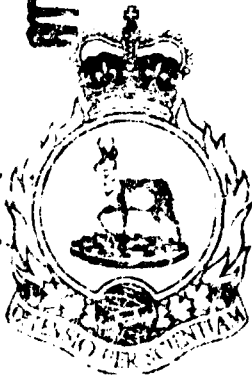
by

J. McFee, C.E. Mendoza,
J. Smith and D. Rigby

Project No. 0518B

July 1985

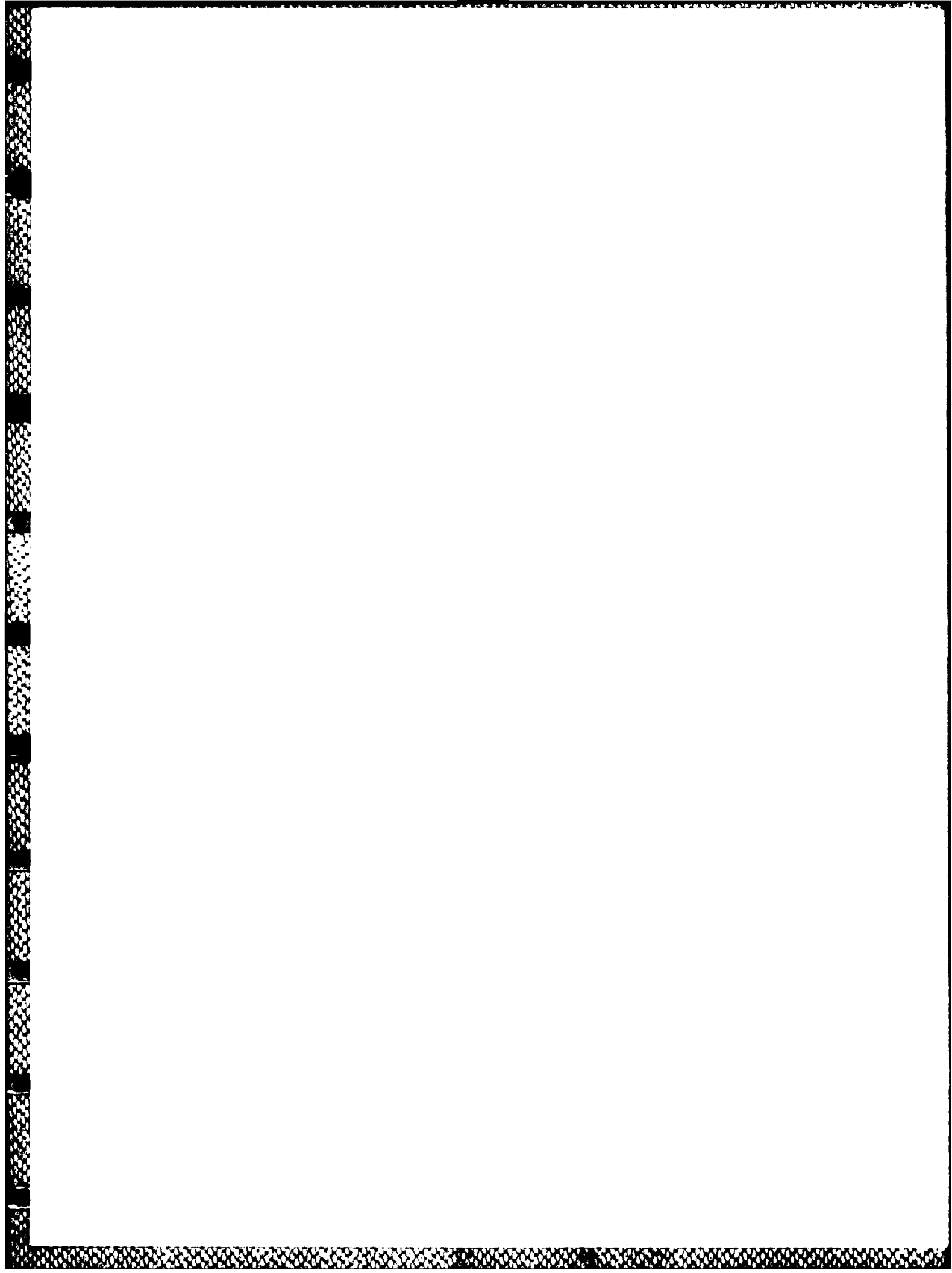
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ABSTRACT

This report describes an interactive computer program, PROBIT, which performs automated probit analysis. The code is written in the FORTRAN IV language using a modified iterative maximum likelihood algorithm and runs on the DRES Honeywell DPS-8/70 and VAX 11/780 computers.

A series of tests were performed to compare PROBIT with other probit analysis programs. These include the old DRES PROBT (modified IBM PROBT) and programs contained in the commercial statistical packages S103 and SAS. PROBIT clearly outperformed DRES PROBT and performed as well as S103 and as well or slightly better than SAS.

The input methods and output format of PROBIT can be modified whereas those of most commercial statistical packages cannot. Finally, PROBIT cost substantially less to develop than the purchase price of typical commercial statistical packages containing a good probit analysis program.

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ACKNOWLEDGEMENT

The technical advice of Ms. P. Morse, Central Experiment Station, Agriculture Canada, Ottawa, concerning probit analysis in general and specific probit analysis programs is gratefully acknowledged.

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1.0 INTRODUCTION

There are numerous ways to quantify the effect of a substance on an organism. One of the most widely used is the ED_{50} , the quantity of substance which produces the effect of interest in 50% of the population.

Most experimental designs used to determine the ED_{50} consist of a finite number of treatment groups, each of which comprises a finite number of organisms. Organisms within each group are given the same quantity of substance and the quantity differs from group to group. Usually the number of treatment groups and the number of organisms within a group are small (<10).

A variety of methods exists to estimate ED_{50} levels from the data. These include the methods of extreme lethal doses, the Dragstedt-Behrens method, Reed-Muench, Spearman-Kärber, moving average, and probit analysis (Finney 1971). Of these, only probit analysis is completely self consistent. The other methods will commonly give the same answer as probit analysis, but lead to serious errors if the dose range is very asymmetric about $\ln(ED_{50})$.

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There are several methods for performing probit analysis. Some are graphical and therefore not readily suited for automated data analysis. Others cannot estimate ED levels other than the ED_{50} or do not determine uncertainties of estimated quantities. A complete discussion of the various ways of estimating ED levels may be found in Finney (1971).

In the past, DRES carried out probit analysis using a program, PROBT (Chenier et al. 1962), based on a modified form of the subroutine PROBT (IBM PROBT)¹ which is contained in the IBM Scientific Subroutine Library². The subroutine is based on a modified version of the iterative maximum likelihood method of Finney (1971). This is a popular method for automated probit analysis since it requires no further user intervention once data has been provided and is quite robust. (Robustness of an algorithm or program is a measure of its ability to converge rapidly to a solution, and to function without producing meaningless numbers or encountering fatal errors.) A number of faults had been demonstrated with the DRES PROBT program. DRES PROBT did not function well with data sets which included a number of null and/or 100% response rates. Further, the program calculated only the ED_{50} ; whereas in some applications, other ED levels such as the ED_1 , E_{95} or ED_{99} were often required. Recently, it was also found that the code contains errors in calculation. These included incorrect estimates of the number of degrees of freedom and the variance of the regression slope, as well as some generally incorrect equations which fortuitously yielded correct answers only for ED_{50} . An even more serious shortcoming of DRES PROBT was the fact that it issued no warnings for a number of cases where results would be suspect, such as $g > 1$ or heterogeneous data. These shortcomings, together with the fact that the original program had been written for the obsolete IBM 1130 computer in an outmoded programming language (FORTRAN II), prompted us to design a new program that would eliminate the above problems, be cost effective, run on the DRES Honeywell DPS-8 computer and be transportable to different computers.

¹ In this report, the modified IBM PROBT will be referred to as DRES PROBT.

² System/360 Scientific Subroutine Package (360A-CM-03X) Version 3 Programmers Manual, IBM Technical Publications Department, White Plains, N.Y., 44 (1968).

The method of probit analysis used for the new program is also based on the iterative maximum likelihood method of Finney. Robustness for Finney's method is determined primarily by two key items in the program. The first is the method of handling null and 100% responses in the initial iteration. Null responses must be eliminated for the first iteration since they correspond to probits equal to minus infinity. The inclusion of 100% responses can also cause instabilities in the program particularly if several null and 100% responses are present in the data, but it is debatable whether they should be eliminated from the initial iteration or merely weighted differently than the other responses. The second key item is the method of testing for convergence. There are several quantities that can be used to test convergence but which one provides the most accurate answers for the minimum number of iterations is not clear. Since most successful commercial probit analysis programs have their own methods of handling these two operations and they do not provide details of their algorithms, one can only determine how to handle convergence and null/100% responses by trying different approaches. After extensive tests, it was decided to weigh both the null and 100% responses by zero in the first iteration and to use the sensitivity (slope of the regression line) as the test of convergence.

The new PROBIT code is an interactive FORTRAN IV program which yields a complete analysis of probit experiments, or, if desired, a condensed summary of results. The program provides a far more thorough analysis and is markedly less sensitive to the dynamic range of the input data than many personal computer probit programs (Lieberman, 1983) and IBM PROBT.

There are equally sophisticated programs available for mainframe computers, but these were not deemed cost effective for use at DRES, since they are a part of large statistical program packages, such as SAS³ and S103⁴, which

³ Statistical Analysis System, SAS Institute Inc., SAS Circle, Box 8000, Cary, N.C.

⁴ S103 Statistical Package, Engineering and Statistical Research Institute, Agriculture Canada, Ottawa, K1A 0C6

must be purchased or rented in their entirety. Also, these programs cannot normally be modified. This is a significant problem, since it was found that a number of individuals at DRES wanted certain output formats which these codes did not allow. This would be a continuing problem as scientists and their tastes change with time. A DRES program, however, could be tailored to suit needs now and be modified later.

An overview of the mainline program is discussed in Section 2.0. Sections 2.1 and 2.2 discuss the pertinent input and output parameters. Section 3 describes the subprograms required by the main program. Results of tests of the program, including a comparison of a number of probit analysis programs are presented in Section 4. The underlying theory behind the program is described in Appendices 1 and 2. A description of operating instructions for the program as implemented on the DRES Honeywell DPS-8/70 and Ordnance Detection Group (ODG) VAX 11/780 is given in Appendix 3. A sample input data file and sample output are given in Appendix 4. Finally, Appendix 5 contains a listing of PROBIT.

2.0 MAIN PROGRAM

Figure 1 shows the hierarchial chart of the probit analysis program. Figure 2 is the flowchart of the main program, PROBIT. The main program controls the input of data, the output of results and the actual iterative maximum likelihood calculation. Once the necessary data have been entered, the iterative procedures begins. It continues until convergence occurs (Appendix 1) or until the number of iterations exceeds a specified value, indicating nonconvergence.

The user has the option of printing intermediate results of the iterative regression at the end of each iteration. This option is controlled by a switch parameter during the input portion of the program, and is particularly useful in analysing the results obtained from data which produced nonconvergence or results which should be viewed with scepticism.

The output comprises some of the best features of a number of probit analysis programs designed for mainframe computers, notably SAS and S103.

2.1 Input

All of the input required for the probit analysis program is "interactive" and is entered directly into the computer, by means of the terminal keyboard. The data is entered in "free" format (excluding the alphanumeric strings), with the numbers separated by a comma or a blank space. The program itself need not be altered for execution; and the user is told what values to enter with default values provided where they might be needed. If the input is entered incorrectly, execution may be interrupted and the values re-entered. Some initial data are printed with the final results. These are shown in Table 1. (In Tables 1 or 2, symbols in brackets refer to the corresponding variables used in Appendices 1 and 2.)

2.2 Output

The output from a sample analysis is given in Appendix 4. Intermediate results have been printed by setting the IYNSW switch to YES. The first three iterations are shown for brevity.

The output for the program PROBIT consists of an initial list of the input data, followed by intermediate results if required for further analysis, and finally the results of the analysis (see Appendices 1 and 2). These include the doses, dose metameters, number of responses, probits, NEDS, standard errors, and weights used for each trial; the means and fiducial limits of the estimated responses, the sensitivity with its standard error; the value of chi-square (χ^2) for the corresponding number of degrees of freedom; the heterogeneity factor; the values of G and T (see below); the effective dose (ED) levels; and finally, the upper and lower fiducial limits corresponding to the given ED tolerance levels. All data are displayed in table form with suitable headings, and the title is printed at the top of each new page. Error messages have also been included where they may be needed. The final output quantities are summarized in Table 2.

Data which may be used to calculate relative potency are printed in a format suitable for direct entry to a program, RPOTC (Appendix 6). The theory behind the program is beyond the scope of this report, but is found in Chenier, 1966 and Finney, 1971.

3.0 FUNCTION SUBPROGRAMS

Four function subprograms (one of which calls two more function subprograms) are required by the main program to transform between NED values and probability of response, and to compute values of the χ^2 and Student-t distributions. The subprograms are briefly described below.

3.1 Name: Function XNED(Q) (Figure 3)

Purpose: The function XNED(Q) is called by the main program to calculate the normal equivalent deviate (NED) value for a probability of no response, Q. XNED(Q) has a maximum error of ± 0.0004 over the given range ($0.0 < Q < 1.0$). When Q is outside of this range, values are set accordingly: i.e., if $Q = 0$, $NED = 5.0$; if $Q = 1$, $NED = -5.0$. The transformation used for this function is from Hastings (1955).

Input Parameters: The one input parameter for this function is passed directly from the mainline program.

Q - real; probability of no response

Output Parameters: None (except possible error messages).

3.2 Name: Function RESP(Y) (Figure 4)

Purpose: This function is called from the mainline program to calculate the probability of response, P, given the NED value, Y. RESP(Y) has a maximum error of $\pm 3 \times 10^{-7}$ and uses the transformation from Hastings (1955).

Input Parameters: The only input parameter for the function RESP(Y) is passed from the main program.

Y - real; normal equivalent deviate value (NED)

Output Parameters: None.

3.3 Name: Function PCHISQ(CHISQR, NFREE) (Figure 5)

Purpose: This function is called from the main program, to evaluate the probability of exceeding χ^2 , given the estimate of reduced χ^2 , CHISQR, and the number of degrees of freedom, NFREE (Bevington, 1969). It should be noted that for NFREE odd and $\chi^2 > 50$, the calculation is only an approximation.

Input Parameters: The following parameters are passed from the mainline program.

CHISQR - real; estimate of reduced χ^2

NFREE - integer; number of degrees of freedom

Output Parameters: None, except possible error messages.

3.4 Name: Function GAMMS(X) (Figure 6)

Purpose: The function GAMMS(X) is called by PCHISQ to evaluate the gamma function for integers and half-integers (Bevington, 1969).

Input Parameters: The only parameter for this function is passed from the function PCHISQ.

