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LOGISTIC REGRESSION FOR THE MODELING OF LOW-DOSE RADIATION EFFECTS

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A Thesis
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Abstract

The primary goal of this thesis is to examine statistical procedures that determine if a nonlinear threshold dose effect occurs in cancer incidence in animal experiments. This is to say, does there exist a level of radiation which does not increase the risk of cancer in animals? This question will be explored on data over several species of animals (beagles, rats, and mice) and several different sources of radiation (e.g. radium, or plutonium). Here we consider experiments with several groups of animals at several dose levels

In mathematical terms, this thesis will determine if a "knee" fit to a logistic regression models the data better than a simple logistic regression curve. The knee is a non-linear kink in the dose response relationship at a specific dose. If there is evidence to support the knee model hypothesis, it can be interpreted to mean that there is evidence of a threshold effect in the dose response.

A secondary goal is to determine if two knees will suffice for data sets of this nature. The motivation behind this goal, is that a two knee model should be able to model both a low dose threshold and a high dose drop-off (due to over exposure to radiation, past the Maximally Tolerated Dose, MTD). Any knees above two will generally only contribute to overfitting of the model.

Another goal is to give guidelines on the design of experiments, that will assist researchers in determining if a threshold does in fact exist.

Acknowledgments

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Dedication

To my parents and Terry for their support and patience and to Peter Wright for pioneering the way.

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Chapter 1

Introduction

1.1 Summary

Research in low dose radiation is gaining momentum. Conclusions that were originally drawn from anecdotal observations are now being replaced with experiments whose sole purpose is to determine if there is a threshold of tolerance for radiation. This thesis examines the design and analysis of such experiments. This first chapter introduces the concept of low dose radiation and the Linear No-Threshold Hypothesis, as well the tools and methods are briefly described. Each is further developed in subsequent chapters.

The current paradigm of radiation researchers and policy makers is the Linear Non-Threshold Hypothesis (LNTH) (International Centre for Low Dose Radiation Research, 1999). The belief is that any amount of radiation will harm DNA and exposure is cumulative, i.e. if a subject is exposed to one Gray now, and one Gray later, the subject will have the DNA damage of two Grays. Some researchers now believe that there is a threshold, an amount which the body can absorb without sustaining any damage. The point of view of scientists who believe in a threshold effect is that the body has natural

mechanisms to repair damaged DNA so that low doses do not have any effect on cancer rates, and perhaps that low-dose exposure might even improve the function of these mechanisms in a manner similar to the use of vaccines to bolster the immune system.

This debate is not easy to settle for various reasons, the main reason being that low doses of radiation have such a small effect on cancers rates that extremely large sample sizes would have to be used in order to achieve any conclusive results. This is usually not feasible due to the cost per subject and the restrictions on time and space. Also hampering research into low dose radiation is the inability to measure all sources of radiation. For this reason it is nearly impossible to study humans who have been exposed to low doses of radiation (sunlight, for example) (International Centre for Low Dose Radiation Research, 1999). This leads to other issues that will not be addressed here, such as the ability to interpret the effects of radiation on humans based on results from animal experiments.

Several papers discuss the difficulties with this type of research. They discuss the difficulty of demonstrating the threshold effect (Moolgavkar et al., 1999) and several ways to model and conduct experiments are examined (Burnett et al., 1995; National Research Council, 1999; Ma et al., 1999).

The initial approach to be used in this thesis was to be as follows: a collection of existing published data sets from low dose radiation experiments was collected and was to be analyzed together (combined analysis) in an attempt to increase the statistical power of tests used on the data. This means that due to the greater number of data points it may be possible to draw statistical conclusions that were not possible when each data set was looked at individually. It will be seen that such a meta-analysis is not likely to be successful in resolving the Linear No-Threshold Hypothesis (LNTH) due to the dosing and scope of existing experiments. Using the data, however, we establish a family of dose-response models in logistic regression that can be used to plan and analyze these kinds of experiments.

1.2 The LNTH and Society

The Linear No-Threshold Hypothesis (LNTH) is the current scientific belief that any amount of radiation is harmful. A new, emerging belief is that the body has a certain threshold for radiation where levels of radiation below that level cause no harmful effects.

The results of this type of research could have pronounced effects on the way we live. Currently, radiation is closely monitored and feared. Research in this field is attempting to reduce the fear that the general population has towards radiation by demonstrating the threshold effect.

There are also financial implications to this type of work. It would have implications from the biomedical field (X-rays, low level medical waste) to mineral mining. This is not to say that the nuclear industry could start dumping radioactive waste into water or landfills, rather that regulations such as the way employees are monitored could be relaxed.

1.3 A Typical Experiment

The typical low dose experiment focuses on the effect of radiation on bone cancer in small mammals. Depending on the type of radionucleotide used, the radiation is either transmitted to the animal through its food or an injection. A frequent size for an experiment is in the neighborhood of 400 animals. Subject numbers decrease as the dose increases and the largest group usually is the control group. In dosing studies a large control group is not necessary, but many of the experiments gathered for this thesis were studying an effect other that just the difference among dose levels.

There are several issues that must be taken into consideration when attempting to undertake an analysis using low dose radiation studies: the measured dose, species, nucleotide, and population size.

Measuring dose is not straightforward with radiation. Depending on the etiology of the radiation on the cancer, dose must be measured in different ways. For some experiments it is better to record the amount of radiation to which the animal is subjected, in other experiments it is better to approximate the amount of radionucleotide absorbed by the body part being studied. This difference in measurement can make studies incomparable if the transformation of the radiation rate cannot be properly retraced.

When any studies are being combined and compared care must be taken to ensure that the independent variables are as homogeneous as possible. In this thesis, data sets can be regrouped by radionucleotide or by species. It is also possible to regroup across radionucleotide or species with much more variation in the results, but these groupings will not be pursued in this thesis.

1.4 Analytic Tools

The principal statistical tool that will be used here is logistic regression. This tool is described in some detail in Chapter 2. An innovation in dose-response modeling introduced here is the use of "knee" functions to represent the possible threshold characteristics of dose-response.

Knee functions

The "knee" transformation to variables sets the value of the variable to zero when it is below the knee and to the original value of the variable minus the knee above the knee value. The knee can be written as follows:

$$kneevar = \begin{cases} 0 & if\ var < knee \\ var - knee & if\ var > knee \end{cases}$$

This means that below a certain dose (the value of the knee), the effect of dose differs from that above the knee. This is the hypothesis of the threshold model, that below a certain dose, dose does not increase the subjects chances of developing cancer.

1.5 Application to Selected Data Sets

Using the datasets provided, the thesis will attempt to determine if the model using the knee function shows a statistically significant increase in the fit of the model for each data set separately. The algorithm will be tested on each data set individually to determine if there is statistical evidence of a threshold in the data.

This will also be done by combining data sets (combined analysis) which have similar characteristics in order to increase the number of animals used (and therefore the statistical power of the experiment). The datasets were chosen with combining of results together in mind, in other words, the experiments were fairly uniform in design and the variables measured allow for the combination of these datasets. Had all the various data sets been kept, the results would not have been comparable with one another, therefore losing the ability to test the combination of the datasets.

The purpose of combined analysis is to strengthen the power of the test involved by using more observations. It must be determined beforehand what is an acceptable level of power and how large a population is required to meet that power. This is true for two reasons. The first is that if there is no hope of attaining a high enough population then time is wasted trying to collect the data sets available. The second reason is if there are very many different types of data sets available then collecting more than necessary will dilute the homogeneity of the combined analysis and can reduce the interpretability of the results.

1.6 Experimental Design

Part of the goal of this thesis is to help determine under what experimental conditions the test statistic is best able to detect a threshold effect. The number of parameters being used (dose, number of animals, anticipated threshold level, baseline cancer rate), make for a very dynamic range of experiments. If the experiment is designed without taking into consideration the limitations of the power of the test statistic then it is

very possible that the experiment will not be able to determine whether or not the threshold effect is present.

Some of the difficulty lies with the variation in each group. With extremely large groups we get very small variations. For example if we had a control group of 100,000 mice, and 100 mice got cancer we would draw the conclusion that 1 in 1,000 mice naturally get cancer. If our group only contains 50 mice and none get cancer it is difficult to get a strong idea of what the baseline cancer rate is for mice. This is the difficulty with threshold analysis, if the baseline group is measured inadvertently low and low doses (below the threshold) are measured slightly high then it will appear that there is no threshold effect, despite the fact that this can be due to random chance.

In Chapter 5 we will use simulation to develop some guidelines to help researchers design studies of low dose thresholds.

1.7 Thesis Content.

The following 5 chapters will expand on the research done on the selected data sets. Chapter 2 covers the methods and models, including a detailed review of the logistic regression model and the corresponding SAS output (section 1.4). Chapter 3 details the algorithm being used, it gives examples of how it works using different patterns of data. Chapter 4 examines the data sets provided and analyzes the experiments individually as well as the meta analyses (section 1.3 and 1.5). Chapter 5 discusses the design of future experiments and looks at simulations run on the algorithm (section 1.6). Chapter 6 is the conclusion.

Chapter 2

Methods and Models

2.1 Review of Logistic Regression

The following section is a review of logistic regression, sources include Hosmer and Lemeshow (1989) and SAS/STAT (1996).

