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Log-Likelihood Ratio Tests for Comparing Dose-Response Data Fitted to the Logistic Function

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ABSTRACT

The homogeneity of quantal dose responses between different treatments can be tested by comparing a hypothesis-restricted logistic model with a model of which the restricted model is a subset. The hypotheses considered here are 1) independent dose responses for each treatment, 2) a common median effective dose for all treatments, 3) a common dispersion of responses around each median effective dose, and 4) a common dose response for all treatments. The ratio of their likelihoods, given the observed results, is transformed to have an approximately chi-square distribution when the restricted model holds. Because the justification of the chi-square distribution is based on large-sample assumptions, the appropriateness to small-sample conditions is verified in this paper by simulating a large number of random replicates of experiments with small sample size (7 doses, 15 specimens per dose).

CONTENTS

INTRODUCTION

In bioassays, logistic and probit functions are commonly used to describe quantal dose response and to estimate median concentrations of toxicant that cause an effect (i.e., TLm, ED50, LD50); however, the bioassayist must still decide whether dose response varies significantly between two or more treatments. Much has been written on fitting dose-response curves (Berkson 1955; Silverstone 1957; Finney 1971). Some authors discuss general methods of discriminating between different models (Chambers and Cox 1967; Prentice 1976), and Finney explains how to compute confidence limits around the probit function. However, a method needs to be pointed out to specifically test the homogeneity of dose responses of two or more different treatments.

In this paper, I demonstrates tests of homogeneity that are based on likelihood ratios. The logistic function is used to model the probability of response as a function of concentration. Because the distribution of the test statistic under the null hypothesis is determined from large-sample theory, I also briefly examine the appropriateness of applying these tests to the typical small-sample conditions of bioassay experiments. The distribution of the test statistic, as computed from the large-sample theory, is compared with the distribution of the test statistic observed in randomly replicated trials of simulated small-sample experiments.

The appropriateness of the logistic model is assumed here. Proper goodness of fit tests of this assumption, which are beyond the scope of this paper, are proposed in Brown (1982) and Hosmer and Lemeshow (1980).

LIKELIHOOD AND THE LOGISTIC MODEL

In dose-response experiments based upon quantal (all or nothing) responses, the usual assumption is that the probability of obtaining r responses from n individuals exposed to a particular dose can be described by the binomial probability function:

$$\text{Prob}\,[r|P] = \begin{bmatrix} n \\ r \end{bmatrix} P^{r}(1-P)^{n-r},$$

where p is the probability of obtaining a response from a randomly sampled individual at that dose.

The likelihood, L, of P, given the observed r, is defined to be proportional to the probability of obtaining the results, r, given P (Edwards 1972); i.e.,

$$L(P|r) = \text{Prob}\,[r|P] = \begin{bmatrix} n \\ r \end{bmatrix} P^{r}(1-P)^{n-r}$$

when the constant of proportionality equals 1.0.

The fundamental difference between probability and likelihood is that with probability, r is variable and P is constant; and with likelihood, P is variable and r is constant. In practice, likelihood would be used to compare P's given a fixed r. The p that maximizes the likelihood L[P(r] can be determined by applying the minimum-maximum theorems of calculus and solving the equation $\frac{\partial L[P|r]}{\partial P} = 0.$

The solution is P) = r/n, as might be expected intuitively. When examining a independent groups, each group exposed to a different dose, the joint likelihood of the a P_i's is:

$$L(P_1, P_2, \ldots, P_a | r_1, r_2, \ldots, r_a) = \prod_{i=1}^{a} L[P_i | r_i] = \prod_{i=1}^{a} \binom{n_i}{r_i} P_i^{r_i} (1 - P_i)^{n_i - r_i}.$$

When there are no constraints on the P_i's, the solutions to

$$\frac{\partial L(P_1, P_2, \ldots, P_a | r_1, r_2, \ldots, r_a)}{\partial (P_i)} = 0$$

are $\hat{P}_i = \frac{r_i}{n_i}$, which will be referred to as the observed model in this paper.

The P's are normally related to dose level, and the logistic equation is often proposed to model the relation between p_i and the dose in whatever scale is chosen: $Pi = [1 + e^{\beta(\gamma - x_i)}]^{-1}$, where is the dose level of x at which $P_- = 0.50$ (ED50), and B is proportional to dP/dx at ED50. Described in terms of the distribution of tolerance within the population, the median dose would be y, and the dispersion around the median would be measured by B.

When P_j is constrained to some model, such as the logistic, the model parameters replace the P_i's as the variables in the likelihood function. The parameters 6 and y that maximize the likelihood $L[\beta, \gamma | r_1, r_2, \ldots, r_a]$ are obtained from solutions to the equations:

$$\frac{\partial L(\beta, \gamma | r_1, r_2, \ldots, r_a)}{\partial \beta} = \frac{\partial L(\beta, \gamma | r_1, r_2, \ldots, r_a)}{\partial \gamma} = 0. \qquad (1)$$

These do not have explicit solutions for 6 and y, as the observed model did for p, but must be solved using iterative techniques such as the Newton-Paphson (Edwards 1972), which will be explained later in this paper.

When the dose-response experiment is conducted under b = 2 or more treatments, e.g., temperatures or toxicants, a general model can be assumed initially that allows each treatment level to assume its own parameters (i.e., its own logistic model):

(Model 1) $$P_{ij} = (1 + e^{\beta_j(\gamma_j - x_{ij})})^{-1}. \quad (2)$$

Thus, there is a full set of 2 x b parameters, designated by the vector $\theta_1 = (\beta_1, \beta_2, \ldots, \beta_b\ \gamma_1, \gamma_2, \ldots, \gamma_b)$. Observations of each treatment are independent of observations of other treatments. The joint likelihood of the b experiments is the product of the likelihoods of the individual treatments:

$$L(\theta_1 | r_{ij}) = \prod_{j=1}^{b} \prod_{i=1}^{a} \binom{n_{ij}}{r_{ij}} P_{ij}^{r_{ij}} (1 - P_{ij})^{n_{ij} - r_{ij}}, \quad (3)$$

where P_{ij} is determined from Model 1 (0, used in Equation 3).