X - real; real form of the integer or half-integer argument.

Output Parameters: None.

3.5 Name: Function FACTOR(N) (Figure 7)

Purpose: This function subprogram is called by GAMMS to calculate the factorial function for integers (Bevington, 1969). This is used when the argument is integral, and thus when the gamma function is identical to the factorial function: $\text{FACTOR}(N) = N!$. For N less than 11, this computation is straightforward multiplication, but logarithms are needed for larger values in order to preserve precision.

Input Parameters: The only input parameter used in this function is passed from GAMMS(X).

N - integer; integer argument used for calculations.

Output Parameters: None.

3.6 Name: Function TPROB(FREE,ALPHA) (Figure 8)

Purpose: This function is called from the main program to find the value of 'T' from a Student's-t distribution of FREE degrees of freedom, which is exceeded with probability ALPHA (2 sided test). The T distribution table (Thompson, 1941) is stored in a data file, and is read as input into a 2-dimensional array. The values are then read and interpolation is carried out where necessary to get an accurate value of 'T'. Tests are conducted throughout the program to determine special cases for FREE and ALPHA. If $\text{FREE} < 1$ or $\text{ALPHA} < 0.5$, the program terminates. If $\text{FREE} > 120$ the value of $\text{FREE} = \infty$ is used, and if $\text{ALPHA} > 0.995$ the value of $\text{ALPHA} = 0.995$ is used. Tests are also used to determine if interpolation is necessary, and if so, whether it is needed for either the ALPHA or FREE variables, or both. A simple first order (linear) interpolation is used.

Input Parameters: As well as the two parameters passed from the main program there is the data array read from a data file. Thus, the following are all classed as input:

FREE - real; number of degrees of freedom
ALPHA - real; confidence level of fiducial limits
T - real; data array of 'T' distribution table

Output Parameters: None, except possible error messages.

4.0 TESTS OF THE PROBIT PROGRAM

In order to test how well the new probit analysis program performed, sample data were analysed using the PROBIT, DRES PROBT, SAS and S103 programs. The first two programs are based on modified forms of the iterative maximum likelihood method of Finney (1971). No information is available on the specific algorithms used for SAS and S103, since most commercial statistical packages heavily guard their methods. However, because of the popularity of Finney's method, it is suspected that they too employ a form of it.

4.1 Comparison of "PROBIT" and "DRES PROBT"

The first test compared the DRES programs, PROBIT and DRES PROBT.

The data sets which were used are listed in Table 3. The data sets are typical of those analysed at DRES and provide a mixture of homogeneous and heterogeneous data.

Estimates of representative quantities estimated by both programs are presented in Table 4. Other quantities, such as other ED levels and corresponding fiducial limits, are available from the new program PROBIT but those listed are sufficient to allow a satisfactory comparison of the programs.

Both programs consistently agree on only two quantities, sensitivity and ED_{50} estimates. It is immediately clear that DRES PROBT miscalculates the number of degrees of freedom, ν , since this should be the number of samples in a series minus 2. The reason for the miscalculation is understood, but a discussion of it

is beyond the scope of this report. Also, DRES PROBT does not estimate "g" when data are found to be homogeneous, nor does it estimate other ED values or their fiducial limits.

The two programs disagreed on their estimates of reduced χ^2 . This would be expected for the series where DRES PROBT miscalculated v , but surprisingly occurred even when v was correct. The estimates of the standard error in the sensitivities agreed in all series except for the first, where the DRES PROBT estimate was 1.96 times larger than that of PROBIT. This can be explained, however, by noting that in the first series, DRES PROBT declared the data to be heterogeneous whereas PROBIT determined it to be homogeneous. Thus, DRES PROBT multiplied the PROBIT estimate of the standard error by the square root of the heterogeneity factor (=1.96). The discrepancy in heterogeneity related to the error in DRES PROBT caused the number of degrees of freedom to be miscalculated.

Finally, PROBIT generally converged much more quickly than DRES PROBT. In 22% (2/9) of the series, convergence required the same number of iterations as DRES PROBT, but in 66% (6/9) of the series, PROBIT converged using on the average 1/3 of the number of iterations of DRES PROBT. In one series, DRES PROBT failed to converge whereas PROBIT succeeded.

4.2 Comparison of "PROBIT", "SAS" and "S103"

PROBIT results were tested against two commercial PROBIT analysis programs, SAS and S103, using data sets listed in Table 5. The data sets included several series with single and multiple null and 100% responses. Such data, which are incompatible with DRES PROBT, provide a severe test of program robustness.

Estimates of representative quantities obtained for PROBIT (Table 6) were very similar to those obtained for S103 and slightly different from those of SAS. In any case, the differences in values from one program to another were not statistically significant. S103 did not have a convergence criterion but rather ran for a fixed number of iterations, in this case 20, which is far more than is normally required. This suggests that SAS may have been one or two iterations

away from true convergence. In 33% (3/9) of the series, PROBIT required one less iteration than SAS and in one series, SAS required one less iteration than PROBIT. The biggest differences between all three programs occurred in the calculation of ED_{95} and the fiducial limits, being the most pronounced for the ED_{95} . This is because fiducial limits are quite sensitive to slight errors in estimation of the regression slope, and because any error in calculating the regression slope is compounded as one estimates quantities progressively further from the mean of the data.

4.3 "PROBIT" Transportability

Finally, to test transportability of the code, the PROBIT source file was transferred on 9 track digital magnetic tape to the ODG Digital Equipment VAX 11/780, recompiled, and relinked. The data sets of Table 3 and 5 were reanalysed and the results were found to be identical to those from the Honeywell computer.

5.0 DISCUSSION AND CONCLUSIONS

Clearly, PROBIT performs much better than the old DRES PROBT program and is comparable to the probit programs contained in the two commercial packages, S103 and SAS. It may, indeed, actually perform slightly better than SAS.

Commercial statistical package programs are provided in an executable image form, which means that they cannot be modified. This can be a major drawback, since output must then be tailored to satisfy a large number of scientists of differing disciplines. The output of the PROBIT program is currently configured to the needs of a much smaller number of DRES scientists with relatively similar interests. Further, it can be modified as needs change.

Finally, commercial statistical packages are exceedingly expensive. Currently, they are rented for upwards of \$1000 per month or are purchased for between \$10000 and \$25000. The development of PROBIT cost approximately \$8000.

In light of these facts, the development of the PROBIT program has been a cost effective and worthwhile endeavour.

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APPENDIX 1

ITERATIVE ESTIMATION OF EFFECTIVE DOSE

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APPENDIX 1

Iterative Estimation of Effective Dose

A complete discussion of the theory of probit analysis is beyond the scope of this report and may be found in the definitive text of Finney (1971) and Eisenhart et al. (1947). The present technique is a modification of those of a number of authors, primarily Finney (1971). We present here sufficient theory to make the method clear.

The probability that an organism will respond, (e.g., die) if given a dose, x' , of a drug can be represented by assuming that:

1. Each organism is characterized by a definite sensitivity, s' , (the minimum dose at which it will respond),
2. sensitivities are log-normally distributed and
3. organism responses are uncorrelated.

The justification and validity of these assumptions have been discussed extensively (Finney, 1971), but for most biological experiments, the assumptions appear valid.

Thus if we define

$$s = \ln(s') \tag{1}$$

$$x = \ln(x') \text{ (x is called a "dose metameter")}$$

then the probability density function of s , $p(s)$, is given by:

$$p(s) = \sigma^{-1} (2\pi)^{-1/2} \exp \{-(s-\mu)^2/2\sigma^2\} \tag{2}$$

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The proportion of animals that do not respond for an infinite sample, denoted $Q(x)$, is given by

$$Q(x) = \sigma^{-1} (2\pi)^{-1/2} \exp \int_{s=x}^{\infty} \exp \{-(s-\mu)^2/2\sigma^2\} ds \quad (3)$$

The proportion that responds, called the 'response', for a dose metameter x , is given by

$$P(x) = 1 - Q(x) \quad (4)$$

In practice, the sample size is not infinite and instead there is a set of trials (i.e. treatment groups) $\{i = 1, 2, \dots, n\}$ in which a given dose metameter, x_i , yields a number of responses, r_i , for n_i organisms. If we can estimate μ and σ from the data, the entire distribution is known and hence the effective dose for any percentile can be calculated.

We define $P_i = r_i/n_i$ and $Q_i = 1 - P_i$. It can be easily shown that P_i and Q_i are samples from a binomial distribution. Q_i is an estimate of $Q(x_i)$ where

$$\begin{aligned} Q(x_i) &= \sigma^{-1} (2\pi)^{-1/2} \int_{s=x_i}^{\infty} \exp \{-(s-\mu)^2/2\sigma^2\} ds \\ &= (2\pi)^{-1/2} \int_{s=Y(x_i)}^{\infty} \exp \{-s^2/2\} ds \end{aligned} \quad (5)$$

$$\text{where } Y(x_i) = (x_i - \mu)/\sigma \quad (6)$$

Y in this form is said to be a 'normal equivalent deviate', or 'NED'. A probit, Y' , is defined as:

$$Y' = Y + 5 \quad (7)$$

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Y can be estimated by y_i where

$$Q_i = (2\pi)^{-1/2} \int_{s=y_i}^{\infty} \exp \{-s^2/2\} ds \quad (8)$$

y_i may be obtained from Q_i by means of tables or, more appropriately for computer usage, by means of a transformation ($y_i = T_1(Q_i)$) such as is found in Hastings (1955). (It should be noted at this point that if the natural response rate, P_0 , defined as the fraction of organisms that respond in the absence of stimulus for an infinite population, is significant with respect to the response rates when the stimulus is present, then it is straightforward to show that the estimate of the response due to the stimulus for trial i , denoted P'_i is given by:

$$P'_i = (P_i - P_0)/(1 - P_0) \quad (9)$$

$$\text{and } Q_i = 1 - P'_i \quad (10)$$

Q_i is then used in equation (8) and subsequent equations.

We thus obtain a set of pairs of data (x_i, y_i) which should be linearly related if the assumptions listed previously are correct, since:

$$Y(x_i) = A_0 + A_1 x_i \quad (11)$$

$$\text{where } A_0 = -\mu\sigma^{-1}$$

$$\text{and } A_1 = \sigma^{-1}$$

Using equation (11) as a model, the coefficients A_0 , A_1 may be estimated by performing a weighted linear least squares regression of y_i to x_i .

Assuming appropriate weights, w_i , for each trial i , are known (we shall return to this point), the estimate of A_1 , called the 'sensitivity', is denoted a_1 , and it and its estimated variance, $S_{a_1}^2$, are given by:

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$$a_1 = S_{xy}^2 / S_x^2 \quad (12)$$

$$S_{a_1}^2 = (\hat{\chi}_v^2 \nu^{-1}) / S_x^2 \quad (13)$$

The variance element S_x^2 and covariance element S_{xy}^2 are given by:

$$S_x^2 = (\sum_{i=1}^n n_i w_i)(\sum_{i=1}^n n_i w_i x_i^2) - (\sum_{i=1}^n n_i w_i x_i)^2 \quad (14)$$

$$S_{xy}^2 = (\sum_{i=1}^n n_i w_i)(\sum_{i=1}^n n_i w_i x_i y_i) - (\sum_{i=1}^n n_i w_i x_i)(\sum_{i=1}^n n_i w_i y_i) \quad (15)$$

and $\hat{\chi}_v^2$ is an estimate of the chi-square parameter for the regression (number of degrees of freedom, $\nu = n-2$) given by:

$$\hat{\chi}_v^2 = S_y^2 - a_1 S_{xy}^2 \quad (16)$$

where

$$S_y^2 = (\sum_{i=1}^n n_i w_i)(\sum_{i=1}^n n_i w_i y_i^2) - (\sum_{i=1}^n n_i w_i y_i)^2 \quad (17)$$

($\hat{\chi}_v^2 \nu^{-1}$ is called an estimate of the "reduced chisquare")

We also define:

$$\bar{x} = (\sum_{i=1}^n n_i w_i x_i) / (\sum_{i=1}^n n_i w_i) \quad (18)$$

$$\bar{y} = (\sum_{i=1}^n n_i w_i y_i) / (\sum_{i=1}^n n_i w_i) \quad (19)$$

Then we can estimate $Y(x_i)$ by $y(x_i)$

$$y(x_i) = a_1 (x_i - \bar{x}) + \bar{y} \quad (20)$$

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The parent probability density function from which y_i is a sample is not actually known. Generally, it is not a normal distribution and thus a least squares estimate of A_1 would not be a maximum likelihood estimate. To a first approximation, this is equivalent to saying that the variance of $y(x_i)$ is a function of $y(x_i)$. Thus the problem can be circumvented by weighting each sample (Bevington, 1969) but the appropriate weights to use, w_i , are not a priori known. To estimate the proper weights, an iterative procedure (given for the k th iteration where iteration number is shown as a bracketed superscript) is used):

1. calculate $a_1^{(k)}$, $S_{a_1}^2(k)$, $S_x^2(k)$, $S_{xy}^2(k)$, $S_y^2(k)$, $\hat{x}_v^{(k)}$, $\bar{x}^{(k)}$, $\bar{y}^{(k)}$, $y(x_i)^{(k)}$ using (12) - (20)

2. calculate $P_i^{(k)} = T_2(y(x_i)^{(k)})$, (21)

$$= (2\pi)^{-1/2} \int_{s=-\infty}^{y(x_i)^{(k)}} \exp \{-s^2/2\} ds$$

3. calculate $Q_i^{(k)} = 1 - P_i^{(k)}$ (22)

4. calculate $Z_i^{(k)} = (2\pi)^{-1/2} \exp \{-y_i^{(k)}/2\}$ (23)

5. calculate $y_i^{(k+1)} = y^{(k)}(x_i) + (Q_i^{(k)} - Q_i)/Z_i^{(k)}$ (24)

6. $w_i^{(k+1)} = Z_i^{(k)} / \{Q_i^{(k)} [(1-P_0)^{-1} - Q_i^{(k)}]\}$ (25)

7. go to 1 for $k+1$ iteration.

To begin the iteration process, the following are used as initial values:

$$Q_i^{(1)} = Q_i$$

$$w_i^{(1)} = 1$$

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$$y_i^{(1)} = T_1(Q_i^{(1)})$$

The iteration is repeated until convergence occurs or until a maximum number of iterations have been performed. The criterion $\delta = |a_1^{(k)} - a_1^{(k-1)}|$ may be used to test for convergence.

Failure to converge is usually caused by one of two conditions:

1. The data are heterogeneous (see Appendix 2).
2. The experimental design is not adequate, usually because the input data contains several trials with null and/or 100% observed responses.

The justification for the method is not obvious and is beyond the scope of this report, but it can be shown that convergence is assured and that maximum likelihood estimates of the parameters are obtained, provided that the previously discussed assumptions are valid (Finney, 1971). Reasons for estimating A_0 , A_1 instead of σ , μ are also discussed.