Logistic regression is a statistical method for fitting mathematical models similar to linear regression. The goal of both linear and logistic regression is to determine the most plausible model using the explanatory variables ("covariates") available. What makes logistic regression different from linear regression is that the outcome variable in logistic regression is binary (takes values 0 or 1), whereas, linear regression requires that the outcome variable be continuous and range over the real numbers. Binary outcome variables are important in many different situations where the experimenter is concerned with only whether an event has happened or not. The outcome variable can be coded with any two values, although most often an event is coded "1" and a non-event is coded "0".

Logistic regression calculates the probability that an event ("1") will occur given a certain covariate pattern. The covariate pattern is the combination of observed values from

the explanatory variables. Therefore the predicted value, $\pi(x)$, for a given covariate pattern, x, must range between 0 and 1. The form of the model used to estimate the chance the outcome "1" occurs is:

$$\pi(x)=\frac{e^{(b_0+b_1x_1+..+b_nx_n)}}{1+e^{(b_0+b_1x_1+..+b_nx_n)}}$$

where $x_1,..,x_n$ are the explanatory variables and $b_0,..,b_n$ are the unknown parameters. An important transformation of this formula is the logit transformation:

$$g(x)=\ln\left[\frac{\pi(x)}{1-\pi(x)}\right]=b_0+b_1x_1+..+b_nx_n$$

The use of this transformation facilitates the estimation of the parameter $b_0,..,b_n$ since it is linear in its parameters and can range over all real values of x. In this form the parallel between logistic and linear regression is clear. Overall the techniques used in logistic and linear regression are quite similar.

Major differences include the assumption of how the error is distributed and the method for fitting the model. In linear regression the distribution of the error is assumed to be normal, in logistic regression error is assumed to be binomial. This difference means that least-squares is no longer the most appropriate method for estimating the parameters. Instead, Maximum Likelihood Estimation is used to estimate the coefficients of the explanatory variables.

In linear models the dependent variable, y, is modeled as $y=y(x)+error$ (where $y(x)=b_0+b_1x_1+..+b_nx_n$), in logistic regression the model is $y=\pi(x)+error$. The error in linear models is assumed to be normal with mean 0 and a variance which is constant across all values of x. This is not possible with logistic regression since the outcome variable can only take two values: 1 or 0 (or two other numerical values). If $y=1$ then the error is equal to $1-\pi(x)$ with probability $\pi(x)$: if $y=0$ then the error is equal to $-\pi(x)$ with probability $1-\pi(x)$. As an example, suppose that for a certain level of the explanatory variables the estimated probability of an

event is 0.7 ($\pi(x) = 0.7$). If $y = 1$ then the error is equal to 0.3 with probability 0.7. If $y = 0$ then the error is equal to -0.7 with probability 0.3. This is a $binomial(0,0.21)$ or, more generally, ($binomial(0,\pi(x)(1-\pi(x)))$.

To determine the values of the unknown parameters, logistic regression uses Maximum Likelihood Estimation (MLE). MLE calculates the values of the unknown parameters which maximize the probability density function for the given data set. To do this MLE maximizes a function called the Likelihood function. This function expresses the probability of the observed data as a function of the parameters (i.e. $f(\theta|x)$ instead of $f(x|\theta)$). For logistic regression the likelihood function, for one observation, is equal to $l(g(x)|y) = \pi(x)^y(1-\pi(x))^{(1-y)}$. This is the binomial distribution as a function of its parameters.

Since each observation is assumed to be independent the likelihood function for the entire sample is the product of the individual distributions. While this function is correct, it is easier to work with the log of the likelihood function:

$$L(g(x)) = \sum_i (y_i \ln[\pi(x_i)] + (1-y_i)\ln[1-\pi(x_i)])$$

because the log function is a strictly increasing function, the log of the likelihood function is maximized at the same point as the likelihood function. To maximize the function we take its derivative with respect to each explanatory variable and set it equal to 0:

$$\sum_i (y_i - \pi(x_i)) = 0$$

$$\sum_i x_{ij}(y_i - \pi(x_i)) = 0$$

where $i = 1..n$ is the observations and $j = 1..p$ is the number of explanatory variables.

The results from MLE estimation will yield a coefficient for each explanatory variable. If, after testing, the variable is included in the model, the coefficient will help

explain the relationship between the explanatory variable and the outcome variable. Raising e to this coefficient will be the odds ratio for that variable. The odds ratio is the relative risk associated with a certain pattern of covariates when compared to a "standard" pattern. It is interpreted differently depending on whether the predictor variable is dichotomous, polytomous or continuous. If the variable is dichotomous the odds ratio is the ratio of increase in risk of the "event" happening with the variable being one value instead of the other. For example in a study of heart disease, if high blood pressure is a dichotomous variable with value 1 if the patient has high blood pressure and 0 if not and where the odds ratio of a high blood pressure variable is 2 means that the person is twice as likely to suffer from heart disease then someone without high blood pressure. If the predictor variable is polytomous then the odds ratio is the ratio of the likelihood of the event standardized against one of the levels for the variable. For example if the blood pressure variable had three values: low, normal, and high then the odds ratio would be the increase in chance of the levels of the variable with respect to one of the levels. It is good form to choose the level of the variable with the lowest chance, i.e. makes all of the odds ratios greater than 1. If a predictor variable is continuous, the odds ratio is the increase with change in one unit. So if the variable was age, the odds ratio would represent the relative risk in chance from one year to the next. It can be calculated many years at a time, but the original coefficient will have this interpretation.

Once a model has been fit, the next step is to determine the suitability of the model. There are three criteria that need to be verified: the significance of the model, the significance of each variable, and the goodness of fit of the model. The significance of the model determines whether the model does a significantly better job at explaining the variation in values of the outcome variable than the model of a horizontal line through the mean ($\hat{y} = \bar{y}$). If a model is significant it means that at least one of the explanatory variables is significant, each variable must be checked to determine if it adds to the strength of the model. Even if a model explains a significant amount of the variance it is possible that the wrong family of models is being used. This can be determined using goodness of fit testing and residual checking.

Testing The Model

For logistic regression the deviance plays the same role as does the Sums-of-Square Regression (SSR) for linear regression. It measures the amount of deviation explained by the model. The equation for deviance is:

$$D = -2\sum_i (y_i \ln\left[\frac{\hat{\pi}_i}{y_i}\right] + (1-y_i)\ln\left[\frac{1-\pi_i}{1-y_i}\right])$$

which is equivalent to

$$D = -2\ln(\frac{likelihood\ of\ the\ current\ model}{likelihood\ of\ the\ saturated\ model})$$

The saturated model is a model with exactly the same number of parameters as there are data points i.e. a perfect fit. Another important statistic is $G = D(for\ the\ old\ model) - D(for\ the\ new\ model)$. It is used when two models are being compared. Because G is a function of D and because of properties of the log function, G can be rewritten as:

$$G = -2\ln(\frac{likelihood\ of\ the\ old\ model}{likelihood\ of\ the\ new\ model})$$

When the sample is large, the statistic G has approximately a χ^2 distribution with p degrees of freedom, where p is the number of explanatory variables beyond that in the old model. When testing models, the first model is usually tested against $H_0: \hat{y} = \bar{y}$.

Two other related methods for determining whether a model is better than another is the Akaike Information Criterion (AIC) and the Schwarz Criterion (SC). They are calculated as follows:

$$AIC = -2loglikelihood + 2(k+s)$$

$$SC = -2loglikelihood + (k+s)\log\sum_j f_j$$

Here k is the total number of response levels minus 1 (2-1=1 for binary outcomes) and s is the number of explanatory variables, f is the frequency of the j th observed covariate pattern. Although these criteria determine a method for deciding if a model is a better choice than another, they base their decision on the number of variables and the number of response levels and do not follow a statistical distribution so they can not be tested. With all three statistics the lower the absolute value of the statistic the better the choice of model.

A fourth method for determining the fit of the model is the Score Test. The Score Test is a function of the first and second derivatives of the log likelihood function which has a χ^2 distribution. The Score statistic is:

$$Score = \mathbf{U}'(\hat{\gamma}_0)\mathbf{I}^{-1}(\hat{\gamma}_0)\mathbf{U}(\hat{\gamma}_0)$$

where $\mathbf{U}(\hat{\gamma}_0)$ is the vector of first partial derivatives of the log likelihood with respect to the parameter vector γ and $\mathbf{I}(\gamma)$ is the negative of the matrix of second derivatives of the log likelihood with respect to γ (or the expected value of the matrix). The Score statistic has a χ^2 distribution with r degrees of freedom where r is the number of restrictions imposed on γ by the null hypothesis.

Testing The Influence Of Explanatory Variables

To test the individual explanatory variables, a Wald's normal test (or Wald's χ^2 test) is used. The test statistic is

$$W = \frac{\hat{b}_j}{\hat{\sigma}(\hat{b}_j)}$$

where $\hat{b}_j$ is the parameter estimate for the j th explanatory variable and $\hat{\sigma}(\hat{b}_j)$ is the standard error of that estimate. Under the hypothesis that b_j is equal to zero W will

approximately follow the standard normal distribution. The χ^2 test statistic (the test used by SAS) is:

$$W^2 = \left[\frac{\hat{b}_j}{\hat{\sigma}(\hat{b}_j)}\right]^2$$

It is possible to calculate confidence intervals for the coefficients. These are calculated using a 100(1-α)% normal confidence interval, the bounds are:

$$\hat{b}_j \pm z(1-\frac{\alpha}{2})\hat{\sigma}(\hat{b}_j)$$

where $z(1-\frac{\alpha}{2})$ is the value from the standard normal distribution. Care should be taken in realizing the effect on the interpretation of the coefficient when confidence intervals are added. Even thought the confidence band is symmetric around the estimate, when transformed (as for the odds ratio) the result will be a skewed confidence interval on the odds ratio. For example if the value of the estimate is 2.094 with standard error 0.529, then the odds ratio will have a value of 8.1 but the 95% confidence interval will be (2.9,22.9).