Because none of the treatments share a common parameter, solving

$$\frac{\partial L(\theta_1 | r_{ij})}{\partial \theta} = 0$$

to obtain the maximum-likelihood estimate, $\hat{\theta}_1$, simplifies to separate maximization for each treatment. That is, proceed through the b treatments one at a time and solve for B. and y. in each treatment as in the previous discussion. The maximized L(e,(r_{ij}) is, thus, obtained with θ_1 in Equations (2) and (3) and will be denoted as L(6,1r_{ij}).

In addition to the general logistic model for multitreatment experiments, simpler but more restrictive models occur from reduction of the general model.

For example, a model can be hypothesized in which the treatments have a common median dose, $\gamma_.$:

$$\text{(Model 2)} \qquad P_{ij} = (1 + e^{\beta_j(\gamma_. - x_{ij})})^{-1}. \tag{4}$$

Model 2 is simpler than Model 1: Model 2 has one B parameter for each treatment, as in Model 1, but only one $\gamma_.$ for all the treatments. For Model 2, let $\theta_2 = (\beta_1, \beta_2, \ldots, \beta_b, \gamma_.)$ be the vector of b + 1 parameters. Likelihood $L(\theta_2|r_{ij})$ can then be obtained using Equation (4) in the right-hand side of Equation (3). Solving

$$\frac{\partial L(\theta_2|r_{ij})}{\partial \theta_2} = 0$$

to obtain the maximum-likelihood estimate, $\hat{\theta}_2$, requires that all treatments be considered simultaneously because of the common $\gamma_.$.

Another model hypothesizes that the treatments have a common dispersion parameter, $\beta_.$:

$$\text{(Model 3)} \qquad P_{ij} = (1 + e^{\beta_.(\gamma_j - x_{ij})})^{-1} \tag{5}$$

with a $\underline{b} + 1$ parameter vector, $\hat{\theta}_3 = (\beta_., \gamma_1, \gamma_2, \ldots, \gamma_b)$. Obtaining the maximum-likelihood estimate, $\hat{\theta}_3$, is similar to obtaining $\hat{\theta}_2$, i.e., simultaneously solving for $\underline{b} + 1$ parameters.

The simplest logistic model assumes that all treatments have the same median dose, $\gamma_.$, and the same dispersion parameter, $\beta_.$:

$$\text{(Model 4)} \qquad P_{ij} = (1 + e^{\beta_.(\gamma_. - x_{ij})})^{-1}. \tag{6}$$

There are only two parameters in the model, θ_4, = (B., v.), and solving

$$\frac{\partial L(\theta_4 | r_{ij})}{\partial r_{ij}} = 0$$

for o_4 of maximum likelihood simplifies to the single-treatment problem with the observations pooled across treatments.

TESTS

Bioassayists commonly must decide or speculate from their dose-response results, r.., whether tolerance varies between treatments, species, toxicants, etc. Comparing Models 1-4 by their maximum likelihood could help in making these decisions. For example, in one test, to determine whether ED50's are different, the maximum-likelihood values of Model 1, which allows for independent logistic curves, could be compared with the maximum-likelihood values of Model 2, which restricts the curves to a common ED50 (y).

The ratio of likelihoods, $X = \frac{L(\ddot{\theta}_2 | r_{ij})}{L(\hat{\theta}_1 | r_{ij})}$, tells us the number of times the observed vector r.. is expected to occur after many repetitions of the experiment if Model 2 (common y) is the underlying situation relative to the number of times the observed vector r.. is expected to occur if Model 1 (independent y and B) is the underlying situation. In addition, G = -2 In X is approximately chi-square distributed when Model 2 is true, so a hypothesis test can be conducted (Wilks 1962). Thus, the probability of Type I error is determined in the usual manner by choice of significance level (typically, 1% or 5%), and Model 2 is accepted or rejected depending on whether it is less or greater, respectively, than the appropriate critical value from a table of chi-square values.

In a second test, Model 4 (which assumes a common dose response) can be compared to Model 1 to determine whether the EC50's and the dispersion (as measured by B) around the EC50 are the same for each treatment.

If dispersion is assumed to be the same for all treatments, a third test might be conceived to determine whether the EC50's are equal. Then, Model 4 can be compared with Model 3, which assumes the dispersions are equal.

These three tests will be referred to as Tests I, II, and III, respectively. The tests, their null hypotheses, alternative hypotheses of more likelihood, test statistics 5, and degrees of freedom are:

I. logistic with common y versus independent logistics,

$$G = -2 \ln \frac{L(\hat{\theta}_2 | r_{ij})}{L(\hat{\theta}_1 | r_{ij})}, \quad \text{d.f.} = 2b - (b + 1);$$

II. common logistic versus independent logistics

$$G = -2 \ln \frac{L(\hat{\theta}_4 | r_{ij})}{L(\hat{\theta}_1 | r_{ij})}, \quad \text{d.f.} = 2b - 2;$$

III. common logistic versus logistics with common B

$$G = -2 \ln \frac{L(\hat{\theta}_4 | r_{ij})}{L(\hat{\theta}_3 | r_{ij})}, \quad \text{d.f.} = b + 1 - 2;$$

METHODS

As stated, Equation (1) cannot be solved explicitly for B and y and must be solved iteratively. It is equivalent, but simpler, to work with the natural logarithm, so let $S(\beta, \gamma) = \ln L(\beta, \gamma | r_1, r_2, \ldots, r_a)$. Then, at

$$\frac{\partial S(\beta,\gamma)}{\partial \beta} = \frac{\partial S(\beta,\gamma)}{\partial \gamma} \equiv 0,$$