When iteration is terminated, we can determine the effective dose at the λ percentile level or ED_λ ; that is the dose at which λ percent of an infinite population of the organisms would respond. The ED_λ , denoted symbolically as x'_λ , is calculated as follows:

$$P_\lambda = \lambda/100 \tag{26}$$

$$y_\lambda = T_1(1-P_\lambda) \tag{27}$$

$$x_\lambda = a_1^{-1} (y_\lambda - \bar{y}) + \bar{x} \tag{28}$$

where a_1 , $\bar{y}$, $\bar{x}$, are the values of $a_1^{(k)}$, $\bar{y}^{(k)}$, $\bar{x}^{(k)}$ after the last iteration and

$$ED_\lambda = x'_\lambda = \exp(x_\lambda) \tag{29}$$

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APPENDIX 2

ERROR ANALYSIS

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APPENDIX 2

Error Analysis

Error analysis must be carried out after the effective dose estimation in order to determine the following:

1. the uncertainties of the estimated parameters, and
2. the validity of the assumptions concerning the data as discussed in Appendix 1.

As in Appendix 1, only an outline of the error analysis will be given and the interested reader should refer to any standard text on probit analysis (e.g., Finney, 1971) for theoretical justifications and a discussion of limitations.

$\chi^2_{\alpha}(v)$ is defined as the value of a variable from a chi-squared distribution such that

$$\int_{\chi^2 = \chi^2_{\alpha}(v)}^{\infty} P_v(\chi^2) d\chi^2 = \alpha, \quad (30)$$

where $P_v(\chi^2)$ is the probability density function of a chi-square distribution of v degrees of freedom. $P_v(\chi^2)$ may be calculated from an equation or from tables in any standard statistical text.

If $\hat{\chi}^2_v > \chi^2_{\alpha}(v)$ (see (16)), it is said that the data is "heterogenous". A heterogeneity factor, h , is defined as

$$h = \hat{\chi}^2_v / v \text{ if } \hat{\chi}^2_v > \chi^2_{\alpha}(v) \\ = 1 \text{ otherwise.} \quad (31)$$

The significance of the heterogeneity factor is frequently misunderstood. Data will be heterogenous if the iterative regression analysis of Appendix 1 does not correspond to a maximum likelihood estimation. This may be caused by:

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1. correlation of response within a trial due to a lack of independence of subjects within the treatment group (This may lead to increased dispersion about the regression line and a large value of $\hat{\chi}_v^2$. If this is the case, h can be regarded as a factor by which all weights have been underestimated since for homogeneous data $\hat{\chi}_v^2 \approx v$. The variance and covariances S_x^2, S_y^2, S_{xy}^2 can then be multiplied by h .), or
2. an incorrect mathematical model. (One cannot compensate for such deviations within the framework of the analysis.)

It is generally impossible to separate the first type of deviation (random deviation) from the second type (systematic deviation).

The best advice is to treat all data which are found to be heterogeneous with great caution, and never to multiply variances by h as a "cure" for heterogeneity unless one can be sure that systematic deviations do not occur. Inspection of the regression data and line is essential. In the present program, a warning message is issued whenever heterogeneous data occur, but the multiplication of variances by h is still carried out. Frequently it is found that if convergence occurs the data will be homogeneous.

A final check of goodness of fit can be obtained by computing the expected frequency of response, p_i from the final model after regression, for each trial. If a number of expected frequencies (or their complements) are very small, one should suspect any large value of χ^2 .

Let $t_\alpha(v)$ be a variable from a Student's t distribution (see any standard statistics text) for v degrees of freedom such that

$$\int_{-t_\alpha(v)}^{t_\alpha(v)} P(t) dt = 1 - \alpha \quad (32)$$

where $P(t)$ is the probability density function of t . We define a quantity g (the g factor) as

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$$g = t_{\alpha}^2 S_{a_1}^2 / a_1^2 = h t_{\alpha}^2 / (a_1 S_{xy}^2) \quad (33)$$

$$\text{where } t_{\alpha}^2 = t_{\alpha}^2(v) \quad h > 1 \quad (34)$$

$$= t_{\alpha}^2(\infty) \quad h = 1.$$

Fiducial limits for x_{λ} (the range of x over which the true x_{λ} is certain to lie at the α confidence level) is given by:

$$f_{\lambda} = x_{\lambda} + \frac{g}{1-g} (x_{\lambda} - \bar{x}) \pm \left\{ \frac{(1-g)}{\sum_{i=1}^n n_i w_i} + \frac{(x_{\lambda} - \bar{x})^2}{S_x^2} \right\}^{1/2} \left\{ \frac{t_{\alpha}}{a_1(1-g)} \right\} \quad (35)$$

where the plus sign corresponds to the upper limit, $f_{u\lambda}$, and the minus sign corresponds to the lower limit, $f_{l\lambda}$.

The fiducial or Fieller limits on x'_{λ} , i.e., the ED_{λ} are then

$$f'_{\lambda} = \exp \{f_{\lambda}\} \quad (36)$$

It can be readily shown that

$$g = t_{\alpha}^2 v^{-1} (r^{-2} - 1) \quad (37)$$

where r is the correlation coefficient (Bevington, 1969) for the regression. Since $-1 < r < 1$, then $g > 0$.

Clearly if the regression data are highly correlated or anti correlated ($r \approx \pm 1$), g will be approximately zero and the fiducial limits are well defined. If $g > 1$, ie, $r^2 < (v t_{\alpha}^2 + 1)^{-1}$ then the lower fiducial limit is greater than the upper, a nonsensical result. Detailed analysis shows that when this occurs, the range of x over which the true x_{λ} is certain to occur at the α confidence level is outside the range given by the two limits. Values of g for "well behaved" data are typically 0.1 and seldom exceed 0.4 (Finney, 1971). For values of g larger than 0.4, the experimenter should view the experiment with some skepticism.

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APPENDIX 3

OPERATING INSTRUCTIONS

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APPENDIX 3

Operating Instructions

The probit analysis program PROBIT is currently running on the DRES Honeywell DPS-8 and the ODG Digital Equipment VAX 11/780 computers. Procedures for operating the program on both computers follow.

Procedure for Interactive Use on the Honeywell Computer:

- (1) Log on the terminal with the following account number and password: BIO00200,STATS,DRES. Press the RETURN key. Enter N to profile change.
- (2) A menu consisting of several statistical analysis options will appear. Find the number corresponding to the probit analysis option (2). Enter the number and press the RETURN key.
- (3) User will be prompted with question:
Do you have an input file already created? (Y/N)
- (4) If answer to #3 is N, then user is prompted with:
Do you want to create an input file before running PROBIT? (Y/N)
- (5) If answer to #4 is N, then PROBIT program will prompt user to input data while the program is running.
- (6) If answer to #4 is Y, then a paragraph of steps of explanation detailing how to build a file and the format for the data is described. A sample file is also provided as an example.
- (7) If answer to #3 is Y, then user is prompted with:
'Enter file name'
After that entry, PROBIT will run successfully.

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- (8) Perform interactive probit analysis for a data set. The computer, using simple instructions, asks the user for the appropriate input data. Numbers on a line are separated by a blank or comma. If incorrect information has been entered and the RETURN key has not been pressed, the BACKSPACE key may be used to delete the erroneous data which may then be re-entered. If incorrect information has been entered and the RETURN key has been pressed, the ESC Y key must be pressed and all previous data must be re-entered.
- (9) After analysis of each data set, PROBIT will ask if you wish to exit the program. If 'yes' is chosen, the main menu will be returned and you may carry out other analyses or exit from the statistics package.
- (10) Afterwards, the output may be picked up from the line printer.

Procedure for the VAX 11/780 Computer:

- (1) Log on the terminal under your account.
The terminal should previously be set for 132 columns of output.
- (2) If input and output are to be via your terminal type the following:
@ DISK\$MRCG1:[JEM.STATS]PROBITTERM
- (3) Alternatively, the user can enter the input from and place the output in data files by typing:
@ DISK\$MRCG1:[JEM.STATS]PROBITFILE
It is assumed that the data to be entered have already been placed in a file using the EDT editor. The input data format is demonstrated in Appendix 4. You will be prompted for the file name and for an output filename. The output file need not initially exist.
- (4) Perform probit analysis for a data set. When using PROBITTERM the interactive process is the same as for the Honeywell computer except that the RUBOUT and CTRL Y keys are used for data correction instead of the BACKSPACE and ESC Y keys respectively.

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- (5) After analysis of each data set, the computer will ask the user whether he/she wishes to terminate analysis. If 'yes' is chosen, you will be returned to the monitor (DCL) level.
- (6) To logoff, type LOG.

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APPENDIX 4

SAMPLE INPUT DATA FILE AND
SAMPLE OUTPUT OF PROGRAM PROBIT

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SAMPLE INPUT DATA FILE :

SERIES 9 GROUP 2

4,50

YES

10. 585. 10.

10. 526.5 6.

10. 473.9 2.

10. 426.5 3.

0.95

0.0 0.001

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PROBIT ANALYSIS
SERIES 9 GROUP 2

SAMPLE PROBIT OUTPUT:

INITIAL INPUT DATA:

GROUP NUMBER	NUMBER OF ANIMALS	DOSE	NUMBER OF RESPONSES
1	10.00	585.0	10.00
2	10.00	526.5	6.00
3	10.00	473.9	2.00

PROBIT ANALYSIS
SERIES 9 GROUP 2

NUMBER OF GROUPS: 4
 MAXIMUM LOOP COUNT: 50
 OUTPUT OF INTERMEDIATE RESULTS: YES
 CONFIDENCE LEVEL OF FIELLER LIMITS: 0.9500
 FRACTION OF NATURAL MORTALITY: 0.00000
 CONVERGENCE CRITERION: 0.00100

INITIAL CALCULATED VALUES:

GROUP NUMBER	DOSAGES	EMPIRICAL RESPONSES	EMPIRICAL NEDS	WEIGHTS
1	0.63710E+01	1.000	0.50000E+01	0.000
2	0.62663E+01	.6000	0.25293E+00	1.000
3	0.61610E+01	.2000	-0.84146E+00	1.000
4	0.60556E+01	.3000	-0.52400E+00	1.000

PROBIT ANALYSIS
SERIES 9 GROUP 2

INTERMEDIATE RESULTS:

LOOP NUMBER: 1													
REGRESSION COEFF. (SLOPE) --B		VARIANCE OF DOSAGES --SXX		VAR. OF PREVIOUS LOOP WORKING NEDS --SYX		COVAR. OF PREVIOUS LOOP WORKING NEDS AND DOSAGES--SXY		MEAN OF DOSAGES --XBAR		MEAN OF PREVIOUS LOOP WORKING NEDS --YBAR		CHISQ	
0.36871E+01		0.73948E-02		0.21134E+00		0.27265E-01		0.61610E+01		-0.37084E+00		0.33244E+01	
GROUP NUMBER --I		DOSAGES --X(I)		EXPECTED NEDS FROM PROVISIONAL LINE--Y(I)		WORKING NEDS --YNEW(I)		Q FROM REGRESSION --QREG(I)		ORDINATE CORRESPONDING TO Y(I)--Z(I)		WEIGHT CORRESPONDING TO Y(I)--W(I)	
1		0.63716E+01		0.40588E+00		0.13379E+01		0.34242E+00		0.36740E+00		0.59947E+00	
2		0.62863E+01		0.17402E-01		0.25070E+00		0.49306E+00		0.39888E+00		0.63655E+00	
3		0.61610E+01		-0.37068E+00		-0.78801E+00		0.84456E+00		0.37245E+00		0.60550E+00	
4		0.60556E+01		-0.75924E+00		-0.50461E+00		0.77615E+00		0.29904E+00		0.51471E+00	
LOOP NUMBER: 2													
REGRESSION COEFF. (SLOPE) --B		VARIANCE OF DOSAGES --SXX		VAR. OF PREVIOUS LOOP WORKING NEDS --SYX		COVAR. OF PREVIOUS LOOP WORKING NEDS AND DOSAGES--SXY		MEAN OF DOSAGES --XBAR		MEAN OF PREVIOUS LOOP WORKING NEDS --YBAR		CHISQ	
0.64133E+01		0.13224E-01		0.67847E+00		0.84808E-01		0.62200E+01		0.95377E-01		0.31709E+01	
GROUP NUMBER --I		DOSAGES --X(I)		EXPECTED NEDS FROM PROVISIONAL LINE--Y(I)		WORKING NEDS --YNEW(I)		Q FROM REGRESSION --QREG(I)		ORDINATE CORRESPONDING TO Y(I)--Z(I)		WEIGHT CORRESPONDING TO Y(I)--W(I)	
1		0.63716E+01		0.10677E+01		0.17008E+01		0.14282E+00		0.22561E+00		0.41576E+00	
2		0.62863E+01		0.39203E+00		0.24997E+00		0.34752E+00		0.36943E+00		0.60191E+00	
3		0.61610E+01		-0.28300E+00		-0.77503E+00		0.61141E+00		0.38328E+00		0.61832E+00	
4		0.60556E+01		-0.95886E+00		-0.43812E+00		0.83118E+00		0.25192E+00		0.45229E+00	
LOOP NUMBER: 3													
REGRESSION COEFF. (SLOPE) --B		VARIANCE OF DOSAGES --SXX		VAR. OF PREVIOUS LOOP WORKING NEDS --SYX		COVAR. OF PREVIOUS LOOP WORKING NEDS AND DOSAGES--SXY		MEAN OF DOSAGES --XBAR		MEAN OF PREVIOUS LOOP WORKING NEDS --YBAR		CHISQ	
0.70615E+01		0.11985E-01		0.80590E+00		0.84634E-01		0.62104E+01		0.86288E-01		0.43490E+01	

PROBIT ANALYSIS
SERIES 9 GROUP 2

FINAL OUTPUT DATA:

** ITERATIVE REGRESSION CONVERGED AFTER 5 ITERATIONS **

GROUP NUMBER	DOSE	DOSAGES (LN OF DOSE)	EMPIRICAL % RESPONSE	MAXIMUM LIKELIHOOD EXPECTED PROBITS	MAXIMUM LIKELIHOOD EXPECTED NEDS	STANDARD ERROR	WEIGHT
1	585.0	0.63716E+01	100.00	0.62478E+01	0.12478E+01	0.41191E+00	0.35381E+00
2	528.5	0.62663E+01	60.00	0.54945E+01	0.49454E+00	0.25682E+00	0.58215E+00
3	473.9	0.61610E+01	20.00	0.47420E+01	-0.25802E+00	0.24311E+00	0.62138E+00
4	428.5	0.60556E+01	30.00	0.39885E+01	-0.10115E+01	0.38617E+00	0.43478E+00