Testing The Goodness Of Fit

One of the most important details in fitting a model is determining if the correct family of models is being tested. The test and estimations so far will only result in fitting the best model for the family of models that was selected to be tested. If the wrong family is chosen, the model may still be judged significant but will not model the data as well as a model chosen from a different family. This is called the goodness of fit of the model.

Two statistics which can facilitate this test are the Pearson χ^2 statistic and the Deviance Residual. Both are measures which are like the residuals measured in linear regression. These statistics are measured for each covariate pattern as opposed to each observation.

The equation for the Pearson χ^2 is:

$$r(y_j,\hat{\pi}_j)=\frac{y_j-m_j\hat{\pi}_j}{m_j\hat{\pi}_j\sqrt{1-\hat{\pi}_h}}$$

and the equation for the Deviance Residual:

$$d(y_j,\hat{\pi}_j)=\pm\left\{2\left[y_j\ln\left(\frac{y_j}{m_j\hat{\pi}_j}\right)+(m_j-y_j)\ln\left(\frac{m_j-y_j}{m_j(1-\hat{\pi}_j)}\right)\right]\right\}$$

where the sign is the same as $(y_j-m_j\hat{\pi}_j)$.

If $y_j=0$ then $d(y_j,\hat{\pi}_j)=-\sqrt{2m_j\left|\ln(1-\hat{\pi}_j)\right|}$

if $y_j=m_j$ then $d(y_j,\hat{\pi}_j)=\sqrt{2m_j\left|\ln(1-\hat{\pi}_j)\right|}$

where y_j is the number of events with the jth covariate pattern and m_j is the number of observations with the jth covariate pattern. Let J be the number of distinct covariate patterns. Then both the Pearson χ^2 and the Deviance Residual follow a χ^2 distribution with $J-(p+1)$ degrees of freedom where there are $p+1$ parameters. A necessary condition for these statistics to follow a χ^2 distribution is that J is not close to n (the number of observations). J will be close to n when the distribution is n-asymptotic, n-asymptotic means that new observations will have different covariate patterns then the old observations (this means that as n increases, J increases). The distribution is said to be m-asymptotic if increases in the number of observations leads to increase in the number of observations in already existing covariate patterns (increasing the value of m_j).

Hosmer and Lemeshow (Hosmer, Lemeshow 1989) devised a statistic which is always m-asymptotic and therefore can always test the goodness of fit of a model. The method for calculating their statistic divides the covariate patterns into 10 groups based on either (roughly) equal sizes or fixed values of the estimated event probability. The observations are grouped in increasing order of their estimated event probability. Covariate patterns are not divided if their population straddles a cut point, and if the last group contains less than half the number it should, it is collapsed into the second last group.

The Hosmer Lemeshow goodness of fit statistic is:

$$\hat{C} = \sum_{k=1}^{g} \frac{(o_k - n_k \overline{\pi}_k)^2}{n_k \overline{\pi}_k (1 - \overline{\pi}_k)}$$

where n_k is the number of observations in the k th group

g is the number of groups

$$o_k = \sum_{j=1}^{c_k} y_j$$

c_k is the number of covariate patterns in the j th group

$\overline{\pi}_k = \sum_{j=1}^{c_k} \frac{m_j \hat{\pi}_j}{n_k}$ the weighted mean of the group.

This statistic follows a χ^2 distribution with $g-2$ degrees of freedom. This statistic will determine if a model fits well or not. If the value of the statistic is high (it has a low p value) then the model does not fit properly. In addition to this statistic, there are other methods to help determine the goodness of fit. Graphical analysis of the Pearson χ^2 and Deviance Residuals aids in detected problems with the model. If a pattern emerges in the residuals it is a sign that the model is not fitting the data properly. This method is qualitative rather than quantitative, it requires a judgment rather than providing a testable number.

Covariate Pattern Analysis

There are several statistics available to help determine if an observation (or covariate pattern) is having a strong effect on the estimated coefficients for the explanatory variables. If one covariate pattern is having a strong effect on the model it may mean that the rest of the covariate patterns are not being modeled properly. Five statistics that are used by SAS are: DFBETAs, C, CBAR. DIFDEV, and DIFCHISQ (each computed for each covariate pattern).

The DFBETA statistics are used to calculate the standardized difference in the estimates for a parameter due to eliminating the observation (covariate pattern) from the data. This helps determine if an observation is having too strong an influence on the estimated coefficient for that response variable. This statistic produces a value for each explanatory variable by each observation. The calculation of the DFBETAs are:

$$\text{DFBETA}i_j = \frac{\Delta_i \mathbf{b}_j^{\text{l}}}{\hat{\sigma}(b_i)}$$

where $i = 1..p$ is the i th observation of the matrix of parameters $\mathbf{b}$

$\hat{\sigma}(b_i)$ is the standard error of the i th element of $\mathbf{b}$

$$\Delta \mathbf{b}_j^{\text{l}} = \frac{w_j(r_j - n_j \hat{p}_j)}{(1 - h_{jj})\hat{\mathbf{V}}_b \begin{pmatrix} 1 \\ \mathbf{x}_j \end{pmatrix}}$$

where w_j is the weight of the j th observation

r_j is the number of events for the j th observation

n_j is the number of trials for the j th observation

$\hat{p}_j$ is the estimate of p_j evaluated by $\mathbf{b}$

h_{jj} is the j th diagonal element of the hat matrix

$\hat{\mathbf{V}}_b$ is the estimated covariance matrix of $\mathbf{b}$

C and CBAR are two diagnostic statistics which measure the influence of an observation on the matrix of parameters $\mathbf{b}$. They take into account the effect of an observation on all the estimates at the same time, unlike the DFBETAs which only looked at the estimates one at a time.

$$C_j = \frac{\chi_j^2 h_{jj}}{(1-h_{jj})^2}$$

$$\overline{C}_j = \frac{\chi_j^2 h_{jj}}{1-h_{jj}}$$

where χ_j^2 is the Pearson χ^2 residuals for the j th observation.

These statistic can be used to look for outliers.

DEFCHISQ and DIFDEV are statistics that look at the effect of one observation on the value of the Pearson χ^2 residuals and the Deviance Residuals. This can be used to detect observations which are not well fitted by the model. DIFCHISQ and DIFDEV are computed using:

$$\Delta_j \chi^2 = \frac{\overline{C}_j}{h_{jj}}$$

$$\Delta_j D = d_j^2 + \overline{C}_j$$

where d_j is the deviance residual for the j th observation.

These five statistics aid in determining if any of the observations are not fitting the model well or are having too big an influence on the estimates of the parameters.

Hypothesis Testing

It is also possible to test linear hypotheses on the estimated coefficients. These tests can determine if a hypothesized reduced model is a possible candidate for the true model. The model must be of the form:

$$H_0: \mathbf{L}\beta = \mathbf{c}$$

where $\mathbf{L}$ is the matrix of coefficients in the linear hypotheses, β is the vector of estimated coefficients and c is the vector of constants. The statistic, which has a χ^2, is:

$$\chi^2_W = (\mathbf{L}\beta - \mathbf{c})' \left[\mathbf{L}\hat{\mathbf{V}}(\hat{\beta})\mathbf{L}'\right]^{-1} (\mathbf{L}\hat{\beta} - \mathbf{c})$$

where $\hat{\mathbf{V}}(\hat{\beta})$ is the estimated covariance matrix. This statistic has a χ^2 with r degrees of freedom, where r is the rank of the $\mathbf{L}$ matrix.

Summary

Logistic regression is a powerful tool for fitting binary response models. The estimated coefficients have a useful interpretation in that the odds ratio and the distribution of several statistics allow us to determine how good the model fits. Attention should be paid to the fact that this is only a statistical method for finding the best model with the given data. Variables which are known to be important from other sources should not be sacrificed on the basis that the data from one experiment shows that the variable is not statistically important. Models should be built both by using logistic regression and through general knowledge of the field of research.

2.2 Selection Algorithm

There are many forms of regression selection methods, these methods select variables which should be included in the model. When a regression selection method is not used the model must be selected beforehand. These methods allows the algorithm to test which variables are the best suited to create a model of the dose-response.

Four forms of regression selection method are: stepwise, forward, backward, and best subset. The only two used in this analysis are the forward and best subset analysis. Forward regression tests each variables significance as if it were the only variable in the model, then it selects the next best variable and includes it in the model. This is done until there are no other variables that meet the entrance criteria. This is the opposite of a

backwards regression, where the variables are selected based on how much is lost when the variable is removed from the model. Best subset calculates the best grouping of a certain number of variables (in this case two). Forward regression was used when the model only selected two variables. When the forward method selected more than two variables, the best subset method was applied to determine which two variable model was the best. Stepwise selection is the most frequently encountered method, but will not be pursued here.