B and y will be the maximum-likelihood estimates. Using Taylor's theorem for functions of two variables, the first derivatives can be approximated:

$$\frac{\partial S(\hat{\beta}, \hat{\gamma})}{\partial \hat{\beta}} = \frac{\partial S(\beta', \gamma')}{\partial \beta'} + (\hat{\beta} - \beta') \frac{\partial^2 S(\beta', \gamma')}{\partial \beta'^2} + (\hat{\gamma} - \gamma') \frac{\partial^2 S(\beta', \gamma'}{\partial \beta' \partial \gamma'}$$

and $$\frac{\partial S(\hat{\beta}, \hat{\gamma})}{\partial \hat{\gamma}} = \frac{\partial S(\beta', \gamma')}{\partial \gamma'} + (\hat{\beta} - \beta') \frac{\partial^2 S(\beta', \gamma')}{\partial \beta' \partial \gamma'} + (\hat{\gamma}, \gamma') \frac{\partial^2 S(\beta', \gamma')}{\partial \gamma'^2},$$

where B' and y' are initial guesses of B and y. . Because the first and second partial derivatives can be computed at the guessed values, a system of two linear equations with two unknown values, $\delta\beta = \hat{\beta} - \beta'$, $\delta\gamma = \hat{\gamma} - \gamma'$, is obtained which in matrix form is

$$\begin{bmatrix} \frac{\partial^2 S(\beta',\gamma')}{\partial \beta'^2} & \frac{\partial^2 S(\beta'\gamma')}{\partial \beta' \partial \gamma'} \\ \frac{\partial^2 S(\beta'\gamma')}{\partial \beta' \partial \gamma'} & \frac{\partial^2 S(\beta',\gamma')}{\partial \gamma'^2} \end{bmatrix} \begin{bmatrix} \delta\beta \\ \delta\gamma \end{bmatrix} = \begin{bmatrix} \frac{\partial S(\beta',\gamma')}{\partial \beta'} \\ \frac{\partial S(\beta',\gamma')}{\partial \gamma'} \end{bmatrix} . \quad (7)$$

These are easily solved, and the procedure repeated with new guesses $\beta'' = \beta' + \delta\beta$, $\gamma'' = \gamma' + \delta\gamma$ until $\delta\beta$ and $\delta\gamma$ are negligible. It is worth noting that the matrix of second derivatives evaluated at $\hat{\beta}$ and $\hat{\gamma}$ estimates the negative of the inverse of the variance-covariance matrix for $\hat{\beta}$ and $\hat{\gamma}$, $V(\hat{\beta}, \hat{\gamma})$.

The two-parameter equation system (Equation 7) is used for Model 1 (solving for each treatment, one at a time) and in Model 4 (all observations pooled as if in one treatment). Models 2 and 3 require a system of b + 1 parameters because these models contain a parameter (y. in Model 2, B. in

Model 3) common to all treatments. Thus, for Model 2, let $S(e_2) = \ln L(ezlrij)$ and find the solution where

$$\frac{\partial S(\theta_2)}{\partial \beta_1} = , \quad , \quad , = \frac{\partial S(\theta_2)}{\partial \beta_b} = \frac{\partial S(\theta_2)}{\partial \gamma.} = 0 .$$

Again, Taylor's theorem is used to approximate the derivatives and a system of b + 1 equations

$$\begin{bmatrix} \frac{\partial^2 S(\theta_1)}{\partial^2 \beta_1'} & \cdots & 0 & \frac{\partial^2 S(\theta_1)}{\partial \beta_1' \partial \gamma.'} \\ \vdots & \ddots & \vdots & \vdots \\ 0 & \cdots & \frac{\partial^2 S(\theta_1)}{\partial^2 \beta_b{}^{12}} & \frac{\partial^2 S(\theta_1)}{\partial \beta_b' \partial \gamma.'} \\ \frac{\partial^2 S(\theta_1)}{\partial \beta_1' \partial \gamma.'} & \cdots & \frac{\partial^2 S(\theta_1)}{\partial \beta_b' \partial \gamma.'} & \frac{\partial^2 S(\theta_1)}{\partial_2 \gamma.'} \end{bmatrix} \begin{bmatrix} \delta\beta_1 \\ \vdots \\ \delta\beta_b \\ \delta\gamma. \end{bmatrix} = \begin{bmatrix} \frac{\partial S(\theta_1)}{\partial \beta_1'} \\ \vdots \\ \frac{\partial S(\theta_1)}{\partial \beta_b'} \\ \frac{\partial S(\theta_1)}{\partial \gamma.'} \end{bmatrix}$$

is solved iteratively as before. The solution to Model 3 is found in a similar manner.

This iterative fitting technique for solving the maximum-likelihood equations is referred to as the Newton-Raphson method (Edwards 1972) and can be applied to each of the Models 1-4. The procedures are easily programmed in BASIC computer language and run on a 32 K-byte microcomputer with a matrix function ROM (read only memory) device. (A program listing is available from the author.)

In practice, the test statistic, 5, is obtained by first calculating the support function, 2, for each model, k,

$$S(\theta_k) = \sum_{j=1}^{b} \sum_{i=1}^{a} \{r_{ij} \ln[p_{ij}(\theta_k)] + (n_{ij} - r_{ij}) \ln[1 - P_{ij}(\theta_k)]\}$$

for each set of hypothesized parameters, e_k, and noting that $S(\theta_k) - \ln L(\theta_k | r_{ij})$ is a constant for a given set of observed data, regardless of 0, then G =

$$-2 \ln \frac{L(\theta_{k'} | r_{ij})}{L(\theta_k | r_{ij})} = -2[S(\theta_{k'}) - S(\theta_k)].$$

Data from a bioassay at Auke Bay Laboratory can be used to demonstrate application of the tests. Kelp shrimp (Eualus suckleyi) were exposed for 48 h to seven concentrations of toluene at two different temperatures (4" and 12°C) (Table 1). Models k = 1 to 4 are fit to the data, and the support functions, S(e,), are given for each model (Fig. 1, Table 2). Computation of the support function for Model 1 is demonstrated in Table 3. Restricting the curves to a common y (Model 2) produces curves much different from curves produced by not restricting y (Model 1). Restricting the curves to a common B (Model 3) produces a curve indistinguishable from the curve of Model 1. The coincidence of these two curves indicates temperature has little or no effect on dispersion (as measured by B), but the difference between the Model 1 and Model 2 curves shows that there is a difference in median lethal dose estimated to be $\gamma_1 - \gamma_2 = 22.258 - 18.193 = 4.065$ units. Test I (Table 4) indicates that this difference is significant. Although Tests II and III are unnecessary (because Test I is significant), they are shown to illustrate their use. A test for common B'S (Model 3 versus Model 1) could also be done to evaluate whether temperature has no effect on dispersion.