GROUP NUMBER	DOSE	DOSAGES	NUMBER TESTED	OBSERVED	NUMBER REACTING		
					MEAN	95.00% FIDUCIAL LIMITS	UPPER
1	585.0	0.63716E+01	10.00	10.00	0.67021E+01	0.98007E+01	
2	528.5	0.62663E+01	10.00	6.00	0.49648E+01	0.84084E+01	
3	473.9	0.61610E+01	10.00	2.00	0.23132E+01	0.58647E+01	
4	428.5	0.60556E+01	10.00	3.00	0.38498E+00	0.39952E+01	

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PROBIT ANALYSIS
SERIES 9 GROUP 2

THE EQUATION FOR THE REGRESSION LINE IN NEDS IS:

$$Y = -44.30805 + 7.1498 X$$

REGRESSION SLOPE (SENSITIVITY) = 7.1498 +OR- 2.0892 (STANDARD ERROR)

CHI SQUARE = 4.7779 FOR 2 DEGREES OF FREEDOM

THE DATA IS HOMOGENEOUS; THE HETEROGENEITY FACTOR IS $H = 1.0$; $G = 0.32801E+00$
 $T = 0.19600E+01$ WITH INFINITE DEGREES OF FREEDOM

EXACT FIELLER LIMITS BELOW GIVE THE 95.00% FIDUCIAL LIMITS

ED LEVEL %	EFFECTIVE DOSE	FIELLER LIMITS	
		LOWER	UPPER
-----IN NATURAL LOGARITHMIC SCALE-----			
RESPONSE			
1.00	5.87165	0.54136E+01	0.60031E+01
50.00	6.19708	0.61173E+01	0.62680E+01
90.00	6.37635	0.62962E+01	0.66227E+01
95.00	6.42719	0.63323E+01	0.67378E+01
99.00	6.52252	0.63971E+01	0.69568E+01
-----IN ORIGINAL SCALE-----			
RESPONSE			
1.00	0.35483E+03	0.2244E+03	0.40470E+03
50.00	0.49131E+03	0.45385E+03	0.52741E+03
90.00	0.58778E+03	0.54249E+03	0.75195E+03
95.00	0.61843E+03	0.56248E+03	0.84370E+03
99.00	0.68029E+03	0.60010E+03	0.10502E+04

***** PARAMETERS NECESSARY FOR RELATIVE POTENCY TEST PROGRAM *****

CHISQ	SNW	XBAR	SXX*SNW	SXY*SNW	DFREE	YBAR	SYY*SNW
0.47779E+01	19.92195	6.20617	0.22911	1.63807	2	0.64935E-01	0.16490E+02

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APPENDIX 5

SOURCE LISTING OF PROGRAM PROBIT

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26-Feb-1986 16:03:43

VAX

26-Feb-1986 14:18:08

DIS

```
0001 C **** MAINLINE PROGRAM ****
0002 C
0003 C ----- A PROBIT ANALYSIS PROGRAM USED MAINLY TO DETERMINE THE -----
0004 C PROBABILITY THAT AN ANIMAL WILL RESPOND IF GIVEN A CERTAIN
0005 C EFFECTIVE DOSAGE OF A DRUG. ALSO USED TO CALCULATE THE REGRESSION
0006 C SLOPE, PROBITS, HETEROGENEITY FACTOR, AND FIDUCIAL LIMITS FOR THE
0007 C GIVEN DATA.
0008 C
0009 C
0010 C **** SUBROUTINES AND FUNCTION SUBPROGRAMS CALLED ****
0011 C
0012 C ----- FUNCTION XNED(Q) -----
0013 C
0014 C CALLED TO CALCULATE THE NED (NORMAL EQUIVALENT DEVIATE) VALUE
0015 C FOR A PROBABILITY OF NO RESPONSE, Q.
0016 C
0017 C ----- FUNCTION RESP(Y) -----
0018 C CALLED TO CALCULATE THE PROBABILITY OF RESPONSE, P, GIVEN THE
0019 C NED VALUE, Y.
0020 C
0021 C ----- FUNCTION PCHISQ(CHISQR,NFREE) -----
0022 C
0023 C CALLED TO EVALUATE THE PROBABILITY FOR EXCEEDING CHI SQUARE,
0024 C GIVEN THE COMPARISON VALUE OF REDUCED CHI SQUARE (CHISQR) AND
0025 C THE NUMBER OF DEGREES OF FREEDOM (NFREE).
0026 C
0027 C ----- FUNCTION TPROB(FREE,ALPHA) -----
0028 C
0029 C USED TO FIND THE VALUE OF 'T' FROM A T DISTRIBUTION TABLE OF
0030 C 'FREE' DEGREES OF FREEDOM, WHICH IS EXCEEDED WITH PROBABILITY
0031 C OF 'ALPHA' (2 SIDED TEST).
0032 C
0033 C
0034 C **** DESCRIPTION OF VARIABLES ****
0035 C
0036 C ----- INPUT VARIABLES -----
0037 C
0038 C ID/ ALPHABETIC; IDENTIFICATION TITLE (PRINTED ON EACH PAGE)
0039 C NT/ INTEGER; NUMBER OF GROUPS
0040 C MAXCNT/ INTEGER; MAXIMUM LOOP COUNT FOR ITERATIVE REGRESSION
0041 C IYNSW/ ALPHABETIC; SWITCH FOR OUTPUT OF INTERMEDIATE RESULTS
0042 C IY - YES
0043 C IN - NO
0044 C TN/ REAL; NUMBER OF ANIMALS IN THE GROUP
0045 C XIN/ REAL; DOSE GIVEN IN THE GROUP
0046 C R/ REAL; NUMBER OF RESPONSES IN THE GROUP
0047 C ALPHA/ REAL; CONFIDENCE LEVEL OF FIDUCIAL LIMITS
0048 C DEFAULT = 0.95
0049 C C/ REAL; FRACTION OF NATURAL MORTALITY
0050 C DEFAULT = 0.0
0051 C DELTA/ REAL; CONVERGENCE CRITERION
0052 C DEFAULT = 0.001
0053 C
0054 C ----- CALCULATED VARIABLES -----
0055 C
0056 C I,J,K/ INTEGER; LOOP COUNTERS
0057 C X/ REAL; DOSAGES (NATURAL LOG OF THE DOSE,XIN)
```

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VAX FO

26-Feb-1986 14:18:08

DISKSM

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0058 C P/ REAL; PROB. OF RESPONSE AT A GIVEN DOSAGE LEVEL
0059 C Q/ REAL; PROB. OF NO RESPONSE AT A GIVEN DOSAGE LEVEL
0060 C W/ REAL; CORRECT WEIGHTING COEFF. CORRESPONDING TO Y
0061 C Y/ REAL; EXPECTED NEDS FROM PROVISIONAL LINE (EMPIRICAL)
0062 C PLMBDA/ REAL; ARRAY FOR EFFECTIVE DOSE LEVELS
0063 C BOLD/ REAL; OLD (PREVIOUS) CALCULATED REGRESSION SLOPE
0064 C SNW,SNWX,SNWY,SNWXX,SNWYY,SNWXY/ REAL; INTERMEDIATE SUMS
0065 C XBAR/ REAL; MEAN OF THE DOSAGES
0066 C YBAR/ REAL; MEAN OF THE WORKING NED'S
0067 C SXX/ REAL; VARIANCE OF THE DOSAGES
0068 C SYY/ REAL; VARIANCE OF THE WORKING NED'S
0069 C SXY/ REAL; COVARIANCE OF THE WORKING NED'S AND DOSAGES
0070 C B/ REAL; CURRENT REGRESSION SLOPE (REGRESSION COEFFICIENT)
0071 C QREG/ REAL; Q FROM REGRESSION -- CORRESPONDING TO Y
0072 C Z/ REAL; ORDINATE CORRESPONDING TO Y
0073 C CHISQ/ REAL; VALUE OF CHI SQUARE
0074 C NFREE/ INTEGER; NUMBER OF DEGREES OF FREEDOM
0075 C FREE/ REAL; NUMBER OF DEGREES OF FREEDOM
0076 C CHISQR/ REAL; REDUCED CHI SQUARE
0077 C H/ REAL; HETEROGENEITY FACTOR
0078 C H = 1.0; HOMOGENEOUS
0079 C H < 1.0 OR H > 1.0; HETEROGENOUS
0080 C T/ REAL; VALUE OF 'T' DISTRIBUTION
0081 C SIGMAB/ REAL; ERROR IN SLOPE
0082 C QLMBDA,YLMBDA,XLMBDA,EDLMB/ REAL; TOLERANCE LEVELS OF VALUES
0083 C G,FACT,FACT1,FACT2,DIV,EX/ REAL; INTERMEDIATE VALUES
0084 C FUX,FLX/ REAL; UPPER AND LOWER FIDUCIAL LIMITS FOR X (ERRORS)
0085 C FUED,FLED/ REAL; UPPER AND LOWER FIDUCIAL LIMITS FOR ED
0086 C YR/ REAL; MAXIMUM LIKELIHOOD EXPECTED PROBITS (NEDS - 5)
0087 C PLB/ REAL; ED LEVEL (DOSE LEVEL * 100)
0088 C APA/ REAL; PERCENT CONFIDENCE LEVEL
0089 C RP/ REAL; EMPIRICAL PERCENTAGE RESPONSE
0090 C FST/ REAL; FIRST COEFFICIENT OF REGRESSION LINE EQUATION
0091 C YNEW/ REAL; WORKING NEDS (NORMAL EQUIVALENT DEVIATES)
0092 C YK/ REAL; MAXIMUM LIKELIHOOD EXPECTED NEDS
0093 C SIGY/ REAL; STANDARD ERROR
0094 C FLY/ REAL; LOWER FIDUCIAL LIMITS OF EXPECTED NUMBER REACTING
0095 C FJL/ REAL; UPPER FIDUCIAL LIMITS OF EXPECTED NUMBER REACTING
0096 C RS/ REAL; MEAN OF THE EXPECTED NUMBER REACTING
0097 C DUMMY/ REAL; ARRAY FOR DUMMY VARIABLE
0098 C SWXY,SWX,SWY/ REAL; INTERMEDIATE VALUES
0099 C
0100 C
0101 C **** PROGRAMMER / DAWN RIGBY ****
0102 C **** DATE / 22/06/82 ****
0103 C **** Updated / John McFee ****
0104 C **** Date / 26/02/86 ****
0105 C
0106 C
0107 C IMPLICIT REAL*8 (A-H, O-Z)
0108 C DIMENSION TN(100),XIN(100),R(100),ID(50),P(100),Q(100),W(100)
0109 C DIMENSION X(100),Y(100),QREG(100),Z(100),YR(100),YNEW(100)
0110 C DIMENSION QLMBDA(10),YLMBDA(10),XLMBDA(10),PLMBDA(10),EDLMB(10)
0111 C DIMENSION FACT(10),FACT1(10),FACT2(10),FLX(10),FUX(10),FLED(10)
0112 C DIMENSION PLB(10),RP(100),YK(100),FLY(100),FUL(100),SIGY(100)
0113 C DIMENSION DUMMY(100),RS(100),FUED(10)
0114 C DATA IY/'YES '/,IN/'NO '/

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0115      data indev/2/,ioutdev/3/,infodev/6/
0116      C
0117      C      ---- INPUT DATA ----
0118      C
0119      write(infodev,404)
0120      404  FORMAT(1X,'IF AN INCORRECT VALUE IS "ENTERED" AS INPUT, INTERRUPT
0121      1THE SYSTEM',/X,'IMMEDIATELY BY PRESSING "ESC Y" TWICE.',/X,
0122      2'BEGIN THE INPUT PROCEDURE FROM THE BEGINNING.')
```

```

0123      write(infodev,1)
0124      1  FORMAT (1X,'TYPE A SUITABLE EXPERIMENT TITLE'/1X,'EXCLUDING DIRECT
0125      1 MENTION OF PROBIT ANALYSIS.')
```

```

0126      read(indev,2)ID
0127      2  FORMAT(50A1)
0128      write(infodev,3)
0129      3  FORMAT (1X,'INPUT THE NUMBER OF GROUPS AND THE MAXIMUM LOOP COUNT'
0130      1/1X,'(IF UNKNOWN, TYPE 50 (DEFAULT = 50));'/1X,'SEPARATE THESE TWO
0131      2 INTEGERS BY A BLANK OR A COMMA.')
```

```

0132      read(indev,*) NT,MAXCNT
0133      write(infodev,4)
0134      4  FORMAT(1X,'TYPE EITHER "YES" OR "NO", DEPENDING UPON WHETHER YOU
0135      1WANT THE'/1X,'INTERMEDIATE RESULTS PRINTED AS OUTPUT OR NOT.')
```

```

0136      read(indev,5)IYNSW
0137      5  FORMAT(A4)
0138      write(infodev,6)
0139      6  FORMAT(1X,'INPUT THE NUMBER OF ANIMALS, THE DOSE, AND THE NUMBER
0140      1OF'/1X,'RESPONSES FOR EACH GROUP, ONE TRIAL PER LINE.'/1X,'THESE
0141      2MUST BE "REAL" NUMBERS, SEPARATED BY A BLANK OR A COMMA.')
```

```

0142      read(indev,*)(TN(I),XIN(I),R(I), I=1,NT)
0143      write(infodev,7)
0144      7  FORMAT(1X,'INPUT THE CONFIDENCE LEVEL OF THE FIELLER LIMITS'/1X, '
0145      1(DEFAULT=.95; REFER TO THE ABOVE "MAX. LOOP COUNT" EXPLANATION',/X,
0146      2,'DEFAULT). THIS MUST BE A "REAL" NUMBER.')
```

```

0147      read(indev,*) ALPHA
0148      write(infodev,8)
0149      8  FORMAT(1X,'INPUT THE FRACTION OF NATURAL MORTALITY (DEFAULT=0.)'/
0150      11X,'AND THE CONVERGENCE CRITERION (DEFAULT=.001).'/1X,'THESE MUST
0151      2BOTH BE "REAL" NUMBERS, SEPARATED BY A BLANK OR A COMMA.')
```

```

0152      read(indev,*) C,DELTA
0153      C
0154      C      ---- OUTPUT OF THE INITIAL DATA ----
0155      C
0156      write(ioutdev,9)ID
0157      9  FORMAT('1',60X,'PROBIT ANALYSIS'/61X,50A1)
0158      write(ioutdev,10)
0159      10  FORMAT(1X,/,21X,'INITIAL INPUT DATA:')
```

```

0160      write(ioutdev,11)
0161      11  FORMAT(1X,/,15X,'GROUP NUMBER',9X,'NUMBER OF ANIMALS',9X,
0162      1'DOSE',9X,'NUMBER OF RESPONSES',/)
```

```

0163      IF (NT.LE.50)GO TO 12
0164      DO 13 I=1,50
0165      write(ioutdev,14)I,TN(I),XIN(I),R(I)
0166      13  CONTINUE
0167      write(ioutdev,9)ID
0168      write(ioutdev,11)
0169      DO 15 I=51,NT
0170      write(ioutdev,14)I,TN(I),XIN(I),R(I)
0171      15  CONTINUE