For the forward selection method of logistic regression the entrance criteria was $\alpha = 0.15$, this is a higher α than usually used to test significance ($\alpha = 0.05$), because we do not want to exclude variables that when combined with other variables become significant at the 0.05 level. This is one drawback of forward selection method, it looks only at the variables one at a time, as opposed to groups at a time (like best subset). Keeping the α rate low could cause the regression to miss variables that are significant when used with other variables, but by themselves do not appear to add greatly to the model. Keeping the level high makes it more likely to keep variables that are significant when used in combination with other variables.

2.3 SAS Output Interpretation

The following data was collected from an experiment where rats were subjected to radiation at different: dose levels, concentration, dose rates and exposure conditions. This data set was later excluded from the study because it dealt with concentration rate, which was unique to this study. This made it difficult to interpret the results in the same manner as for the other experiments. The researchers were interested in determining how many of the rats developed cancer from the exposure. A total of 3990 rats were used of which 1290 were controls. The covariate patterns are presented in Table 2.3.1.

Table 2.3.1 Rat data set

Exposure Group	Dose	Concentration (exposure rate)	Dose rate	Dose times dose rate	Number of animals	Number of lung cancers	Exposure conditions
(WLM)	(mSv)	(WL)	(mSv/h)	(mSv^2/h)			
3	30	0.02	1.18E-03	3.53E-02	1290	12	none (controls)
25	250	2	1.18E-01	2.94E+01	500	3	2106 hrs over 18 months
25	250	100	5.88	1.47E+03	500	11	42 hours over 4 months
25	250	150	8.82	2.21E+03	500	14	28 hours over 6 months
50	500	100	5.88	2.94E+03	500	19	82 hours over 6 months
50	500	115	6.762	3.38E+03	300	11	75 hours over 7 weeks
200	2000	1200	70.56	1.41E+05	200	28	29 hours over 7 weeks
500	5000	1200	70.56	3.53+E05	100	28	70 hours over 8 weeks
1000	10000	1200	70.56	7.06E+05	100	35	142 hours over 8 weeks

The following SAS program was used to test the model based on concentration and dose. These variables were chosen only for the purpose of illustrating the type of output generated by SAS. The output contains test statistics to test all the criteria for testing a model. Comments on the code are written in brackets beside the lines:

```
data ratdata;                                          (the data set created by SAS)
input exposure dose conce doserate dosetime numbera numberc exhr exmth;   (listing the variables to be inputted)
cards;                                                 (inputs the data)
3     30     0.02   1.18E-03   3.53E-02   1290   12   0      0
25    250    2      1.18E-01   2.94E+01   500    3    2106   18
25    250    100    5.88       1.47E+03   500    11   42     4
25    250    150    8.82       2.21E+03   500    14   28     6
50    500    100    5.88       2.94E+03   500    19   82     6
50    500    115    6.762      3.38E+03   300    11   75     7
200   2000   1200   70.56      1.41E+05   200    28   29     7
500   5000   1200   70.56      3.53E+05   100    28   70     8
1000  10000  1200   70.56      7.06E+05   100    35   142    8
;
run;                                                   (processes the dataset)
proc logistic data=ratdata                             (SAS will do a logistic regression
                                                       using the data from above)
model numberc/numbera=dose conce / influence lackfit;  (the model is the rate of cancer
                                                       explained by dose and concentration
                                                       it also produces the lack of fit
                                                       analysis and 5 influence variables
                                                       mentioned in the text)
units dose=250 conce=10;                               (calculates the odds ratios for steps
                                                       of 250 for dose and 10 for
                                                       concentration)
test1: test dose=conce;                                (tests to see if the estimated
                                                       coefficient for dose is equal to the
                                                       estimated coefficient for
                                                       concentration)
output out=ratrslt dfbetas=dfbeta0 dfbetas=dfbeta1 dfbetas=dfbeta2 c=c   (outputs several statistics to a dataset
cbar=cbar difchisq=difchisq difdev=difdev h=h reschi=pearsons            names ratrslt)
resdev=resdev;
run;
proc gplot data=WORK.RATRSLT;                          (prints off several graphs from the
```

```
plot pearsons*dose;
plot pearsons*conce;
plot resdev*dose;
plot resdev*conce;
/*plot dfbeta0*intercpt;*/
plot dfbeta1*dose;
plot dfbeta2*conce;
plot c*dose;
plot c*conce;
plot cbar*dose;
plot cbar*conce;
plot difdev*dose;
plot difdev*conce;
plot difchisq*dose;
plot difchisq*conce;
run;
```

dataset ratrslt)

Output For Testing The Model

Model Fitting Information and Testing Global Null Hypothesis BETA=0

Criterion	*Intercept Only*	*Intercept and Covariates*	*Chi-Square for Covariates*
AIC	*1351.080*	*1099.526*	.
SC	*1357.372*	*1118.400*	.
-2LOGL	*1349.080*	*1093.526*	*255.554 with 2 DF (p=0.0001)*
Score			*491.483 with 2 DF (p=0.0001)*

The results from SAS show that the model explains a significant amount of the variation from the mean. The value for the statistic G (or -2LOG L) =255.554 (2 degrees of freedom) which is significant (p=0.0001). The Score test agrees with this finding, the value of the Score test is 491.483 (2 degrees of freedom) which is also significant (p=0.0001). The AIC and SC criteria are smaller for the model fitting the intercept and covariates rather than just the intercept, but the criteria are usually used to test models with different explanatory variables, not just the intercept. If this data set had been used to fit a different model then checking the AIC and SC values would have been appropriate.

Output For Testing The Variables

Analysis of Maximum Likelihood Estimates

Variable	*Parameter Estimate*	*Standard Error*	*Wald Chi-Square*	*PR > Chi-Square*	*Standardized Estimate*	*Odds Ratio*
INTERCPT 1	*-4.0857*	*0.1291*	*1000.9019*	*0.0001*	.	.
DOSE	*0.00014*	*0.000035*	*15.9642*	*0.0001*	*0.132508*	*1.000*
CONCE	*0.00180*	*0.000222*	*66.0862*	*0.0001*	*0.345668*	*1.002*

Both variables, *dose* and *concentration*, are significant. The variable *dose* had a parameter estimate of 0.00014 and it's Wald χ^2 value was 15.9642 which is significant ($p = 0.0001$). *Concentration* had an estimate of 0.00180 and a Wald χ^2 value of 66.0862 which is significant ($p = 0.0001$). The odds ratio computed for *dose* is 1.000 (but this is in fact $e^{0.00014} = 1.00014$, rounded to three decimal places) and for *concentration* is 1.002. These odds ratios represent the increase in risk for increases in one unit of dose and one unit of *concentration*. *Dose* has a range of nearly 10000 and *concentration* has a range of only 1200.

Conditional Odds Ratio

Variable	*Unit*	*Odds Ratio*
DOSE	*250.0*	*1.036*
CONCE	*10.0000*	*1.018*

Odds ratios, shown above, were calculated using bigger increments and it was determined that an increase in dose of 250 units increased the risk of getting cancer by 3.6% and an increase of 10 units of concentration resulted in an increase of 1.8% in the chance of getting cancer.

Output For Testing The Goodness Of Fit

Hosmer and Lemeshow Goodness-of-Fit Test

		EVENT		*NO EVENT*	
Group	*Total*	*Observed*	*Expected*	*Observed*	*Expected*
1	*1290*	*12*	*21.42*	*1278*	*1268.58*
2	*500*	*3*	*8.59*	*497*	*491.41*
3	*500*	*11*	*10.21*	*489*	*489.79*
4	*500*	*19*	*10.57*	*481*	*489.43*
5	*300*	*11*	*6.51*	*289*	*293.49*
6	*500*	*14*	*11.16*	*486*	*488.84*
7	*400*	*91*	*92.54*	*309*	*307.46*

Goodness-of-fit Statistic = 18.777 with 5 DF (p=0.0021)

The Hosmer and Lemeshow test rejects the model as a well-fitting model. This is determined by the p value; this value should be larger than 0.05 for the model not to be rejected, but the p value for this model is only 0.0021. It has determined that using dose and concentration alone is not an appropriate model even though both the model and the coefficients were significant. It appears the model has overestimated the incidence of cancer in the lowest two and highest group and has underestimated the amount of cancer in the other four groups.

Output For Covariate Pattern Analysis

Case Number	*Covariates*		*Pearson Residual*	*Deviance Residual*
	DOSE	*CONCE*	*Value*	*Value*
1	*30.0000*	*0.0200*	*-2.0520*	*-2.2364*
2	*250.0*	*2.0000*	*-1.9231*	*-2.2197*
3	*250.0*	*100.0*	*0.2486*	*0.2456*
4	*250.0*	*150.0*	*0.8611*	*2.3602*
5	*500.0*	*100.0*	*2.6209*	*2.3602*
6	*500.0*	*115.0*	*1.7781*	*1.6206*
7	*2000.0*	*1200.0*	*-0.8585*	*-0.8755*
8	*5000.0*	*1200.0*	*1.2430*	*1.2130*
9	*10000.0*	*1200.0*	*-0.4715*	*-0.4736*

Although the Pearson and Deviance residuals do not exhibit a pattern (the first thing to examine) the residuals do have some large values. This may indicate the model may be having problems modeling the effect of some covariates.