Table 1.--Bioassay of kelp shrimp, Eualus suckleyi, held 48 h in toluene. (From data on file at the Natmarine Fisheries Service, Northwest and Alaska Fisheries Center, Auke Bay, Alaska 99821.)

4°C							
Concentration x_i of toluene (ppm)	0	8.4	10.5	13.0	18.0	22.5	25.0
Number of shrimp, n_i	15	15	15	15	14	17	15
Number of responses, r_i	0	0	0	0	4	8	11
12°C							
Concentration x_i of toluene (ppm)	0	8.4	10.5	13.0	18.0	22.5	25.0
Number of shrimp, n_i	15	14	16	15	13	15	13
Number of responses, r_i	1	0	0	1	8	11	13

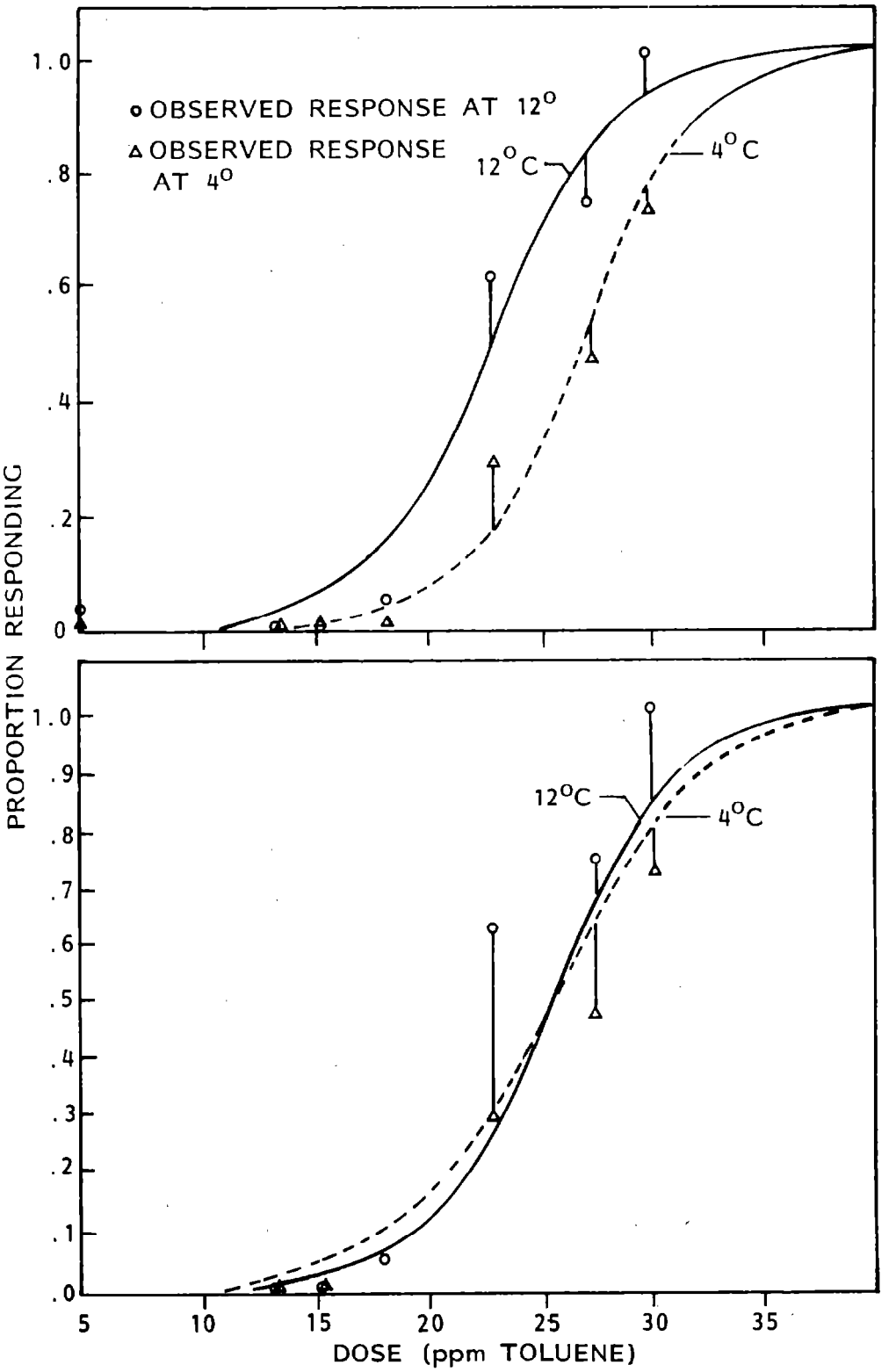

Figure 1.--Results of bioassays with kelp shrimp, Eualus suckleyi, at 4" and 12°C fitted to Model 1 (independent logistic response) and Model 2 (logistic with common EC50). For clarity, Model 3 (logistic with common slope) and Model 4 (common logistic response) are omitted. Models 1 and 3 are indistinguishable; Model 4 is intermediate between the two lines of Model 2.

Table 2.--Parameter estimates and support functions of experimental data fit to dose-response Models 1-4. Kelp shrimp were exposed to different concentrations of toluene at different temperatures (see Table 1).