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```

0172      GO TO 16
0173      12      DO 17 I=1,NT
0174              write(ioutdev,14) I,TN(I),XIN(I),R(I)
0175      14      FORMAT(18X,I4,19X,F7.2,12X,G9.4E2,15X,F7.2)
0176      17      CONTINUE
0177      16      write(ioutdev,9) ID
0178              write(ioutdev,18) NT,MAXCNT,IYNSW
0179      18      FORMAT(1X,/,12X,'NUMBER OF GROUPS:',I4,/,12X,'MAXIMUM LOOP COUNT
0180      1: ',I4,/,12X,'OUTPUT OF INTERMEDIATE RESULTS: ',A4)
0181              write(ioutdev,19) ALPHA,C,DELTA
0182      19      FORMAT(1X,/,12X,'CONFIDENCE LEVEL OF FIELLER LIMITS:',F8.4,/,
0183              112X,'FRACTION OF NATURAL MORTALITY:',F8.5//12X,'CONVERGENCE CRITER
0184      2ION: ',F8.5)
0185      C
0186      C      ---- INITIAL DATA VALUES ----
0187      C      ASSUME SENSITIVITIES ARE LOG NORMALLY DISTRIBUTED
0188      C
0189              write(ioutdev,20 )
0190      20      FORMAT(1X////////21X,'INITIAL CALCULATED VALUES:')
0191              write(ioutdev,21 )
0192      21      FORMAT(1X//10X,'GROUP NUMBER',9X,'DOSAGES',9X,'EMPIRICAL RESPONSES
0193      1',9X,'EMPIRICAL NEDS',9X,'WEIGHTS',/)
0194              DO 22 I=1,NT
0195                  X(I)=DLOG(XIN(I))
0196                  P(I)=R(I)/TN(I)
0197                  P(I)=(P(I)-C)/(1.0-C)
0198                  Q(I)=1.0-P(I)
0199                  W(I)=1.0
0200                  IF((P(I).EQ.0.0).or.(q(I).eq.0.0)) W(I)=0.0
0201                  Y(I)=XNED(Q(I))
0202                  write(ioutdev,23 ) I,X(I),P(I),Y(I),W(I)
0203      23      FORMAT(14X,I4,12X,E12.5,10X,G9.4E2,16X,E12.5,11X,F7.3)
0204      22      CONTINUE
0205              BOLD=1.0+30
0206              KLMBDA = 5
0207              PLMBDA(1)=0.01
0208              PLMBDA(2)=0.50
0209              PLMBDA(3)=0.90
0210              PLMBDA(4)=0.95
0211              PLMBDA(5)=0.99
0212      C
0213      C      ---- REGRESSION LOOP ----
0214      C
0215      C      -- FORM SUMS --
0216      C
0217              IF(IYNSW.EQ.IN) GO TO 24
0218              write(ioutdev,25) ID
0219      25      FORMAT('1',60X,'PROBIT ANALYSIS'/61X,50A1)
0220              write(ioutdev,26)
0221      26      FORMAT(1X,/,21X,'INTERMEDIATE RESULTS:')
0222      24      DO 27 J=1,MAXCNT
0223              SNW=0.
0224              SNWX=0.
0225              SNWY=0.
0226              SNWXX=0.
0227              SNWYY=0.
0228              SNWXY=0.

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0229      DO 28 I=1,NT
0230      SNW=SNW +TN(I) * W(I)
0231      SNWX=SNWX +TN(I) * W(I) * X(I)
0232      SNWY=SNWY +TN(I) * W(I) * Y(I)
0233      SNWXX=SNWXX +TN(I) * W(I) * X(I)**2
0234      SNWYY=SNWYY +TN(I) * W(I) * Y(I)**2
0235      SNWXY=SNWXY +TN(I) * W(I) * X(I) * Y(I)
0236      28 CONTINUE
0237      C
0238      C      -- CALCULATE STATISTICS OF DATA --
0239      C
0240      XBAR=SNWX/SNW
0241      YBAR=SNWY/SNW
0242      SXX=SNWXX/SNW - XBAR**2
0243      SYY=SNWYY/SNW - YBAR**2
0244      SXY=SNWXY/SNW - XBAR*YBAR
0245      IF(SXX-0.0)29,30,29
0246      30 write(ioutdev,31)
0247      31 FORMAT('1',1X,'DOSES HAVE ZERO VARIANCE--REGRESSION IMPOSSIBLE!')
0248      GO TO 32
0249      29 B=SXY/SXX
0250      CHISQ= (SYY - B*SXY) * SNW
0251      DO 33 I=1,NT
0252      Y(I)=B * (X(I) - XBAR) + YBAR
0253      IF(Y(I).GT. 5.0) Y(I) = 5.0
0254      IF(Y(I).LT. -5.0) Y(I) = -5.0
0255      QREG(I) = 1.0 - RESP(Y(I))
0256      EX=(-(Y(I)**2)/2.)
0257      Z(I)=(DEXP(EX))/DSQRT(2.*3.141592653500)
0258      YNEW(I)=Y(I)+(QREG(I)- Q(I))/Z(I)
0259      DIV = (QREG(I) * ((1./(1.- C)) - QREG(I)))
0260      IF(DABS(DIV).LT.1.00D-10)GO TO 34
0261      W(I)=(Z(I)**2)/(DIV)
0262      GO TO 33
0263      34 W(I)=0.0
0264      33 CONTINUE
0265      IF(IYNSW.EQ.IN) GO TO 35
0266      GO TO 36
0267      35 DO 37 I=1,NT
0268      YK(I) = Y(I)
0269      Y(I) = YNEW(I)
0270      37 CONTINUE
0271      IF(J-MAXCNT)38,38,39
0272      39 write(ioutdev,40)
0273      40 FORMAT('1',1X,'WARNING -- REGRESSION MAY NOT BE CONVERGENT')
0274      GO TO 41
0275      38 IF(DELTA - DABS(B-BOLD))42,43,43
0276      42 BOLD = B
0277      CONTINUE
0278      43 GO TO 41
0279      C
0280      C      ---- OPTIONAL OUTPUT OF INTERMEDIATE RESULTS ----
0281      C
0282      36 write(ioutdev,44)J
0283      44 FORMAT(1X,///,2X,'LOOP NUMBER:',I4)
0284      write(ioutdev,45)
0285      45 FORMAT(1X//4X,'REGRESSION',6X,'VARIANCE OF',6X,'VAR. OF PREVIOUS',

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0286      16X,'COVAR. OF PREVIOUS',6X,'MEAN OF',6X,'MEAN OF PREVIOUS',6X,
0287      2'CHISQ'/4X,'COEFF.(SLOPE)',3X,'DOSAGES',10X,'LOOP WORKING NEDS',
0288      35X,'LOOP WORKING NEDS',7X,'DOSAGES',6X,'LOOP WORKING NEDS'/4X,
0289      4'--B',13X,'--SXX',12X,'--SY',17X,'AND DOSAGES--SXY',8X,'--XBAR',
0290      57X,'--YBAR',/)
0291      write(ioutdev,46)B,SXX,SY,SXY,XBAR,YBAR,CHISQ
0292      46      FORMAT(4X,E12.5,4X,E12.5,5X,E12.5,12X,E12.5,7X,E12.5,5X,E12.5,6X,
0293      1E12.5)
0294      write(ioutdev,47 )
0295      47      FORMAT(1X///4X,'GROUP',11X,'DOSAGES',10X,'EXPECTED NEDS',9X,'WORKI
0296      1NG',17X,'Q FROM',7X,'ORDINATE',9X,'WEIGHT'/4X,'NUMBER',10X,'--X(I)
0297      2',11X,'FROM PROVISIONAL',6X,'NEDS',18X,'REGRESSION',5X,'CORRESPOND
0298      3ING',4X,'CORRESPONDING'/4X,'--I',30X,'LINE--Y(I)',12X,'--YNEW(I)',
0299      413X,'--QREG(I)',6X,'TO Y(I)--Z(I)',4X,'TO Y(I)--W(I)')/
0300      DO 48 I=1,NT
0301      write(ioutdev,49 )I,X(I),Y(I),YNEW(I),QREG(I),Z(I),W(I)
0302      49      FORMAT(4X,I4,12X,E12.5,5X,E12.5,12X,E12.5,7X,E12.5,5X,E12.5,6X,
0303      1E12.5)
0304      48      CONTINUE
0305      GO TO 35
0306      C
0307      C      ---- FURTHER CALCULATIONS ----
0308      C
0309      41      NFREE = NT - 2
0310      FREE = NFREE
0311      CHISQR = CHISQ/FREE
0312      IF(PCHISQ(CHISQR,NFREE).GE.(1.-ALPHA))GO TO 51
0313      H=CHISQR
0314      T = TPROB(FREE,ALPHA)
0315      GO TO 52
0316      51      H = 1.0
0317      T = TPROB(900.,ALPHA)
0318      52      SIGMAB =DSQRT(H/(SXX*SNW))
0319      G =(H * T**2)/(B**2 * SXX * SNW)
0320      DO 105 I=1,NT
0321      SIGY(I) = DSQRT((H/SNW) + (H*(X(I)-XBAR)**2/(SXX * SNW)))
0322      FUL(I) = YK(I) + T * SIGY(I)
0323      FLY(I) = YK(I) - T * SIGY(I)
0324      DUMMY(I) = 0.0
0325      105     CONTINUE
0326      DO 53 K=1,KLMBDA
0327      QLMBDA(K)=1.- PLMBDA(K)
0328      YLMBDA(K)=XNED(QLMBDA(K))
0329      XLMBDA(K)= ((YLMBDA(K)-YBAR)/B)+XBAR
0330      EDLMB(K)=DEXP(XLMBDA(K))
0331      IF(G.GT.1.0) GO TO 53
0332      C
0333      C      ---- FIELLER LIMITS (ERRORS IN ED) ----
0334      C
0335      FACT(K)=((H*(1.-G))/SNW)+(H*(XLMBDA(K)-XBAR)**2)/(SXX*SNW)
0336      FACT1(K)=DSQRT(FACT(K))* (T/(B*(1.-G)))
0337      FACT2(K)=XLMBDA(K)+(G/(1.-G))*(XLMBDA(K)-XBAR)
0338      FLX(K)=FACT2(K)-FACT1(K)
0339      FUX(K)=FACT2(K)+FACT1(K)
0340      FLED(K)=DEXP(FLX(K))
0341      FUED(K)=DEXP(FUX(K))
0342      53      CONTINUE

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0343      APA = ALPHA * 100.
0344      C
0345      C      ---- OUTPUT OF FINAL RESULTS ----
0346      C
0347      write(ioutdev,55)ID
0348      55      FORMAT('1',60X,'PROBIT ANALYSIS'/61X,50A1)
0349      write(ioutdev,56)
0350      56      FORMAT(1X,/,/,21X,'FINAL OUTPUT DATA:')
0351      IF(MAXCNT-J)57,58,58
0352      57      write(ioutdev,59)MAXCNT
0353      59      FORMAT(1X,/,/,20X,' !! WARNING -- ITERATIVE REGRESSION FAILED TO
0354      1 CONVERGE AFTER ',I3,' ITERATIONS'/22X,'- RESULTS FOLLOWING MAY BE
0355      2 SUSPECT !! ')
0356      GO TO 60
0357      58      write(ioutdev,61)J-1
0358      61      FORMAT(1X,/,/,20X,' ** ITERATIVE REGRESSION CONVERGED AFTER ',I3
0359      1,' ITERATIONS ** ')
0360      60      write(ioutdev,62)
0361      62      FORMAT(1X,/,/,6X,'GROUP',6X,'DOSE',6X,'DOSAGES',6X,'EMPIRICAL',6X
0362      1,'MAXIMUM LIKELIHOOD',6X,'MAXIMUM LIKELIHOOD',6X,'STANDARD',6X,
0363      2'WEIGHT')
0364      write(ioutdev,63)
0365      63      FORMAT(6X,'NUMBER',15X,'(LN OF',7X,'% RESPONSE',5X,'EXPECTED PROBI
0366      1TS',8X,'EXPECTED NEDS',11X,'ERROR'/27X,'DOSE')//)
0367      IF(NT.LE.50)GO TO 64
0368      DO 65 I=1,50
0369      YR(I)=YK(I) + 5.
0370      RP(I)=P(I)*100.0
0371      write(ioutdev,67)I,XIN(I),X(I),RP(I),YR(I),YK(I),SIGY(I),W(I)
0372      65      CONTINUE
0373      write(ioutdev,99)APA
0374      99      FORMAT(1X,/,/,6X,'GROUP',6X,'DOSE',6X,'DOSAGES',6X,'NUMBER TESTED
0375      1',6X,'-----NUMBER REACTING-----'
0376      2----'/6X,'NUMBER',52X,'OBSERVED',6X,'-----EXPECTED--
0377      3-----'/80X,'MEAN',6X,'--',F6.2,'% FIDUCIAL LIMITS-----
0378      4--'/96X,'LOWER',11X,'UPPER'//)
0379      DO 101 I=1,50
0380      RS(I)=RESP(YK(I)) * TN(I)
0381      FLY(I)=RESP(FLY(I)) * TN(I)
0382      FUL(I)=RESP(FUL(I)) * TN(I)
0383      write(ioutdev,100)I,XIN(I),X(I),TN(I),R(I),RS(I),FLY(I),FUL(I)
0384      100      FORMAT(7X,I3,5X,G9.4E2,2X,E12.5,6X,F7.2,14X,F7.2,8X,F7.2,6X,E12.5,
0385      15X,E12.5)
0386      101      CONTINUE
0387      write(ioutdev,55)ID
0388      write(ioutdev,62)
0389      write(ioutdev,63)
0390      DO 66 I=51,NT
0391      YR(I)=YK(I) + 5.
0392      RP(I)=P(I)*100.0
0393      write(ioutdev,67)I,XIN(I),X(I),RP(I),YR(I),YK(I),SIGY(I),W(I)
0394      66      CONTINUE
0395      write(ioutdev,99)APA
0396      DO 102 I=51,NT
0397      RS(I) = RESP(YK(I)) * TN(I)
0398      FLY(I)=RESP(FLY(I)) * TN(I)
0399      FUL(I)=RESP(FUL(I)) * TN(I)