Case Number	*INTERCPT Dfbeta Value*	*DOSE Dfbeta Value*	*CONCE Dfbeta Value*
1	*-1.8752*	*-0.0425*	*0.99840*
2	*-0.8394*	*-0.0671*	*0.4747*
3	*0.1077*	*-0.00513*	*-0.0469*
4	*0.3711*	*-0.0455*	*-0.1330*
5	*1.1621*	*0.0311*	*-0.5683*
6	*0.5708*	*0.00352*	*-0.2669*
7	*0.1887*	*2.8909*	*-3.4787*
8	*-0.0460*	*-0.1263*	*0.5024*
9	*0.1145*	*-4.5581*	*1.6588*

The Dfbetas for the intercept, *dose*, and *concentration* measure the amount that each covariate pattern has influenced the parameter estimate. For the intercept Dfbeta the covariate patterns with the smaller values of *dose* and *concentration* are having more of an influence on the parameter estimates than the covariate patterns with the larger values. The overall breakdown of the values does not look worrisome. However, the results in the *dose* Dfbeta may be disconcerting. The parameter is estimated using only the covariate patterns with *dose* equal to 2000 and *dose* equal to 10000 (case 7 and 9). This may be the problem with the model fitting seen in the Pearson and Deviance residuals above.

Case Number	*C Value*	*CBAR Value*
1	*3.5165*	*2.2810*
2	*0.7076*	*0.6077*
3	*0.0117*	*0.0101*
4	*0.1428*	*0.1226*
5	*1.3605*	*1.1634*
6	*0.3291*	*0.3006*
7	*16.4376*	*3.1317*
8	*0.7479*	*0.5512*
9	*33.0422*	*2.6016*

C and CBAR measure the combined influence on the parameters by all the covariates in one covariate pattern. It shows that the covariate patterns with dose of 2000

and 10000 are again having an influence on the overall parameter estimations, which is not surprising knowing how much of an effect these two covariate patterns are having on the dose parameter estimate.

Case Number	*DIFDEV Value*	*DIFCHISQ Value*
1	*7.2825*	*6.4918*
2	*5.5348*	*4.3061*
3	*0.0704*	*0.0719*
4	*0.8093*	*0.8640*
5	*6.7338*	*6.0324*
6	*2.9269*	*3.4622*
7	*3.8983*	*3.8688*
8	*2.0227*	*2.0963*
9	*2.8259*	*2.8239*

DIFDEV and DIFCHISQ are two statistics which calculate the difference in the Pearson and Deviance residuals after eliminating a covariate pattern from the data set, a large value implies that the covariate pattern is not well modeled, whereas a small value implies that the covariate pattern is well fitted. This shows that covariate patterns 1 and 5 (the control and the covariate pattern with dose 500 and concentration 100) are the least well explained covariate patterns. On the other hand, the elimination of the third or fourth covariate pattern would not have a strong effect on the residual values.

Output For Hypothesis Testing

Linear Hypotheses Testing

Label	*Wald Chi-Square*	*DF*	*Pr>Chi-Square*
TEST1	*44.7590*	*1*	*0.0001*

This test was used as an example to show what the output for the hypothesis testing looks like. It is not common that two parameter estimates are tested to see if they are equal. In this case we reject the null hypothesis that the parameter for dose is equal to the parameter for concentration, since Pr>Chi-Square is 0.0001 (i.e. the p-value is quite small).

Conclusion

Overall, although the model could explain some of the data well, the goodness of fit of the model was poor and therefore a different family of distributions must be examined to try and determine a better fitting model than the one considered in this example.

2.4 Fitting Models

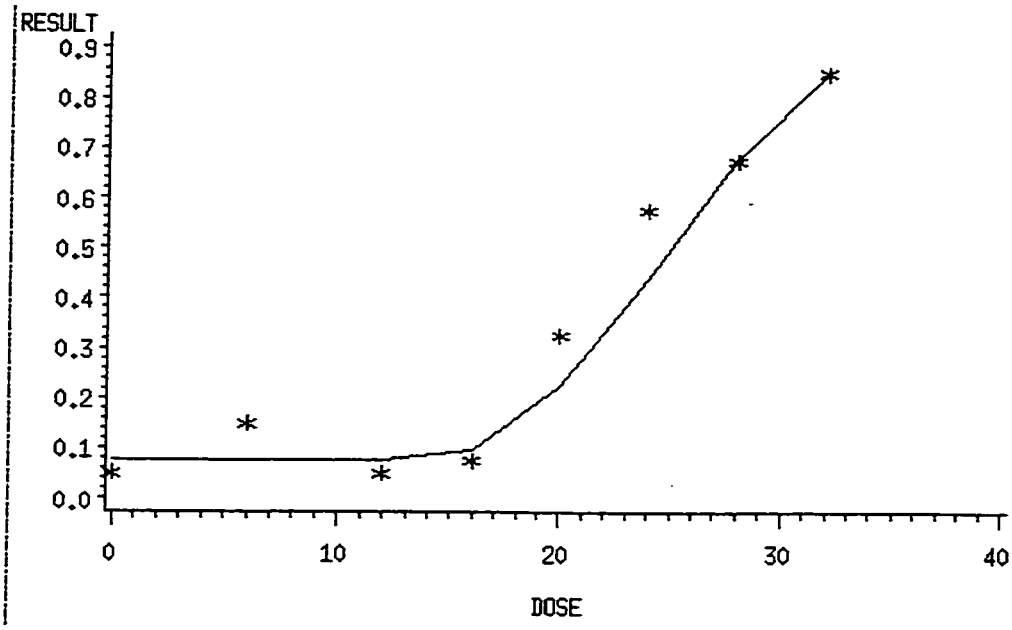
Three different models will be discussed throughout this thesis: Least Squares Regression, Logistic Regression, and Knee Logistic Regression. Least Squares Regression is the most common and simple form of regression model. This model finds a straight line that minimizes the square of the distance from the regression line to the data points. There are several shortcomings to this type of model when dealing with cancer rates. The Logistic Regression model is frequently used when modeling rates or proportions, i.e. values between 0 and 1. The Knee Logistic Regression is the same model as the Logistic Regression except that it has an added feature that allows for logistic model to have different dependence on dose up to and beyond the threshold. This feature is the key to the model being able to detect a threshold effect in the data.

Each model will be discussed using the data set below to illustrate the strengths and weaknesses of each model. The data set was constructed from the following equation:

$$Prob(y=1|dose)=\frac{1}{1+e^{-(-2.5+0.25knee15)}}$$

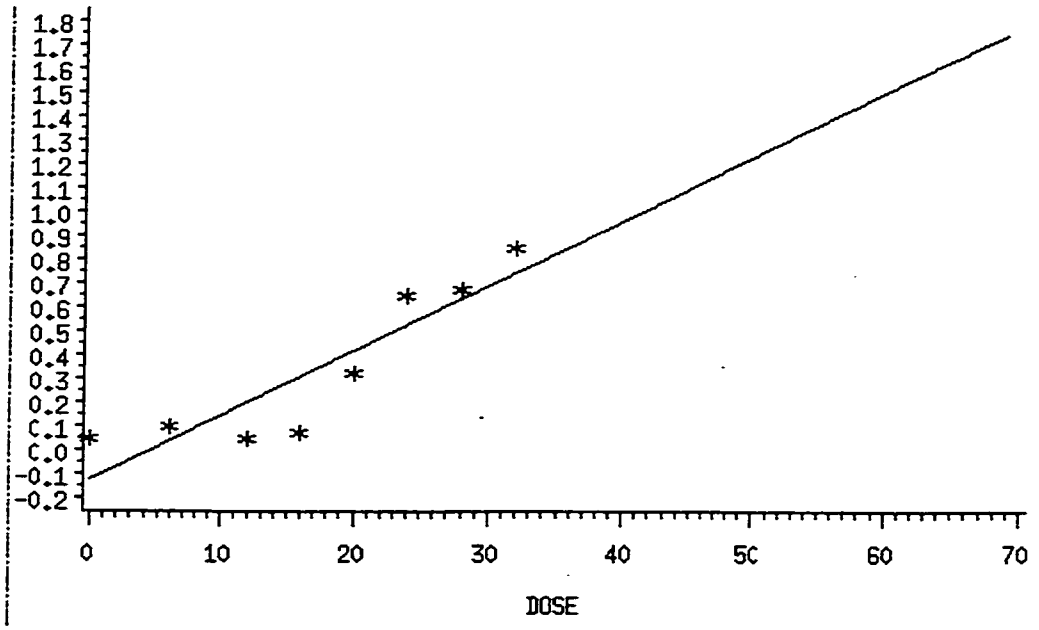
Dose	knee15 max(0,dose-15)	Group Size	Number with Cancer
0	0	40	2
6	0	40	6
12	0	40	2
16	1	40	3
20	5	40	13
24	9	40	23
28	13	40	27
32	17	40	34

Graph 2.4.1



The line represents Prob(y=1|dose) of the model from which the points were generated, the points from data simulated from this model.

Graph 2.4.2: Least Squares Regression



This graph demonstrates the classic problem with Least Squares Regression on incidence data. The model cannot be employed for models that are ratios.