Model	Parameter estimates	Support function S
1. Full model (independent logistic curves for each temperature)	$\beta_1 = 0.376$, $\beta_2 = 0.357$ $\gamma_1 = 22.258$, $\gamma_2 = 18.193$	-61.497
2. Common γ	$\beta_1 = 0.362$, $\beta_2 = 0.298$ $\gamma_\cdot = 20.597$	-66.426
3. Common β	$\beta_\cdot = 0.364$ $\gamma_1 = 22.282$, $\gamma_2 = 18.183$	-61.513
4. Common γ and β (single curve for all temperatures)	$\beta_\cdot = 0.330$ $\gamma_\cdot = 20.377$	-66.615
Observed	$P_{ij} = \frac{r_{ij}}{n_{ij}}$	-53.536

Table 3.--Computation of the support function for Model 1. Data from Table 1.

Estimated probability of response, $P_{ij}(\theta_1)$	Concentration x_i						
	x_1 = 0	x_2 = 8.4	x_3 = 10.5	x_4 = 13.0	x_5 = 18.0	x_6 = 22.5	x_7 = 25.0
4°C							
$P_{i1} = (1 + e^{0.376(22.258 - x_i)})^{-1}$	0.0002	0.0054	0.0118	0.0296	0.1667	0.5207	0.7356
12°C							
$P_{i2} = (1 + e^{0.357(18.193 - x_i)})^{-1}$	0.0015	0.0293	0.0601	0.1349	0.4818	0.8225	0.9188

$$S(\theta_1) = \sum_{j=1}^{2} \sum_{i=1}^{7} r_{ij} \ln[P_{ij}(\theta_1)] + \sum_{j=1}^{2} \sum_{i=1}^{7} (n_{ij} - r_{ij}) \ln[1 - P_{ij}(\theta_1)]$$

$$= 0 + 0 + 0 + 0 + 4 \ln(0.1667) + 8 \ln(0.5207) + 11 \ln(0.7356) + 1 \ln(0.0015) + 0 + 0 + 1 \ln(0.1349)$$

$$+ 8 \ln(0.4818) + 11 \ln(0.8225) + 13 \ln(0.9188) + (15 - 0) \ln(1 - 0.0002) + (15 - 0) \ln(1 - 0.0054)$$

$$+ \ldots + (13 - 13) \ln(1 - 0.9188)$$

$$= -61.497 .$$

Table 4.--Results of log-likelihood ratio tests of heterogeneity due to temperature in a bioassay. Kelp shrimp were exposed to different concentrations of toluene (see Table 1).

Test	d.f.	G
General model goodness of fit	10	$2(-53.536 - -61.497) = 15.922^{n.s.}$
Common γ (Test I)	1	$2(-61.497 - -66.426) = 9.858^{**}$
Common dose response (Test II)	2	$2(-61.497 - -66.515) = 10.236^{**}$
Common dose response | common β (Test III)	1	$2(-61.513 - -66.515) = 10.2040^{**}$

n.s. = not significant, ** $P < 0.01$.

DISTRIBUTION OF THE TEST STATISTIC

Because significance level and power of the tests are derived from theory that assumes large sample sizes, it is appropriate to compare the theoretical distribution with the results of replicated experiments of typical small-sample size. When model parameters are known, the theoretical distribution can be computed, and a small-sample experiment can be simulated.

Estimated from Large-Sample Theory

Theorem 13.8.1 in Wilks (1962) states that when the hypothesis e_k, , a subset of e_k , is true, G = -2 In $\frac{L_{b+} >}{L_{bk)}}$ converges in probability to a random variable having the chi-square distribution with p = k_ - k_' degrees of freedom. Thus, the probability of rejecting a true hypothesis (Type I error) is:

$$P = \int_{\chi_\alpha^2(\rho)}^{\infty} d\chi^2(\rho)$$

the integration of the chi-square distribution from the 100(1-a)% point.

When the hypothesis e_k' iS not true, G converges to the noncentral chi-square distribution (Kendall and Stuart 1961), and the probability of rejecting a false hypothesis is approximated by

$$P = \int_{\frac{\rho+\Lambda}{\rho+2\Lambda}}^{\infty} \chi_\alpha^2(\rho)\, d\chi^2\left(\rho + \frac{\Lambda^2}{\rho + 2\Lambda}\right),$$

an approximation of the noncentral chi-square distribution, x*(P,h) integrated from the 100(1-a)% point of the central chi-square distribution, x,*(P). Degrees of freedom equal p, and A is the noncentral parameter equal to

$$\Lambda = (\theta_\rho - \theta_{\rho o})' \, V_\rho^{-1} \, (\theta_\rho - \theta_{\rho o}),$$

where e_p is the vector of actual differences between the parameters of interest, such as $B_{.J} - 6$ $(j \neq j')$; and e_{pO} is the vector of parameter differences specified by the hypothesis. In most cases, e_{pO} is a vector of zeros. The variance-covariance matrix of $13\sim$ is represented by V_p and is the negative inverse of the estimated variance-covariance matrix; V_p can be determined from the variance-covariances of B'S and y's (estimated using the expected response values in the matrix of second-degree partial derivatives).