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0400      write(ioutdev,100)I,XIN(I),X(I),TN(I),R(I),RS(I),FLY(I),FUL(I)
0401      102  CONTINUE
0402      GO TO 68
0403      64   DO 69 I=1,NT
0404      YR(I)=YK(I) +5.
0405      RP(I)=P(I)*100.0
0406      write(ioutdev,67)I,XIN(I),X(I),RP(I),YR(I),YK(I),SIGY(I),W(I)
0407      67   FORMAT(7X,I3,5X,G9.4E2,2X,E12.5,3X,F7.2,10X,E12.5,12X,E12.5,7X,
0408      1E12.5,3X,E12.5)
0409      69   CONTINUE
0410      write(ioutdev,99)APA
0411      DO 103 I=1,NT
0412      RS(I)=RESP(YK(I)) * TN(I)
0413      FLY(I)=RESP(FLY(I)) * TN(I)
0414      FUL(I)=RESP(FUL(I)) * TN(I)
0415      write(ioutdev,100)I,XIN(I),X(I),TN(I),R(I),RS(I),FLY(I),FUL(I)
0416      103  CONTINUE
0417      68   write(ioutdev,70)ID
0418      70   FORMAT('1',60X,'PROBIT ANALYSIS'/61X,50A1)
0419      FST=YBAR - B * XBAR
0420      write(ioutdev,71 )FST,B
0421      71   FORMAT(1X,///,22X,'THE EQUATION FOR THE REGRESSION LINE IN NEDS IS
0422      1:'/31X,'Y = ',G14.7E2,' + ',G12.5E2,' X')
0423      write(ioutdev,72)B,SIGMAB
0424      72   FORMAT(1X, / ,22X,'REGRESSION SLOPE (SENSITIVITY) = ',G12.5E2,
0425      1' +0R- ', G12.5E2,' (STANDARD ERROR)')
0426      write(ioutdev,73)CHISQ,NFREE
0427      73   FORMAT(1X,/,22X,'CHI SQUARE =',G12.5E2,' FOR',I4,' DEGREES OF FR
0428      1EEDOM')
0429      IF(PCHISQ(CHISQR,NFREE).GE.(1.-ALPHA))GO TO 74
0430      H=CHISQ/FREE
0431      GO TO 75
0432      74   H=1.0
0433      75   IF(H.EQ.1.0)GO TO 76
0434      write(ioutdev,77)H,G,T,NFREE
0435      77   FORMAT(1X,/,22X,'!!!!!! WARNING --- THE DATA IS HETEROGENOUS: THE
0436      1HETEROGENEITY FACTOR IS H = ',E12.5,' !!!!!/22X,'!!!!!! G =',E12.5
0437      2,', T =',E12.5,' WITH',I4,' DEGREES OF FREEDOM. !!!!!/22X,'!!!!!!
0438      3 "TREAT PROBIT RESULTS WITH EXTREME CAUTION" !!!!!')
0439      GO TO 78
0440      76   write(ioutdev,79)G,T
0441      79   FORMAT(1X,/,22X,'THE DATA IS HOMOGENEOUS; THE HETEROGENEITY FACTOR
0442      1 IS H = 1.0; G =',E12.5,/31X,'T =',E12.5,' WITH INFINITE DEGREES
0443      2OF FREEDOM')
0444      78   IF(G.LE.1.0) GO TO 300
0445      write(ioutdev,301)
0446      301  FORMAT(/22X,'!!!!!! WARNING -- G > 1.0; THE FIELLER LIMITS ARE OF
0447      1NO USE AND HENCE NOT PRINTED !!!!!/22X,'!!!!!! SEE FINNEY, PAGE 79
0448      2 !!!!!')
0449      300  write(ioutdev,80)APA
0450      80   FORMAT(/////11X,'EXACT FIELLER LIMITS BELOW GIVE THE ',F6.2,'% FID
0451      1UCIAL LIMITS')
0452      write(ioutdev,81)
0453      81   FORMAT(/11X,'-----
0454      1-----')
0455      write(ioutdev,82)
0456      82   FORMAT(/13X,'ED',10X,'EFFECTIVE',8X,'-----FIELLER LIMITS-----'/

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0457      111X, 'LEVEL %', 7X, 'DOSE', 16X, 'LOWER', 10X, 'UPPER')
0458      write(ioutdev, 83)
0459      83  FORMAT(/11X, 'RESPONSE', 6X, '-----IN NATURAL LOGARITHMIC SCALE----
0460      1--')
0461      DO 84 K = 1, KLMBDA
0462      PLB(K) = PLMBDA(K) * 100.
0463      IF(G.LE.1.0) GO TO 302
0464      write(ioutdev, 303) PLB(K), XLMBDA(K)
0465      303  FORMAT(12X, F7.2, 8X, F8.5)
0466      GO TO 84
0467      302  write(ioutdev, 85) PLB(K), XLMBDA(K), FLX(K), FUX(K)
0468      85  FORMAT(12X, F7.2, 8X, F8.5, 9X, E12.5, 5X, E12.5)
0469      84  CONTINUE
0470      write(ioutdev, 86)
0471      86  FORMAT(/11X, 'RESPONSE', 6X, '-----IN ORIGINAL SCALE-----
0472      1--')
0473      DO 87 K = 1, KLMBDA
0474      PLB(K) = PLMBDA(K) * 100.
0475      IF(G.LE.1.0) GO TO 304
0476      write(ioutdev, 305) PLB(K), EDLMB(K)
0477      305  FORMAT(12X, F7.2, 8X, F8.3)
0478      GO TO 87
0479      304  write(ioutdev, 88) PLB(K), EDLMB(K), FLED(K), FUED(K)
0480      88  FORMAT(12X, F7.2, 8X, E12.5, 9X, E12.5, 5X, E12.5)
0481      87  CONTINUE
0482      write(ioutdev, 81)
0483      SWXY = SNW * SXY
0484      SWX = SNW * SXX
0485      SWY = SNW * SY
0486      write(ioutdev, 389)
0487      389  FORMAT(/11X, '***** PARAMETERS NECESSARY FOR RELATIVE POTENCY T
0488      1EST PROGRAM *****'//13X, 'CHISQ', 9X, 'SNW', 10X, 'XBAR', 7X, 'SXX*SNW',
0489      26X, 'SXY*SNW', 8X, 'DFREE', 8X, 'YBAR', 7X, 'SYY*SNW')
0490      write(ioutdev, 400) CHISQ, SNW, XBAR, SWX, SWXY, NFREE, YBAR, SWY
0491      400  FORMAT(/10X, E11.5, 3X, F10.5, 3X, F10.5, 3X, F10.5, 3X, F10.5, 7X, I4, 5X,
0492      1E11.5, 3X, E11.5)
0493      32  STOP
0494      END
```

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```

0001 C
0002 C
0003 C      **** FUNCTION XNED ****
0004 C
0005 C      ---- THIS FUNCTION CALCULATES THE NORMAL EQUIVALENT DEVIATE ----
0006 C              (NED) VALUE FOR A PROBABILITY OF NO RESPONSE, Q. IT ASSUMES
0007 C              THAT NED(Q) HAS A MAXIMUM ERROR OF + OR -.0004 OVER THE GIVEN
0008 C              RANGE ( MOST LIKELY, 0 < Q < OR = .5 ). THE TRANSFORM USED
0009 C              IS FROM "APPROXIMATIONS FOR DIGITAL COMPUTERS" BY HASTINGS, P
0010 C              RINCETON UNIVERSITY PRESS, PRINCETON, NJ., 1955.
0011 C
0012 C
0013 C      **** USAGE ****
0014 C
0015 C      ---- RESULT = XNED(Q) ----
0016 C
0017 C
0018 C      **** SUBROUTINES AND FUNCTION SUBPROGRAMS CALLED ****
0019 C
0020 C      ---- NONE ----
0021 C
0022 C
0023 C      **** DESCRIPTION OF PARAMETERS AND VARIABLES ****
0024 C
0025 C      ---- PARAMETERS PASSED FROM THE MAINLINE ----
0026 C
0027 C              Q/ REAL; PROBABILITY OF NO RESPONSE ( OF SURVIVAL)
0028 C
0029 C      ---- VARIABLES ----
0030 C
0031 C              ETA/ REAL; INTERMEDIATE VALUE
0032 C              AO,A1,A2,B1,B2,B3/ REAL; CONSTANTS
0033 C
0034 C
0035 C      **** PROGRAMMER / DAWN RIGBY ****
0036 C      **** DATE / 22/06/82 ****
0037 C
0038 C
0039 C      FUNCTION XNED(Q)
0040 C      IMPLICIT REAL*8 (A-H, O-Z)
0041 C      IF(Q.NE.1.0)GO TO 18
0042 C
0043 C      ---- IF Q IS EQUAL TO 1.0 ----
0044 C
0045 C      XNED = -5.0
0046 C      GO TO 14
0047 18  IF(Q-.5)2,2,4
0048 2    IF(Q-0.0)6,7,8
0049 C
0050 C      ---- IF Q IS LESS THAN OR EQUAL TO 0.0 ----
0051 C
0052 6    write(ioutdev,10)
0053 10  FORMAT('1',1X, 'SUBROUTINE XNED--'/1X, 'NED VALUE IS NOT DEFINED;
0054 1Q<0.0')
0055 C      GO TO 13
0056 7    XNED = 5.0
0057 C      GO TO 14

```

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XNED

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```
0058 C
0059 C      ---- IF Q IS GREATER THAN 0.5 ----
0060 C
0061 4      ETA =DSQRT(-2.* DLOG(1.0 - Q))
0062      GO TO 12
0063 C
0064 C      ---- IF Q IS BETWEEN 0.0 AND 0.5 ----
0065 C
0066 8      ETA =DSQRT(-2.* DLOG(Q))
0067 12     A0 = 2.515517
0068      A1 = 0.802853
0069      A2 = 0.010328
0070      B1 = 1.432788
0071      B2 = 0.189269
0072      B3 = 0.001308
0073      XNED= ETA-((A0+A1*ETA+A2*ETA**2)/(1.+B1*ETA+B2*ETA**2+B3*ETA**3))
0074      IF(Q - .5)14,14,16
0075 C
0076 C      ---- IF Q IS GREATER THAN 0.5 ----
0077 C
0078 16     XNED = -XNED
0079      GO TO 14
0080 13     STOP
0081 14     RETURN
0082      END
```

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```

0001 C
0002 C
0003 C      **** FUNCTION RESP ****
0004 C
0005 C      ---- THIS FUNCTION IS USED TO CALCULATE THE PROBABILITY OF ----
0006 C      RESPONSE, P, GIVEN THE NED VALUE, Y. RESP(Y) HAS A MAXIMUM
0007 C      ERROR OF + OR - 3.D-7 AND USES THE TRANSFORMATION FROM
0008 C      "APPROXIMATIONS FOR DIGITAL COMPUTERS" BY C. HASTINGS,
0009 C      PRINCETON UNIVERSITY PRESS, PRINCETON, NJ., 1955.
0010 C
0011 C
0012 C      **** USAGE ****
0013 C
0014 C      ---- RESULT = RESP(Y) ----
0015 C
0016 C
0017 C      **** SUBROUTINES AND FUNCTION SUBPROGRAMS CALLED ****
0018 C
0019 C      ---- NONE ----
0020 C
0021 C
0022 C      **** DESCRIPTION OF PARAMETERS AND VARIABLES ****
0023 C
0024 C      ---- PARAMETERS PASSED FROM THE MAINLINE ----
0025 C
0026 C      Y/ REAL; NORMAL EQUIVALENT DEVIATE (NED) VALUE
0027 C
0028 C      ---- VARIABLES ----
0029 C
0030 C      X, RES/ REAL; INTERMEDIATE VALUES
0031 C      A1, A2, A3, A4, A5, A6/ REAL; CONSTANTS
0032 C      DENOM/ REAL; DENOMINATOR OF THE EQUATION
0033 C
0034 C
0035 C      **** PROGRAMMER / DAWN RIGBY ****
0036 C      **** DATE / 22/06/82 ****
0037 C
0038 C
0039 C      FUNCTION RESP(Y)
0040 C      IMPLICIT REAL*8(A-H, O-Z)
0041 C      X = DABS(Y) / DSQRT(2.0D0)
0042 C      A1 = 7.05230784D-2
0043 C      A2 = 4.22820123D-2
0044 C      A3 = 9.2705272D-3
0045 C      A4 = 1.520143D-4
0046 C      A5 = 2.765672D-4
0047 C      A6 = 4.30638D-5
0048 C      DENOM = 1. + A1*X + A2*X**2 + A3*X**3 + A4*X**4 + A5*X**5 + A6*X**6
0049 C      IF (DENOM.LT.4.869675D+4) GO TO 5
0050 C      RES = 0.
0051 C      GO TO 3
0052 5      DENOM = DENOM**16
0053 C      RES = .5/DENOM
0054 3      IF (Y-0.) 2,2,4
0055 2      RESP = RES
0056 C      GO TO 6
0057 4      RESP = 1. - RES

```

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RESP

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0058
0059

6

RETURN
END

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```

0001 C
0002 C
0003 C      **** FUNCTION PCHISQ ****
0004 C
0005 C      ---- CALLED TO EVALUATE THE PROBABILITY FOR EXCEEDING CHI ----
0006 C      SQUARE, GIVEN THE COMPARISON VALUE OF REDUCED CHI SQUARE
0007 C      (CHISQR) AND THE NUMBER OF DEGREES OF FREEDOM (NFREE). THE
0008 C      CALCULATION IS ONLY AN APPROXIMATION FOR NFREE ODD AND CHI
0009 C      SQUARE GREATER THAN 50.
0010 C
0011 C
0012 C      **** USAGE ****
0013 C
0014 C      ---- RESULT = PCHISQ(CHISQR,NFREE) ----
0015 C
0016 C
0017 C      **** SUBROUTINES AND FUNCTION SUBPROGRAMS CALLED ****
0018 C
0019 C      ---- FUNCTION GAMMS(X) ----
0020 C
0021 C      CALCULATES THE GAMMA FUNCTION FOR INTEGERS AND HALF-INTEGERS
0022 C
0023 C
0024 C      **** DESCRIPTION OF PARAMETERS AND VARIABLES ****
0025 C
0026 C      ---- PARAMETERS PASSED FROM THE MAINLINE ----
0027 C
0028 C      CHISQR/ REAL; COMPARISON VALUE OF REDUCED CHI SQUARE
0029 C      NFREE/ INTEGER; NUMBER OF DEGREES OF FREEDOM
0030 C
0031 C      ---- VARIABLES ----
0032 C
0033 C      Z, TERM, SUM, PWR/ REAL; INTERMEDIATE VALUES
0034 C      NEVEN/ INTEGER; INTERMEDIATE VALUE
0035 C      FREE / REAL; NUMBER OF DEGREES OF FREEDOM
0036 C      I/ INTEGER; LOOP COUNTER
0037 C      FI/ REAL; LOOP COUNTER
0038 C      IMAX/ INTEGER; MAXIMUM LOOP COUNT
0039 C
0040 C
0041 C      **** PROGRAMMER / DAWN RIGBY ****
0042 C      **** DATE / 22/06/82 ****
0043 C
0044 C
0045 C      FUNCTION PCHISQ(CHISQR,NFREE)
0046 C      IMPLICIT REAL*8(A-H, O-Z)
0047 C      IF(NFREE)12,12,14
0048 12  write(ioutdev,11)
0049 11  FORMAT(3X,'SUBROUTINE RESP --')
0050 C      write(ioutdev,13)
0051 13  FORMAT(3X,'** ERROR --- NFREE (DEGREES OF FREEDOM) IS LESS THAN 1;
0052 1 STOP **')
0053 C      GO TO 59
0054 14  FREE = NFREE
0055 C      Z= CHISQR* FREE/2.
0056 C      NEVEN= 2 * (NFREE/2)
0057 C      IF(NFREE - NEVEN)21,21,41

```

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PCHISQ

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DIS