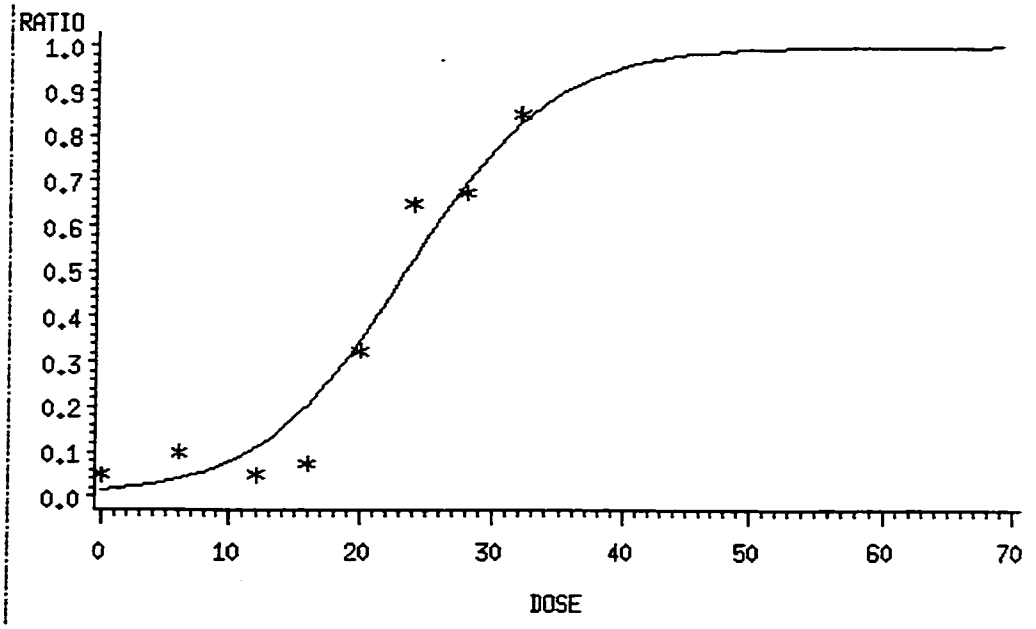
Least Squares Model

$$Prob(y = 1 | dose) = 0.120205 + 0.027077 dose$$

The least squares model is inappropriate for modeling cancer incidence. This type of model cannot account for the upper and lower limits on the fraction of subjects that can develop cancer, as can be seen in the graph above, when a dose of 70 units is taken the incidence of cancer is nearly 180%. It also says that the baseline cancer rate is -12%.

Another problem with the Least Squares model is that for this approach the distribution of the error is supposed to be according to a normal distribution. With ratios, the error is distributed using a binomial distribution. The use of an incorrect error distribution and inadequate class of function means that the results are totally unreliable.

Graph 2.4.3: Logistic Regression



This graph show the problem with logistic models that occurs at low doses. It cannot account for the a threshold and therefore underestimates the baseline cancer rate.

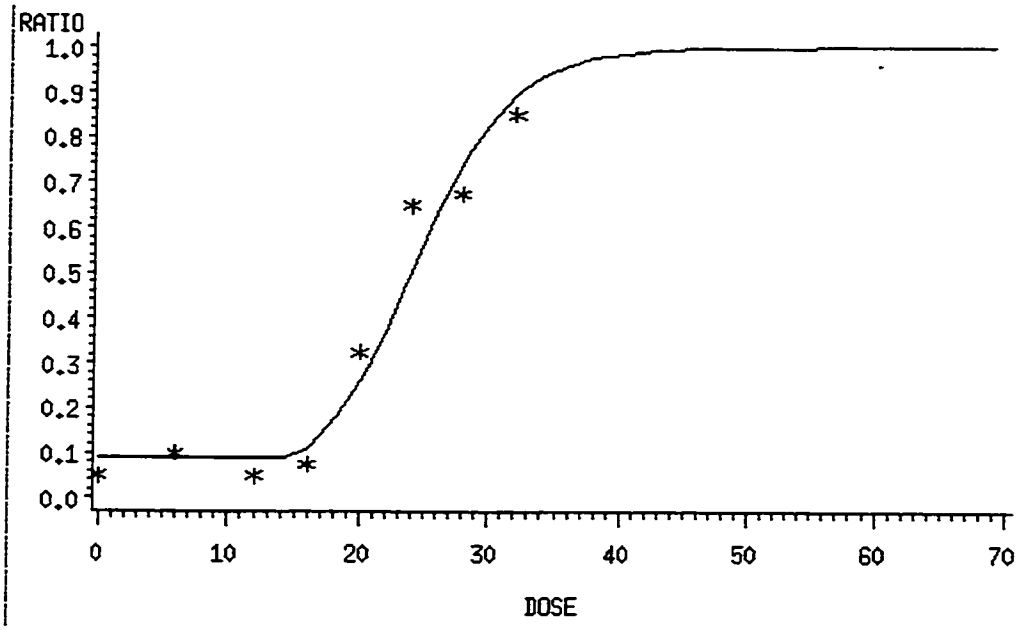
Logistic Regression Model

$$Prob(y=1|dose)=\frac{1}{1+e^{-(-4.2761+0.1828dose)}}.$$

This model is more appropriate than the least squares model for incidence data, but the limitation of not having a knee forces the model to underestimate the baseline cancer rate and immediately predicts an effect from dose at doses below 15. These two results compound each other to make it look like as if dose is having an effect at low levels. In this constructed model we know, however that dose has no effect until at least 15 units. This is a feature of the logistic curve that renders it difficult to use when trying to extrapolate models from high doses to regions with lower doses. One thing to note is the model does not allow values outside of 0 or 1.

This type of model is said to be "linear in the exponent", meaning that the exponent: $-4.2761+0.1828dose$, is a linear model, like the one used in Least Squares regression.

Graph 2.4.4: Knee Logistic Model with One Knee



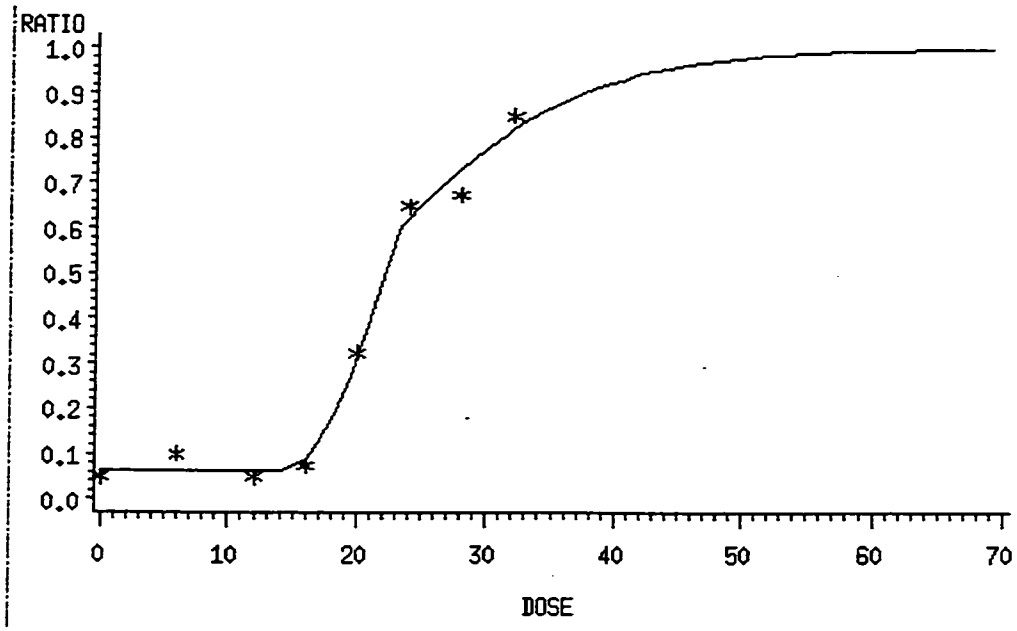
This model correctly captures the threshold up to 15 units of dose.

1 Knee Logistic Regression

$$Prob(y = 1 | dose) = \frac{1}{1 + e^{-(-2.3421 + 0.2618 knee15)}}$$

This model is the "closest" of the three models to the distribution that the data was modeled from. It correctly determines that *knee15* is the best variable for fitting the model. The first thing to notice in the graph is that dose does not have an effect below 15 units. This is how a threshold at dose 15 would look. The estimates of the coefficients are not correct due to the fact that the observations have been sampled from a binomial distribution to mimic the natural fluctuation of empirical cancer rates.

Graph 2.4.5: Knee Logistic Model:



This model correctly captures the threshold up to 15 units of dose. This example does have overfitting which will be discussed later in the thesis.

2 Knee Logistic Regression

$$Prob(y=1|dose)=\frac{1}{1+e^{-(-2.6946+0.3847knee15-0.2587knee23)}}$$

This model was the result of a forward selection logistic regression. It has picked up an additional variable, *knee23*, this is due to the sampling of data points from a binomial distribution to mimic fluctuation in natural occurring cancer rates. At a dose of 15 the model has a linear effect of 0.3847. This type of model allows dose to have different effects at different dose levels. The model correctly captures the fact that there is no effect from dose below 15 units, it also gives a much better estimate of the baseline cancer rate. It does, unfortunately, suffer from some overfitting. The overfit is the variable *knee23* is used to correct the overestimation of the coefficient of *knee15*. The problems surrounding overfitting will be discussed later in the thesis.