For example, consider computing asymptotic power of tests for various hypothetical conditions of $\Delta\beta$ $(= \beta_1 - \beta_2)$ and $\Delta\gamma$ $(= \gamma_1 - \gamma_2)$ where $b = 2$ treatments. For Test I $(H_o: \Delta\gamma = 0)$, $\theta_\rho = (\Delta\gamma)$, $\theta_{\rho o} = (0)$; $= 0$, and $\Delta\beta = 0)$, $\theta_\rho = (\Delta\gamma, \Delta\beta)'$, $\theta_{\rho o} = (0,0)'$. Thus, for Test II:

$$V_\rho = \begin{bmatrix} \mathrm{Var}(\Delta\beta) & \mathrm{Cov}(\Delta\beta, \Delta\gamma) \\ \mathrm{Cov}(\Delta\beta, \Delta\gamma) & \mathrm{Var}(\Delta\gamma) \end{bmatrix}$$

where:

$$\mathrm{Var}(\Delta\beta) = \mathrm{Var}(\beta_1) + \mathrm{Var}(\beta_2)$$

$$\mathrm{Var}(\Delta\gamma) = \mathrm{Var}(\gamma_1) + \mathrm{Var}(\gamma_2)$$

$$\mathrm{Cov}(\Delta\beta, \Delta\gamma) = E[(\beta_1 - \beta_2)(\gamma_1 - \gamma_2) - E(\beta_1 - \beta_2)\, E(\gamma_1 - \gamma_2)]$$

$$= \mathrm{Cov}(\beta_1, \gamma_1) + \mathrm{cov}(\beta_2, \gamma_2) .$$

Figure 2 shows computed power for the tests at various AB and Ay for the hypothetical condition 8. $= \underline{\beta_1 + \beta_2} = 0.2197$ and $\gamma. = \underline{\gamma_1 + \gamma_2} = 20.00$. When

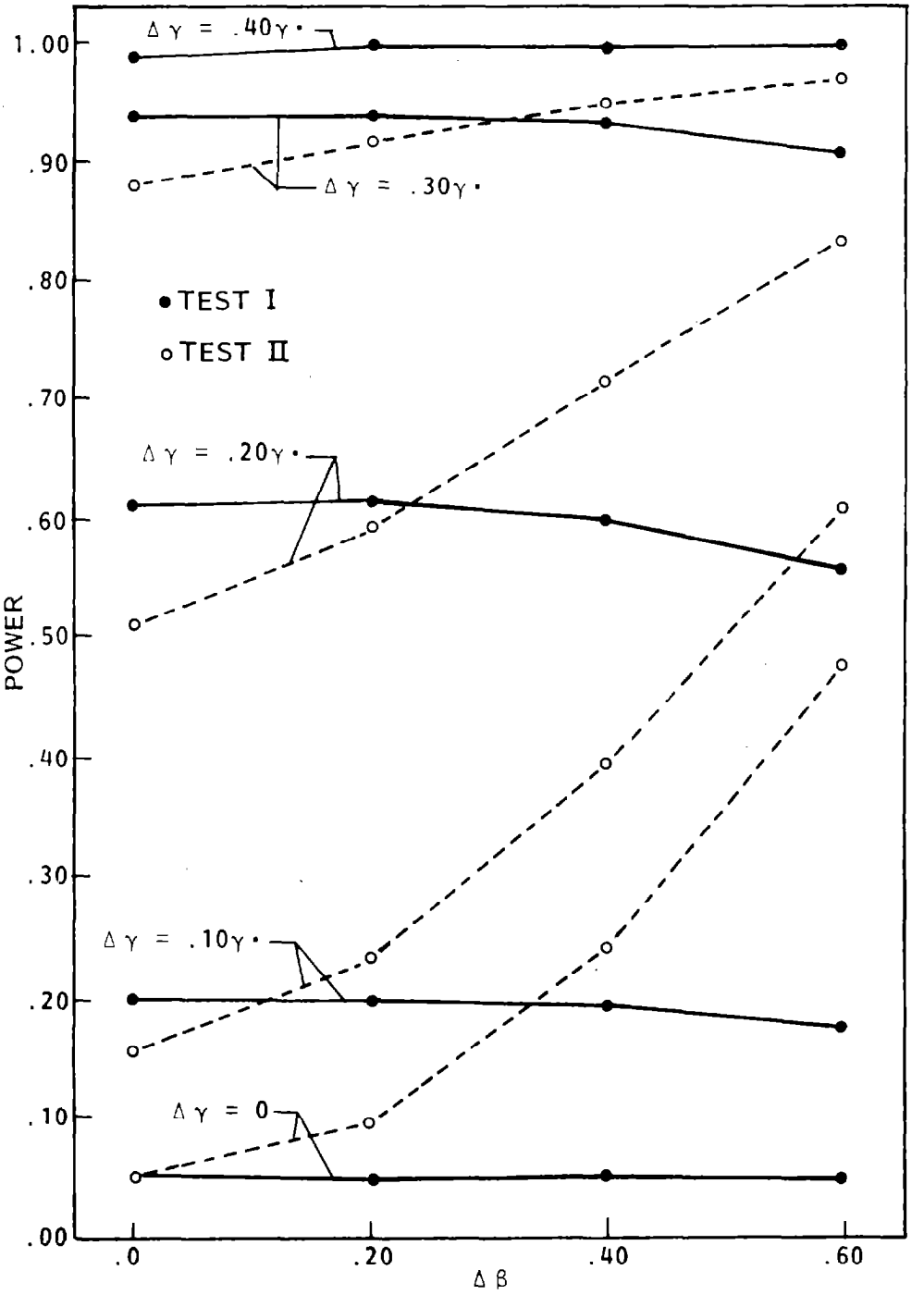

Figure 2. --Asymptotic power of Tests I and II calculated for conditions where there are b = 2 treatments, a = 7 doses (= 0, 5, 10, 15, 20, '25, and 30), n = 16 replicates per dose-treatment, and Af3's and Ay's are symmetrical around B. = 0.2197 and y. = 20.00. Points for Test III when AB = 0 would be indistinguishable from points for Test I. (Test I is logistic with common EC50 independent logistic response; Test II, common logistic responselindependent logistic response; and Test III, common logistic responsellogistic with common 6.)

AB= 0, Test I has greater power in detecting Ay than Test II for intermediate values; however, the power of both tests approach each other at the extremes (at 4~ 2 0.40, power + 1.00; as AY -t 0, power + 0.05). As A6 increases, Test II increases in power.