```
0058 C
0059 C      ---- NUMBER OF DEGREES OF FREEDOM IS EVEN ----
0060 C
0061 21      IMAX = NFREE/2
0062      TERM = 1.
0063      SUM = 0.
0064      DO 34 I=1,IMAX
0065      FI=I
0066      SUM= SUM + TERM
0067 34      TERM = TERM + Z/FI
0068      PCHISQ = SUM* DEXP(-Z)
0069      GO TO 60
0070 C
0071 C      ---- NUMBER OF DEGREES OF FREEDOM IS ODD ----
0072 C
0073 41      IF(Z-25.)44,44,42
0074 42      Z= CHISQR* (FREE-1.)/2.
0075      GO TO 21
0076 44      PWR = FREE/2.
0077      TERM = 1.
0078      SUM = TERM/PWR
0079      DO 56 I=1,1000
0080      FI=I
0081      TERM = -TERM * Z/FI
0082      SUM = SUM + TERM/(PWR + FI)
0083      IF(DABS(TERM/SUM)-.00001)57,57,56
0084 56      CONTINUE
0085 57      PCHISQ = 1.0 - (Z**PWR) * SUM/GAMMS(PWR)
0086      GO TO 60
0087 59      STOP
0088 60      RETURN
0089      END
```

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```
0001 C
0002 C
0003 C      **** FUNCTION GAMMS ****
0004 C
0005 C      ---- USED TO CALCULATE THE GAMMA FUNCTION FOR INTEGERS AND ----
0006 C      HALF-INTEGERS
0007 C
0008 C
0009 C      **** USAGE ****
0010 C
0011 C      ---- RESULT = GAMMS(X) ----
0012 C
0013 C
0014 C      **** SUBROUTINES AND FUNCTION SUBPROGRAMS CALLED ****
0015 C
0016 C      ---- FUNCTION FACTOR(N) ----
0017 C
0018 C      CALCULATES N FACTORIAL FOR INTEGERS
0019 C
0020 C
0021 C      **** DESCRIPTION OF PARAMETERS AND VARIABLES ****
0022 C
0023 C      ---- PARAMETERS PASSED FROM THE FUNCTION PCHISQ ----
0024 C
0025 C      X/ REAL; REAL FORM OF INTEGER OR HALF-INTEGER ARGUMENT
0026 C
0027 C      ---- VARIABLES ----
0028 C
0029 C      N/ INTEGER; INTERMEDIATE VALUE
0030 C      XN,SUM/ REAL; INTERMEDIATE VALUES
0031 C      PROD/ REAL; CONSTANT
0032 C      I/ INTEGER; LOOP COUNTER
0033 C      FI/ REAL; LOOP COUNTER
0034 C
0035 C
0036 C      **** PROGRAMMER / DAWN RIGBY ****
0037 C      **** DATE / 22/06/82 ****
0038 C
0039 C
0040 C      FUNCTION GAMMS(X)
0041 C      IMPLICIT REAL*8(A-H, O-Z)
0042 C
0043 C      ---- INTEGERIZE ARGUMENT ----
0044 C
0045 C      N=X-.25
0046 C      XN=N
0047 C      IF(X-XN-.75)31,31,21
0048 C
0049 C      ---- ARGUMENT IS INTEGER ----
0050 C
0051 21  GAMMS = FACTOR(N)
0052 C      GO TO 60
0053 C
0054 C      ---- ARGUMENT IS HALF-INTEGER ----
0055 C
0056 31  PROD = 1.77245385
0057 C      IF(N)44,44,33
```

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GAMMS

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```
0058 33 IF(N-10)41,41,51
0059 41 DO 43 I=1,N
0060      FI = I
0061 43 PROD = PROD * (FI-.5)
0062 44 GAMMS = PROD
0063      GO TO 60
0064 51 SUM = 0.
0065      DO 54 I=11,N
0066      FI = I
0067 54 SUM = SUM +DLOG(FI-.5)
0068      GAMMS = PROD * 639383.8623 *DEXP(SUM)
0069 60 RETURN
0070      END
```

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```
0001 C
0002 C
0003 C      **** FUNCTION FACTOR ****
0004 C
0005 C      ---- CALLED TO CALCULATE THE FACTORIAL FUNCTION FOR INTEGERS ----
0006 C
0007 C
0008 C      **** USAGE ****
0009 C
0010 C      ---- RESULT = FACTOR(N) ----
0011 C
0012 C
0013 C      **** SUBROUTINES AND FUNCTION SUBPROGRAMS CALLED ****
0014 C
0015 C      ---- NONE ----
0016 C
0017 C
0018 C      **** DESCRIPTION OF PARAMETERS AND VARIABLES ****
0019 C
0020 C      ---- PARAMTERS PASSED FROM THE FUNCTION GAMMS ----
0021 C
0022 C          N/ INTEGER; INTEGER ARGUMENT FOR CALCULATIONS
0023 C
0024 C      ---- VARIABLES ----
0025 C
0026 C          I/ INTEGER; LOOP COUNTER
0027 C          FI/ REAL; LOOP COUNTER
0028 C          SUM/ REAL; INTERMEDIATE VALUE
0029 C
0030 C
0031 C      **** PROGRAMMER / DAWN RIGBY ****
0032 C      **** DATE / 22/06/82 ****
0033 C
0034 C
0035 C      FUNCTION FACTOR(N)
0036 C      IMPLICIT REAL*8(A-H, O-Z)
0037 C      FACTOR = 1.
0038 C      IF(N-1)40,40,13
0039 13  IF(N-10)21,21,31
0040 21  DO 23 I=2,N
0041 C      FI = I
0042 23  FACTOR = FACTOR * FI
0043 C      GO TO 40
0044 31  SUM = 0.
0045 C      DO 34 I=11,N
0046 C      FI = I
0047 34  SUM = SUM + DLOG(FI)
0048 C      FACTOR = 3628800.*DEXP(SUM)
0049 40  RETURN
0050 C      END
```

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```

0001 C
0002 C
0003 C      **** FUNCTION TPROB ****
0004 C
0005 C      ---- THIS FUNCTION FINDS THE VALUE OF 'T' FROM A 'T' ----
0006 C      DISTRIBUTION OF 'NFREE' DEGREES OF FREEDOM, WHICH IS EXCEEDED
0007 C      WITH PROBABILITY ALPHA (2 SIDED TEST). A TABLE IS USED AS A
0008 C      DATA ARRAY AND INTERPOLATION IS OFTEN NECESSARY TO GET THE
0009 C      CORRECT VALUE OF TPROB. THE TABULATED DATA WAS COMPUTED BY
0010 C      MAXINE MERRINGTON, FROM "TABLES OF PERCENTAGE POINTS OF THE
0011 C      INCOMPLETE BETA FUNCTION", BIOMETRIKA, VOL.32 (1941), PAGES 168-
0012 C      181; BY CATHERINE M. THOMPSON.
0013 C
0014 C
0015 C      **** USAGE ****
0016 C
0017 C      ---- RESULT = TPROB(FREE,ALPHA) ----
0018 C
0019 C
0020 C      **** SUBROUTINES AND FUNCTION SUBPROGRAMS CALLED ****
0021 C
0022 C      ---- NONE ----
0023 C
0024 C
0025 C      **** DESCRIPTION OF PARAMETERS AND VARIABLES ****
0026 C
0027 C      ---- PARAMETERS PASSED FROM THE MAINLINE ----
0028 C
0029 C      FREE/ REAL; NUMBER OF DEGREES OF FREEDOM
0030 C      ALPHA/ REAL; CONFIDENCE LEVEL OF THE FIDUCIAL LIMITS
0031 C
0032 C      ---- VARIABLES ----
0033 C
0034 C      T/ REAL; ARRAY FOR T DISTRIBUTION TABLE
0035 C      A/ REAL; 1-ALPHA, FOR READING OF THE TABLE AND CALCULATIONS
0036 C      I,J/ INTEGER; LOOP COUNTERS AND ARRAY POINTERS
0037 C      AK,AJK,H,YK,YJK,DY,TI,TIA,FR/ REAL; INTERMEDIATE VALUES
0038 C      FARRAY/ REAL; ARRAY FOR INTERPOLATED FREE VALUES WHEN BOTH
0039 C      FREE AND A MUST BE INTERPOLATED
0040 C
0041 C
0042 C      **** PROGRAMMER / DAWN RIGBY ****
0043 C      **** DATE / 22/06/82 ****
0044 C      **** Updated / John McFee ****
0045 C      **** DATE / 26/02/86 ****
0046 C
0047 C
0048 C      FUNCTION TPROB(FREE,ALPHA)
0049 C      IMPLICIT REAL*8(A-H, O-Z)
0050 C      DIMENSION T(35,8),FARRAY(7)
0051 C      data itabledev/4/
0052 C      READ(itabledev,1)((T(J,I),I=1,8),J=1,35)
0053 1  FORMAT(8F10.5)
0054 C      A = 1.000 - ALPHA
0055 C      FR=FREE
0056 C
0057 C      ---- CHECK FOR OUT OF RANGE 'A' OR 'FREE' VALUES ----

```

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TPROB

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```
0058 C
0059 IF(A.LT.0.005)GO TO 3
0060 IF(A.GT.0.50)GO TO 5
0061 GO TO 7
0062 3 write(ioutdev,2)
0063 2 FORMAT(/3X,'SUBROUTINE TPROB--')
0064 write(ioutdev,9)
0065 9 FORMAT(3X,'ALPHA IS GREATER THAN 0.995, THEREFORE, ASSUME THAT ALP
0066 1HA IS EQUAL TO 0.995')
0067 A=0.005
0068 GO TO 7
0069 5 write(ioutdev,2)
0070 write(ioutdev,11)
0071 11 FORMAT('1','ALPHA IS LESS THAN 0.50 -- ERROR ')
0072 GO TO 34
0073 7 IF(FR.GT.120.0)GO TO 13
0074 IF(FR.LT.1.0)GO TO 15
0075 GO TO 17
0076 13 write(ioutdev,2)
0077 write(ioutdev,19)
0078 19 FORMAT(3X,'THE NUMBER OF DEGREES OF FREEDOM IS GREATER THAN 120.0;
0079 1'/10X,'THEREFORE ASSUMED TO BE INFINITE')
0080 FR = 900.
0081 GO TO 17
0082 15 write(ioutdev,2)
0083 write(ioutdev,21)
0084 21 FORMAT('1','FREE IS LESS THAN 1.0 -- ERROR ')
0085 GO TO 34
0086 17 IF(FR.LE.30.0)GO TO 23
0087 GO TO 25
0088 23 DO 27 I=2,8
0089 IF(T(1,I).NE.A)GO TO 27
0090 C
0091 C ---- FREE AND A ARE BOTH ON TABLE ----
0092 C
0093 TPROB = T(FR+1,I)
0094 GO TO 33
0095 27 CONTINUE
0096 C
0097 C ---- A IS NOT ON TABLE ----
0098 C
0099 28 DO 31 I=2,8
0100 IF(T(1,I).LT.A)GO TO 35
0101 31 CONTINUE
0102 35 AK=T(1,I)
0103 I=I-1
0104 AJK=T(1,I)
0105 H=AJK-AK
0106 YJK=T(FR+1,I)
0107 YK=T(FR+1,I+1)
0108 DY=YJK-YK
0109 TPROB = (DY * (A-AK)/H) +YK
0110 GO TO 33
0111 C
0112 C ---- FREE IS GREATER THAN 30.0 ----
0113 C
0114 25 DO 37 J=31,35
```

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TPROB

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```
0115      IF(T(J,1).NE.FR)GO TO 37
0116      DO 75 I=2,8
0117      TI=T(1,I)
0118      TIA = TI - A
0119      IF(TIA.LT.1.0D-13) GO TO 76
0120 75     CONTINUE
0121      GO TO 28
0122      C
0123      C      ---- FREE > 30.0; FREE AND A BOTH ON TABLE ----
0124      C
0125 76     TPROB = T(J,I)
0126      GO TO 33
0127 37     CONTINUE
0128 39     DO 41 I=2,8
0129      IF(T(1,I).NE.A)GO TO 41
0130      C
0131      C      ---- FREE IS NOT ON TABLE ----
0132      C
0133      DO 42 J=31,35
0134      IF(T(J,1).GT.FR)GO TO 45
0135 42     CONTINUE
0136 41     CONTINUE
0137      GO TO 43
0138 45     AK=T(J,1)
0139      J=J-1
0140      AJK=T(J,1)
0141      H=AJK-AK
0142      YJK=T(J,I)
0143      YK=T(J+1,I)
0144      DY=YJK-YK
0145      TPROB = (DY * (FR-AK)/H) +YK
0146      GO TO 33
0147      C
0148      C      ---- NEITHER FREE NOR A ARE ON TABLE ----
0149      C
0150 43     DO 47 J=31,35
0151      IF(T(J,1).GT.FR)GO TO 49
0152 47     CONTINUE
0153 49     AK=T(J,1)
0154      J=J-1
0155      AJK=T(J,1)
0156      H=AJK-AK
0157      DO 51 I=2,8
0158      YJK=T(J,I)
0159      YK=T(J+1,I)
0160      DY=YJK-YK
0161      TPROB = (DY * (FR-AK)/H) + YK
0162      FARRAY(I-1)=TPROB
0163 51     CONTINUE
0164      DO 53 I=2,8
0165      IF(T(1,I).LT.A)GO TO 55
0166 53     CONTINUE
0167 55     AK=T(1,I)
0168      I=I-1
0169      AJK=T(1,I)
0170      H=AJK-AK
0171      YK = FARRAY(I-1)
```

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TPROB

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```
0172      YJK = FARRAY(I-2)
0173      DY=YJK-YK
0174      TPROB = (DY * (A-AK)/H) + YK
0175      GO TO 33
0176      34  STOP
0177      33  RETURN
```

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APPENDIX 6

OPERATIONAL DESCRIPTION OF
RELATIVE POTENCY PROGRAM RPOTC

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RELATIVE POTENCY PROGRAM (RPOTC)

--- Revised Edition -- Account B1000200,STATS,DRES ---

Dawn Rigby -- June, 1983

INPUT:

The RPOTC program has now been transferred to the Honeywell CP-6 computer system, and some changes in input are therefore required. The data is typed interactively (excluding the chisq and t table) and read directly by the command file. Each value is asked for separately, so that carriage returns separate the data. The values are as follows.