Models To Be Used In This Thesis

Clearly we will model cancer incidence using logistic functions. The goal is to decide on a suitable class of models for low dose radiation threshold analysis. There are 4 possible logistic functions to consider:

Logistic, no knees

$$Prob(y=1|dose)=\frac{1}{1+e^{b_0+b_1 dose}} \qquad \textbf{(2.4.1)}$$

This model is the correct model if there is no threshold effect and the maximally tolerated dose is not approached during the experiment. The model is based on the error terms being binomially distributed which is correct for this type of data.

Logistic, 1 knee

$$Prob(y=1|dose)=\frac{1}{1+e^{b_0+b_1 kneeX}} \qquad \textbf{(2.4.2)}$$

This model will capture the existence of a threshold at the low dose or the effect of the maximally tolerated dose being exceeded (i.e. a drop in cancer incidence at the higher dose levels). In a well designed experiment (one where the maximally tolerated dose is not exceeded) the 1 knee model should fit best if there is evidence to support the non-linear threshold hypothesis in the data.

Logistic, 2 knee

$$Prob(y=1|dose)=\frac{1}{1+e^{b_0+b_1 kneeX+b2 kneeY}}$$

This model is best suited when there exists both a threshold and there is data approaching and beyond the maximally tolerated dose. This will be reflected in a rise when the lower threshold has been surpassed and a drop when the maximally tolerated dose has been surpassed.

Logistic, 3+ knees

$$Prob(y = 1 | dose) = \frac{1}{1 + e^{b_0 + b_1 kneeX + .. + b_n kneeZ}}$$

This model will begin to display overfitting. Overfitting is when a model fits the exact data points rather than trying to find a pattern within the data. There is no reason to believe that three knees should be required in order to fit a model for the type of data encountered in this thesis. Therefore models from this family will not be used for analysis.

Chapter 3

The Algorithm

3.1 Data Set Construction

The first step to the algorithm is to create a new set of variables, called the knee variables. These variables represent what would happen in the data set if there were a knee at a certain point. For example, the variable *knee21*, would be 0 for all doses up to 21 and the true dose minus 21 for doses over 21. This can be seen in the following two tables which show a data set before the addition of the knee variables and after the addition of three variables, *knee21*, *knee25*, and *knee30*. This is a simulated data set used only for the purpose of demonstrating certain aspects of the algorithm.

Original Data Set		
Number	Cancer	Dose
40	0	0
40	0	15
40	12	22
40	10	30
40	39	35

New Data Set					
Number	Cancer	Dose	Knee21	Knee25	knee30
40	0	0	0	0	0
40	0	15	0	0	0
40	12	22	1	0	0
40	10	30	9	5	0
40	39	35	14	10	5

This new data set now allows for a model to be constructed using a threshold at 21, 25, or 30 or a maximally tolerated dose at 21, 25, or 30 or a model with no threshold. For the purposes of this thesis, knee variables were included in each data set at the following levels of dose: 0.01, 0.1, 0.5, 1 and every odd number up to 53 and then from 60 to 140 in steps of 10. This allows the algorithm to detect a threshold at any one of the values for which a variable was created. These new data sets have a much larger family of models at their disposal than do unmodified data sets.

Stepwise Logistic Regression

The next step is to do a stepwise logistic regression on the new data set to determine if the new variables generate a better model than the model created using only dose. This was described in the previous section. To recap, a forward logistic regression takes the most significant variables from a data set to create a model. Any two logistic models can be compared to each other using the log likelihood generated by the model. The likelihood represents the probability of the observed data as a function of the unknown parameters. A transformation of the ratio of the likelihoods of two models follows a χ^2 distribution. Statistically speaking, this tells us with what probability the newer model is a better fit than the older model.

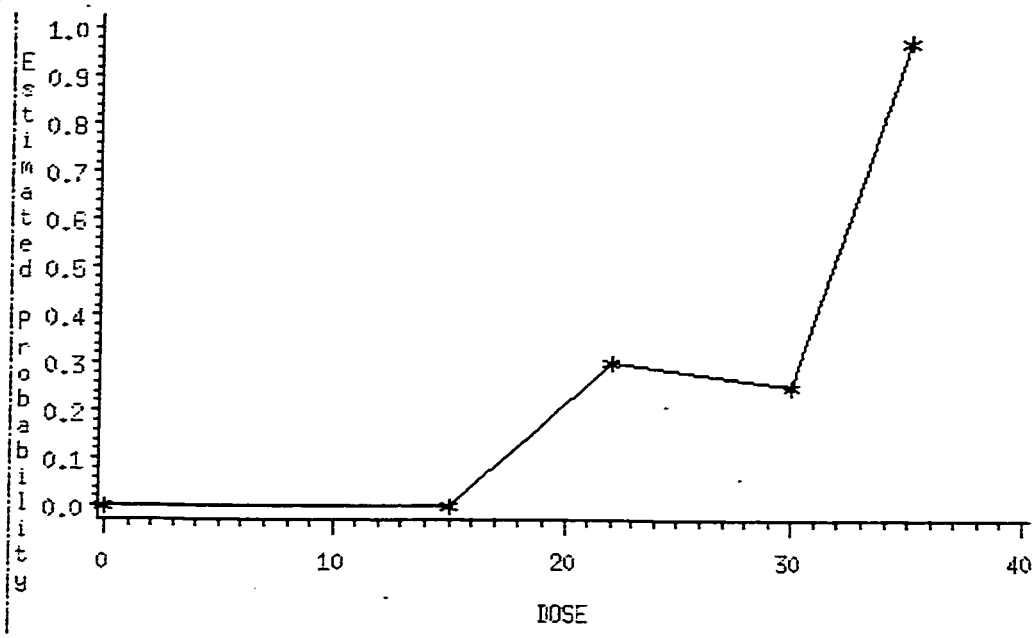
The algorithm has a stopping mechanism that only allows the best two variables into the model, this reduces the chance of overfitting. Overfitting is when the model has such a large choice of variables that it can match points point by point as opposed to looking for a general trend in the data. For example, a using the data set described above, it is very easy to overfit.

When the new data set above is examined by a logistic regression, it results in the following model:

$$Prob(y=1|dose)=\frac{1}{1+e^{-(-9.4202+8.8572knee21-13.7669knee25+6.1465knee30)}}$$

Although not necessarily obvious when we look at the equation, the overfit does appear when we look at graph 3.1.1.

Graph 3.1.1



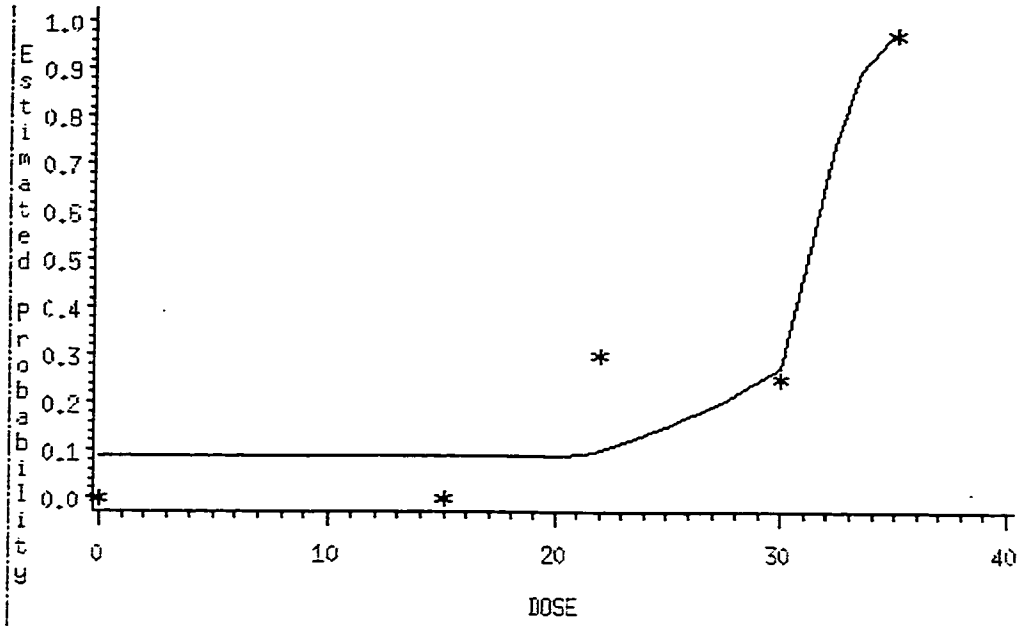
Overfitted model of example data.

It is not likely that radiation affects cancer incidence 4 different ways, so this model would be dismissed as overfitting the model. Using only the best two variables we get the model:

$$Prob(y=1|dose)=\frac{1}{1+e^{-(-2.3339+0.15knee21+0.7795knee30)}}$$

This model gives graph 3.1.2. It is not much better due to the small number of data and the variables, but it does demonstrate the calming effect of only having 2 variables.

Graph 3.1.2



Fit of the example model using only 2 variables.

3.2 Properties of the Algorithm

The following section illustrates the difficulty with improperly placing groups of animals at different levels. The main concern of those who do not agree with the LNT hypothesis is that the extrapolation of incidence rates from the higher dose levels do not properly take into account of the nature of the radionucleotide at lower levels.