Simulated Small-Sample Experiments

Random replicates of dose-response experiments with small sample size were simulated. The observed significance levels and power of these experiments were compared with significance level and power obtained from the large-sample theory. A quantal-response bioassay can be simulated by drawing "i random numbers from a uniform (0,l) distribution for each concentration L_i. The simulated 1_i would be the number of random numbers less than or equal to the I$ prescribed for X_i by the assumed logistic function (Buslenko et al. 1966):

Eight conditions of AB and Ay were chosen to compare simulated results with the corresponding theoretical estimate of power. Each condition was randomly replicated 250 times. Theoretical results were within the 95% confidence interval of the comparable simulated estimate- in 15 of 16 comparisons (Table 5). The frequency distributions of the test statistics of Tests I and II when the hypotheses are true (AB = 0, Ay = 0) were compared with the theoretically appropriate chi-square distribution (Figs. 3 and 4). Kolmogorov-Smirnov goodness-of-fit tests (Conover 1971) were not significant. Thus, it appears that the 1 arge-sample theory adequately describes the power of tests conducted under these conditions ($!_{ij}$ = 16, y. = 20, B. z 0.22).

Table 5. --Power comparisons of Tests I and II as obtained from asymptotic theory versus simulated replications.

Condition	Power of Test I (common γ | logistic)		Power of Test II (common γ and β | logistic)	
	Asymptotic theory	Simulated replicates	Asymptotic theory	Simulated replicates
$\Delta\beta = 0$, $\Delta\gamma = 0$	0.0500	0.044 ± 0.0254	0.0500	0.048 ± 0.0265
$\Delta\gamma = 0.10\gamma$.	0.1936	0.236 ± 0.0526	0.1561	0.220 ± 0.0514*
$\Delta\gamma = 0.20\gamma$.	0.6123	0.568 ± 0.0614	0.5094	0.504 ± 0.0620
$\Delta\gamma = 0.30\gamma$.	0.9386	0.956 ± 0.0254	0.8831	0.908 ± 0.0358
$\Delta\beta = 0.20\beta$, $\Delta\gamma = 0$	0.0500	0.032 ± 0.0218	0.0973	0.096 ± 0.0365
$\Delta\gamma = 0.10\gamma$.	0.1923	0.196 ± 0.0492	0.2280	0.244 ± 0.0532
$\Delta\gamma = 0.20\gamma$.	0.6105	0.580 ± 0.0612	0.5931	0.596 ± 0.0608
$\Delta\gamma = 0.30\gamma$.	0.9396	0.904 ± 0.0365	0.9187	0.896 ± 0.0378

* $P < 0.05$.

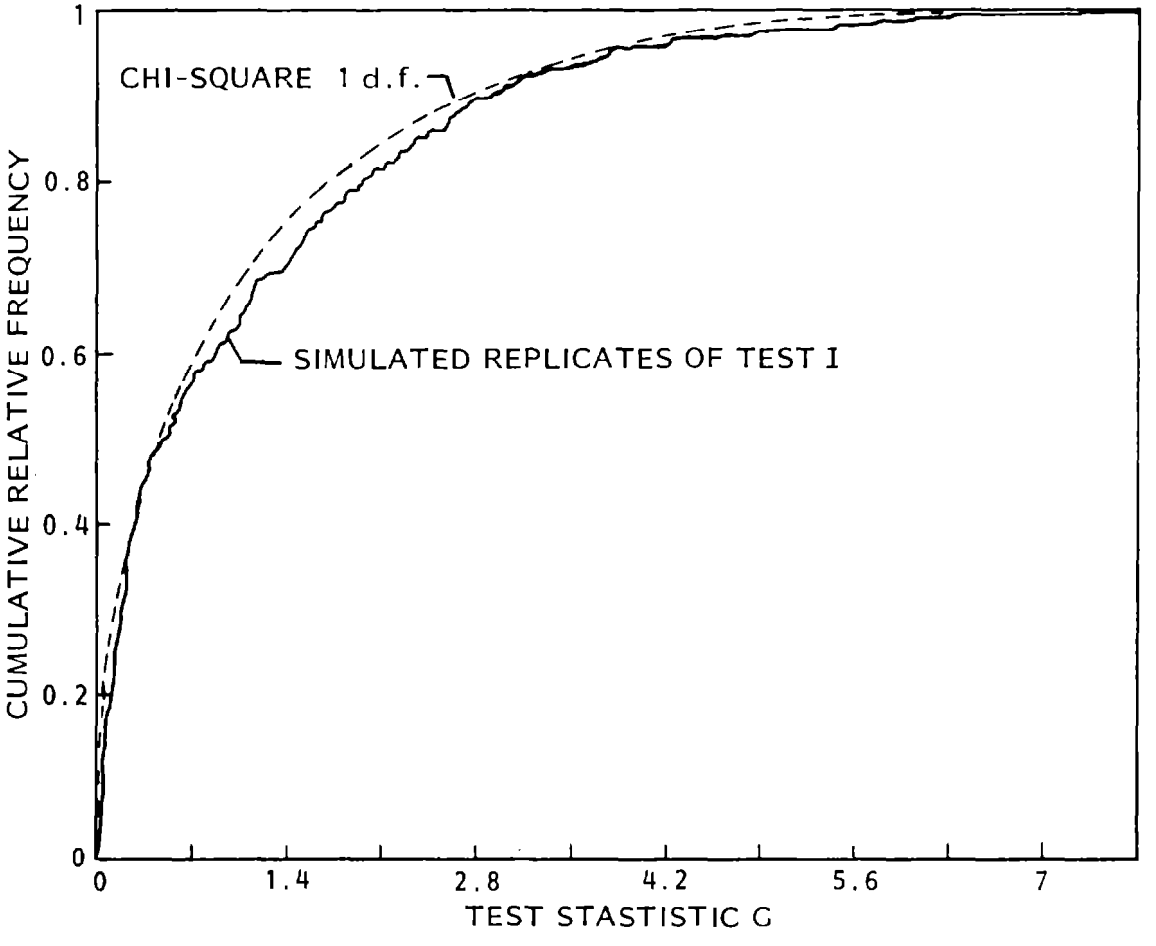

Figure 3. --Cumulative relative frequency distribution of likelihood-ratio test statistic for Test I (logistic with common ECSO(independent logistic response) obtained from 250 randomly replicated simulations (A@ = 0, Ay = 0) compared with the distribution function of the chi-square distribution (1 d.f.).