ISLCT - select value. If ISLCT=1, 6 sets of numbers must follow (limit, lowest datum, and highest datum for each set). This indicates that limits other than 95% (ISLCT=0) are to be used. If a -1 is typed, execution terminates.

LIMIT - percentage limits to be used (integer)

INUM - number of comparisons to be made in the set

I - lowest datum

J - highest datum

ICODE - identification code

CHISO,SNW,XBAR,SXX,SXY,DFREE,YBAR,SYX - results of the PROBIT analysis

EXECUTION

At this time, the mainline RPOTC program is in the file KEEP_RPOTC, and the command file to run this is called RPOTC. These files MUST NOT be deleted under any circumstances. The compilation and linkage files are called RPOTC_OU and RPOTC_RU. These should also be left alone, but can be replaced by typing the following:

```
FORTRAN KEEP_RPOTC OVER RPOTC_OU
```

```
LINK RPOTC_OU OVER RPOTC_RU
```

To execute this program, type:

```
XEO RPOTC
```

The program and additional files are all in the account 31000200,STATS,DRES.

OUTPUT

The output for this program has not been changed, and is sent to both the terminal and the line printer immediately after execution.

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TABLE 1

Initial Data for Program PROBIT

ID - array for the identification label (to begin each page)
format: alphabetic; maximum of 50 characters

NT - number of trials, maximum of 100 (n)

MAXCNT - maximum loop count for iterative regression (default = 50)
format: integer; NT, MAXCNT are entered on the same line.

IYNSW - switch for output of intermediate results
YES - IY, output requested
NO - IN; no output requested
format: alphanumeric; maximum of 50 characters

TN - number of animals in the trial (n_i)

XIN - dose given in the trial (x_i')

R - number of responses in the trial, maximum of 100 (r_i)
format: real; TN, XIN, R are entered on the same line, 1
trial/line

ALPHA - confidence level of fiducial limits (default = 0.95), ($\alpha/100$)
format: real

C - fraction of natural mortality (default = 0.0) (P_0)

DELTA - convergence criterion (default = 0.001) (δ)
format: real; both C and DELTA typed on the same line

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TABLE 2

Quantities Output by Program PROBIT

I	- integer; trial number (i)
J	- integer; loop number (k)
X	- real; dose metameters (x_i)
RP	- real; empirical percentage responses ($P_i * 100$)
RS	- real; mean of estimated number responding ($\hat{R}_i$)
YK	- Real; maximum likelihood expected NEDS ($y(x_i)$)
YR	- real; probits (NEDS + 5)
SIGY	- real; standard error
W	- real; weighting coefficient ($w_i^{(k)}$)
B	- real; current regression slope ($a_i^{(k)}$)
SIGMAB	- real; error in regression slope ($S_{a1}^{(k)}$)
FLY	- real; lower fiducial limits of estimated number responding
FUL	- real; upper fiducial limits of estimated number responding
CHISQ	- real; value of chi square ($\chi^2_\alpha(v)$)
NFREE	- integer; number of degrees of freedom (v)
H	- real; heterogeneity factor (h) H = 1.0 --- homogeneous H $\neq$ 1.0 --- deterogeneous
T	- real; value of T distribution (t_α)
G	- real; G factor (g)
PLB	- real; given ED levels (dose level * 100) (P_λ)
EDLMB	- real; tolerance level in dose units (ED_λ)
XLMBDA	- real; tolerance level in dosage units (x_λ)
FUED	- real; upper fiducial limit for EDLMB ($f'_{u\lambda}$)
FLED	- real; lower fiducial limit for EDLMB ($f'_{l\lambda}$)
FUX	- real; upper fiducial limits for XLMBDA ($f_{u\lambda}$)
FLX	- real; lower fiducial limits for XLMBDA ($f_{l\lambda}$)
APA	- real; percent confidence level (α)

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TABLE 3

Data for Comparison Tests of Programs PROBIT and PROBT

<u>Dose</u> (Relative Units)	<u>Organisms</u>	<u>Responses</u>	<u>Dose</u> (Relative Units)	<u>Organisms</u>	<u>Responses</u>
<u>Series 1</u>			<u>Series 6</u>		
400.	10	7	150.	20	19
320.	10	1	140.	30	26
256.	10	0	130.	40	29
204.	10	1	120.	50	27
163.	10	0	110.	40	14
			100.	30	6
			80.	20	0
<u>Series 2</u>			<u>Series 7</u>		
400.	10	8	499.	10	4
320.	10	4	474.	10	5
256.	10	1	450.	20	6
204.	10	1	427.	10	1
163.	10	0	406.	10	0
			405.	10	1
<u>Series 3</u>			364.	10	1
400.	10	9	327.	10	0
320.	10	5			
256.	10	1	<u>Series 8</u>		
204.	10	1	499.	10	6
163.	10	0	474.	10	6
			450.	20	6
<u>Series 4</u>			427.	10	1
140.	20	17	406.	10	0
130.	20	6	405.	10	2
120.	20	7	364.	10	1
110.	10	5	327.	10	0
100.	20	1			
<u>Series 5</u>			<u>Series 9</u>		
180.	10	10	499.	10	6
170.	10	7	474.	10	6
160.	20	11	450.	20	7
150.	15	7	427.	10	1
140.	10	3	406.	10	0
130.	5	0	405.	10	2
120.	10	1	364.	10	1
			327.	10	0

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TABLE 4
Results of Comparison Tests of Programs PROBIT and PROBT

Series	Program	Reduced Chi-square	Data Hetero- genous	a _i	S _{a_i}	g	ED ₅₀	f _i ₅₀	f _i _{U₅₀}	ED ₉₅	f _i ₉₅	f _i _{U₉₅}	Con- vergence	Iter- ations
1.	PROBIT PROBT	3 2	No Yes	3.36 3.35	1.14 2.23	0.445 0.444	385. 385.	333. ∞	594. ∞	629. -	471. -	2453. -	Yes Yes	5 5
2.	PROBIT PROBT	3 2	No No	3.58 3.58	0.98 0.98	0.287 -	332. 332.	292. 292.	406. 406.	526. -	423. -	1019. -	Yes Yes	3 3
3.	PROBIT PROBT	3 2	No No	4.20 4.20	1.07 1.06	0.248 -	313. 313.	278. 278.	362. 362.	463. -	390. -	732. -	Yes Yes	3 4
4.	PROBIT PROBT	3 3	Yes Yes	5.52 5.51	2.69 2.68	2.41 -	127. 127.	- 29.3	- 1150	172. -	- -	- -	Yes Yes	3 12
5.	PROBIT PROBT	5 5	No No	6.99 6.98	1.57 1.56	0.193 -	153. 153.	145. 145.	161. 160.	194. -	179. -	234. -	Yes Yes	5 9
6.	PROBIT PROBT	5 5	No No	6.11 6.11	0.80 0.80	0.066 -	117. 117.	113. 113.	121. 120.	153. -	145. -	168. -	Yes Yes	3 7
7.	PROBIT PROBT	5 5	No No	5.74 5.74	1.84 1.83	0.394 -	503. 502.	470. 470.	633. 633.	670. -	568. -	1351. -	Yes No	4 41
8.	PROBIT PROBT	6 5	No No	6.77 6.77	1.88 1.87	0.294 -	481. 480.	458. 457.	541. 540.	613. -	544. -	905. -	Yes Yes	4 17
9.	PROBIT PROBT	5 5	No No	6.86 6.85	1.86 1.85	0.282 -	477. 477.	455. 455.	531. 530.	607. -	541. -	871. -	Yes Yes	4 19

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TABLE 5

Data for Comparison Tests of Programs PROBIT, S103 and SAS

<u>Dose</u> (Relative Units)	<u>Organisms</u>	<u>Responses</u>	<u>Dose</u> (Relative Units)	<u>Organisms</u>	<u>Responses</u>
<u>Series 1</u>			<u>Series 5</u>		
6374.	10	10	6374.	10	10
5951.	10	8	5971.	10	10
5371.	10	1	5371.	10	2
4975.	10	2	4975.	10	3
4522.	10	2	4522.	10	2
4048.	10	0	4048.	10	0
3674.	10	1	3674.	10	1
3312.	10	0	3312.	10	0
<u>Series 2</u>			<u>Series 6</u>		
5951.	10	10	50.	10	9
4975.	10	7	40.	10	8
4522.	10	7	32.	10	9
4048.	10	0	25.	10	0
<u>Series 3</u>			<u>Series 7</u>		
6374.	10	4	650.	10	10
5951.	10	1	585.	10	10
5371.	10	1	526.5	10	6
4975.	10	1	473.9	10	2
4522.	10	0	426.5	10	3
4048.	10	0	<u>Series 8</u>		
3674.	10	0	222.	10	10
3312.	10	0	200.	10	3
<u>Series 4</u>			180.	10	2
6374.	10	10	162.	10	0
5951.	10	10	146.	10	0
5371.	10	3	131.	10	0
4975.	10	6	118.	10	0
4522.	10	2	106.	10	0
4048.	10	0	<u>Series 9</u>		
3674.	10	1	585.	10	10
3312.	10	0	526.5	10	6
			473.9	10	2
			426.5	10	3

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TABLE 6
Results of Comparison Tests of Programs PROBIT, S103 and SAS

Series	Program	ν	Reduced Chi-square	Data Hetero- genous	a_1	S_{a_1}	g	ED_{50}	$f'_{i_{50}}$	$f'_{u_{50}}$	ED_{95}	$f'_{i_{95}}$	$f'_{u_{95}}$	Con- vergence	Iter- ations
1.	PROBIT S103 SAS	6 6 6	17.25 17.24 17.25	Yes Yes Yes	5.89 5.88 5.88	2.12 2.12 2.05	0.779 0.780 -	5447. 5447. 5447.	4533. 4533. 4630.	8483. 8487. 8401.	7204. 7204. 7203.	6028. 6028. 6005.	80395. 80610 51108.	Yes - Yes	5 20 6
2.	PROBIT S103 SAS	2 2 2	4.56 4.56 4.56	No No No	11.04 11.04 11.04	3.26 3.26 3.36	0.335 0.355 -	4571. 4571. 4571.	4319. 4319. 4299.	4845. 4845. 4831.	5306. 5305. 5306.	4961. 4960. 4968.	6605. 6604. 6640.	Yes - Yes	7 20 7
3.	PROBIT S103 SAS	6 6 6	1.91 1.91 1.91	No No No	5.08 5.08 5.08	2.06 2.06 2.07	0.633 0.633 -	6953. 6952. 6953.	6209. 6209. 6207.	15328. 15290. 15709.	9613. 9612. 9613.	7558. 7557. 7549.	73752. 73350 78263.	Yes - Yes	5 20 6
4.	PROBIT S103 SAS	6 6 6	14.14 14.14 14.15	Yes Yes Yes	6.77 6.77 6.77	1.98 1.98 1.98	0.512 0.512 -	5043. 5043. 5043.	4349. 4349. 4387.	5877. 5877. 5936.	6430. 6429. 6429.	5632. 5631. 5616.	12292. 12290 12464.	Yes - Yes	5 20 6
5.	PROBIT S103 SAS	6 6 6	18.86 18.84 18.86	Yes Yes Yes	6.70 6.70 6.70	2.36 2.36 2.31	0.745 0.744 -	5222. 5221. 5222.	4220. 4222. 4368.	6903. 6897. 7077.	6675. 6675. 6675.	5732. 5731. 5706.	34786. 34500 29259.	Yes - Yes	6 20 6
6.	PROBIT S103 SAS	2 2 2	9.15 9.16 9.15	Yes Yes Yes	3.90 3.90 3.90	2.35 2.35 2.31	6.68 6.68 -	31.11 31.11 31.10	- - -	- - -	47.41 47.40 47.41	- - -	- - -	Yes - No	7 20 6
7.	PROBIT S103 SAS	3 3 3	5.31 5.31 5.31	No No No	7.65 7.65 7.65	1.87 1.87 1.88	0.231 0.231 -	490.0 490.0 490.0	455.4 455.4 457.1	520.1 520.2 521.1	607.6 607.7 607.6	561.6 561.6 560.1	737.8 737.9 745.6	Yes - Yes	6 20 6
8.	PROBIT S103 SAS	6 6 6	4.03 4.03 4.04	No No No	12.65 12.65 12.66	3.36 3.36 3.43	0.271 0.271 -	199.2 199.2 199.2	189.8 189.8 190.2	209.8 209.8 210.6	226.9 226.9 226.8	214.0 214.0 213.5	265.8 265.8 269.6	Yes - Yes	8 20 8
9.	PROBIT S103 SAS	2 2 2	4.78 4.78 4.78	No No No	7.15 7.15 7.15	2.09 2.09 2.10	0.328 0.328 -	491.3 491.3 491.3	453.6 453.6 455.6	527.4 527.4 529.4	618.4 618.4 618.4	562.5 562.5 560.9	843.7 843.7 855.7	Yes - Yes	5 20 5

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1. ORIGINATING ACTIVITY DEFENCE RESEARCH ESTABLISHMENT SUFFIELD RALSTON, ALBERTA		2a. DOCUMENT SECURITY CLASSIFICATION unclassified	
		2b. GROUP	
3. DOCUMENT TITLE "PROBIT": A PROBIT ANALYSIS PROGRAM FOR THE DRES COMPUTER FACILITY (U)			
4. DESCRIPTIVE NOTES (Type of report and inclusive dates) SUFFIELD REPORT 403			
5. AUTHOR(S) (Last name, first name, middle initial) J. McFee, C.E. Mendoza, J. Smith and D. Rigby			
6. DOCUMENT DATE July 1980		7a. TOTAL NO. OF PAGES 77	7b. NO. OF REFS 8
8a. PROJECT OR GRANT NO. 051SB		9a. ORIGINATOR'S DOCUMENT NUMBER(S) SUFFIELD REPORT 403	
8b. CONTRACT NO.		9b. OTHER DOCUMENT NO.(S) (Any other numbers that may be assigned this document)	
10. DISTRIBUTION STATEMENT UNLIMITED			
11. SUPPLEMENTARY NOTES		12. SPONSORING ACTIVITY	
13. ABSTRACT This report describes an interactive computer program PROBIT, which performs automated probit analysis. The code is written in the FORTRAN IV language using a modified iterative maximum likelihood algorithm and runs on the Honeywell DPS-8/70 and VAX 11/780 computers. A series of tests were performed to compare PROBIT with other probit analysis programs. These include the old DRES PROBT (modified IBM PROBT) and programs contained in the commercial statistical packages S103 and SAS. PROBIT clearly outperformed DRES PROBT and performed as well as S103 and as well or slightly better than SAS. The input methods and output format of PROBIT can be modified whereas those of most commercial statistical packages cannot. Finally, PROBIT cost substantially less to develop than the purchase price of typical commercial statistical packages containing a good probit analysis program.			

KEY WORDS

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