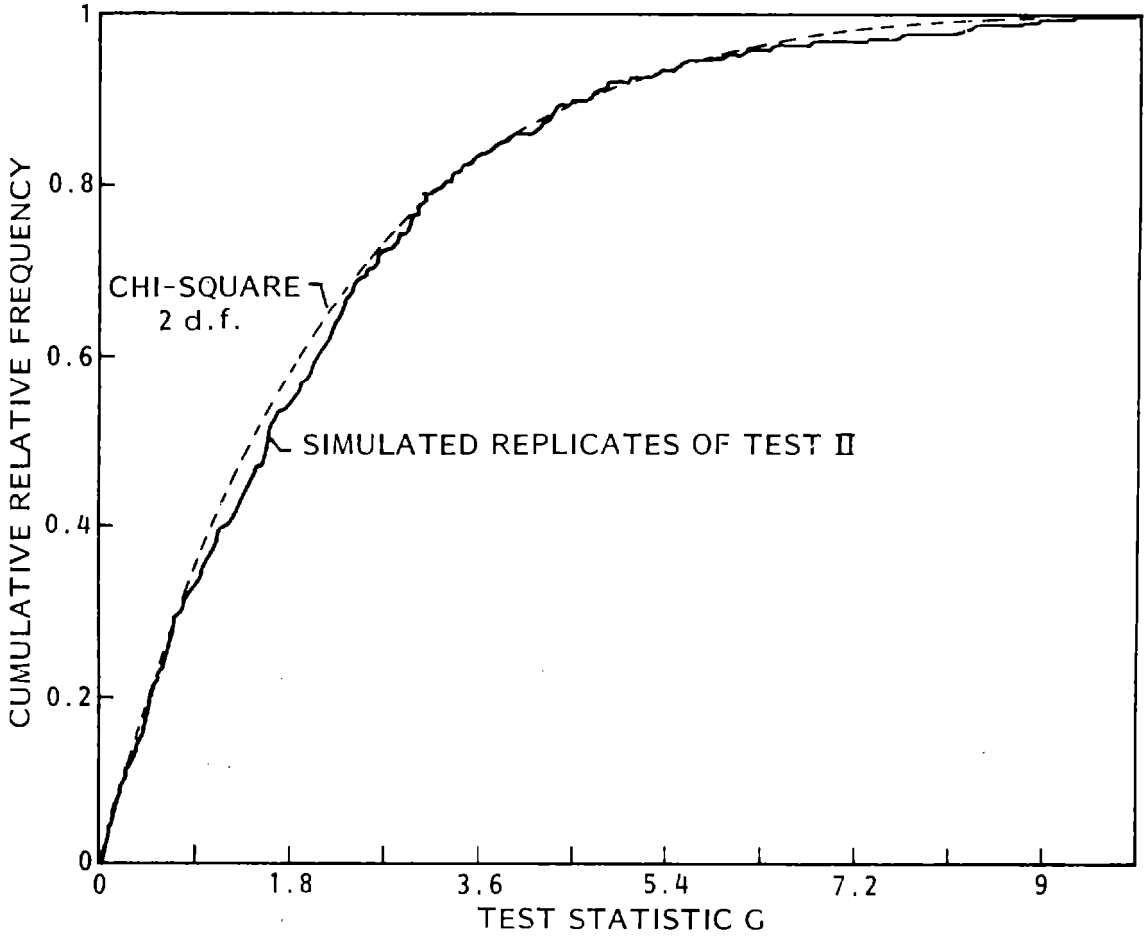

Figure 4.--Cumulative relative frequency distribution of likelihood-ratio test statistic for Test II' (common logistic responselindependent logistic response) obtained dram 3SO randomly replicated simulations (AB = 0, Ay = 0) compared with the distribution function of the chi-square distribution (2 d.f.).

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LITERATURE CITED

BERKSON, J.

1955. Maximum .likelihood and minimum x^2 estimates of the logistic function. J. Am. Stat. Assoc.. 50:130-162.

BROWN, C. C.

1982. On a goodness of fit test for the logistic model based on score statistics. Commun. Statist.-Theor. Meth. 11:1087-1105.

BUSLENKO, N. P., D. I. GOLENKO, Yu. A. SHREIDER, I. M. SOBOL', and V. G. SRAGOVICH.

1966. The Monte Carlo method. In Y. A. Shreider (editor), The method of statistical trials, p. 381. (Translated from Russian by G. J. Tee and D. M. Parkyn.) Pergamon Press, New York.

CHAMBERS, E. A., and D. R. COX.

1967. Discrimination between alternative binary response models. Biometrika 54:573-578.

CONOVER, W. J.

1971. Practical nonparametric statistics. Wiley, New York, 462 p.

EDWARDS, A. W. F.

1972. Likelihood, an account of the statistical concept of likelihood and its application to scientific inference. Cambridge Univ. Press, Cambridge, MD, 235 p.

FINNEY, D. 3.

1971. Probit analysis. 3rd ed. Cambridge Univ. Press, New York, 333 p.

HOSMER, D. W., AND S. LEMESHOW.

1980. Goodness of fit tests for the multiple logistic regression model. Commun. Statist.-Theor. Meth. A9:1043-1069.

KENDALL, M. G., and A. STUART:

1961. The advanced theory of statistics. Volume II, inference and relationship. Hafner, New York, 676 .p.

PRENTICE, R. L.

1976. A generaliiation of the probit and logit methods for dose response curves. Biometrics. 32:761-768.

SILVERSTONE, H.

1957. Estimating the logistic curve. J. Am. Stat. Assoc. 52:567-577.

WILKS, S. S.

1962. Mathematical statistics. Wiley, New York, 644 p.