Using a fictitious radionucleotide as an example it will be shown that if data is only collected at very high dose levels that the interpretation of the model at low dose rates can be quite wrong. The example will also show how difficult it is to get a significant difference from the usual logistic model even with well placed observations.

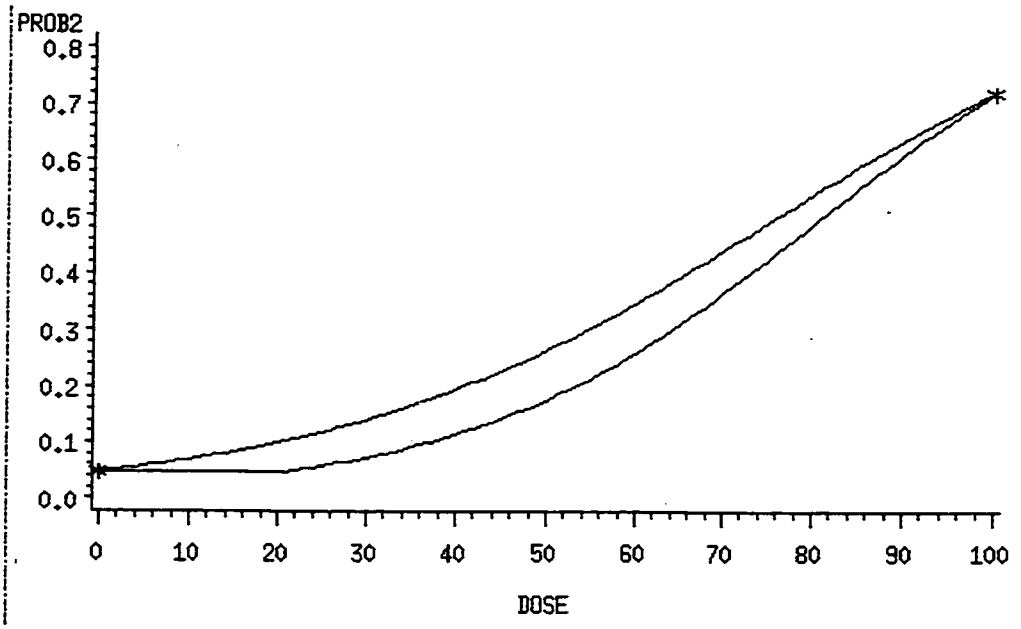
The problem with incorrectly spacing observations is that the weight of the model is largely allocated to the places with the most animals. This feature in turn can render the model completely useless at places other than where the observations were taken. This

means that researchers would not be able to extrapolate (or intrapolate) from those points to where they desire to draw inferences.

The example being used has an intercept coefficient of -3, a dose coefficient of 0.05, a knee at 21 units, a maximally tolerable dose of 100, and 500 animals. Several different arrangements of animals at dose levels are tested to see what effect on the model the placement has.

The first two examples show what happens with data that is acquired at doses that are too high and too low. The three examples after that show exactly how different placements affect the significance of the difference between models.

Graph 3.2.1



The bottom line represents the true dependency of the data on dose. The top line the fitted model.

Example 1

The "Classic" case of high dose extrapolation. In this example 250 animals are used as controls and the remaining 250 animals are given a dose of 100. This is a

simplified version of what happens when a high dose experiment is extrapolated through points of lower doses. The model selected by stepwise logistic regression is the following:

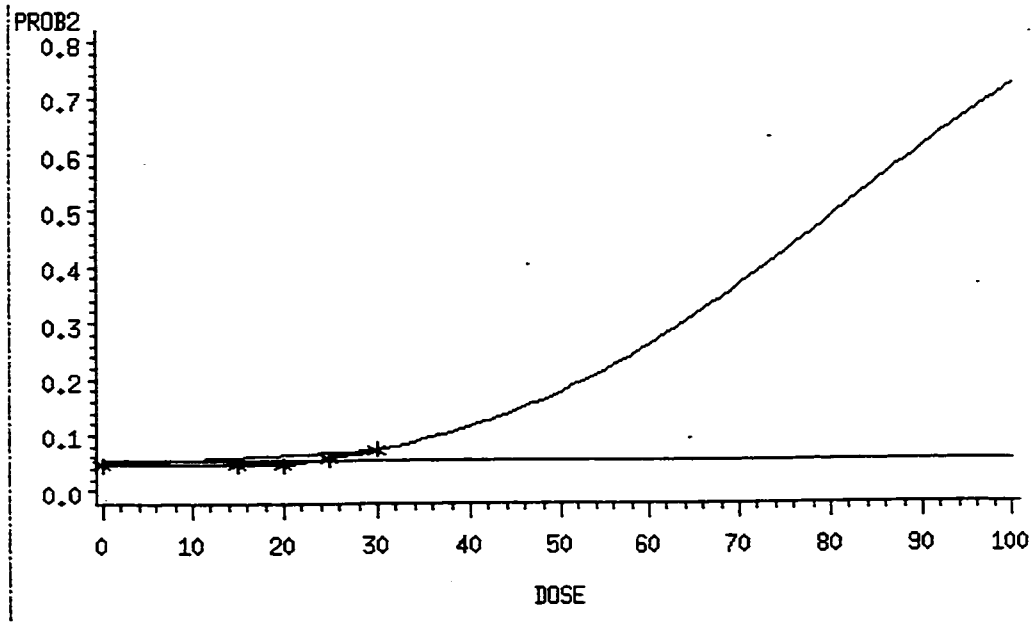
$$Prob(y=1|dose)=\frac{1}{1+e^{-(-3+0.0395dose)}}$$

The coefficient on the variable *dose* is significant at the 0.0001 level. The conclusion of this model is that there is no threshold. This is incorrect since the data was, in fact, constructed with a threshold up until a dose of 21 units. The reason that this happens is that there is no way for the program to pick up any other model than the usual no knee model since there are no data points to support it.

This model leads to a severe overestimation of the radionucleotide's effect at low doses when a knee effect is the true relationship. At a dose of 23 units, the model overestimates the effect by 115%. This is characteristic of the entire model. The graph of the fit model and of the actual model can be seen in graph 3.2.1.

This example is a good indication with the problems of relying on measurements made at high doses to determine the effect at lower doses.

Graph 3.2.2



The top line is the true relationship of the data. The bottom line is the fitted model.

Example 2

This is an example of what happens when higher dose levels are excluded from the analysis. In this example 100 animals are allocated to each of the following dose levels: 0 (controls), 15, 20, 25, and 30. This situation is the opposite of that in example 1. In order to avoid wasting any animals on higher doses (which are known to cause cancer), all the animals were allocated to the lower doses. Since the effect of the radionucleotide is minimal at low doses the model fails to pick up any significant variables:

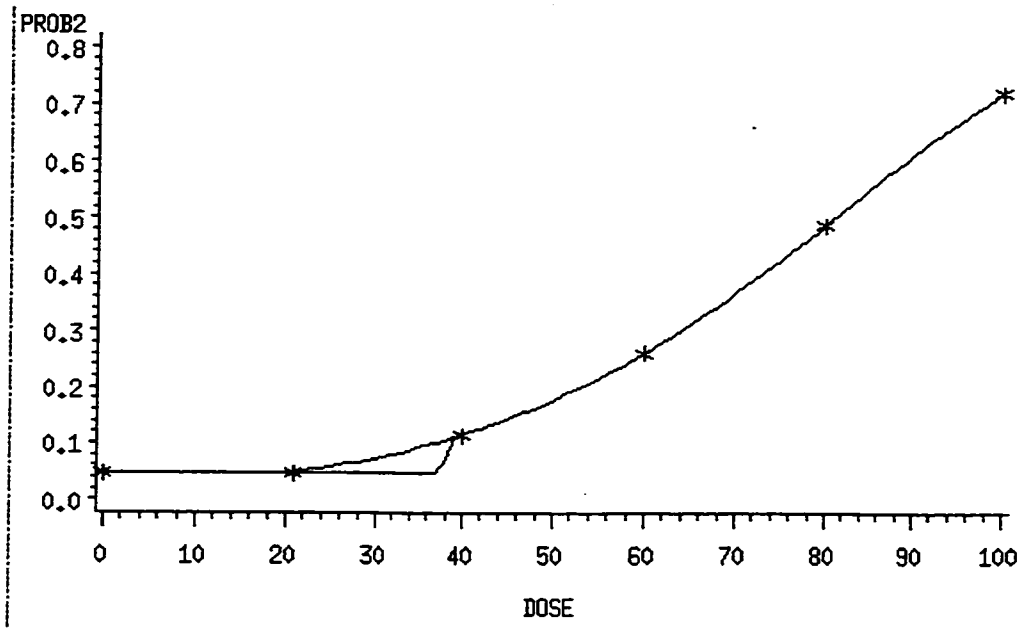
$$Prob(y=1|dose)=\frac{1}{1+e^{-(-2.8553)}}$$

This model fails to detect any effect from the radionucleotide and consequently determines an average cancer rate over the entire dose range. The model does not work because there are not enough animals to detect the slight increase in cancer which occurred at the dose level of 25 and 30 units. The extrapolation to higher dose levels is highly unreliable, and in fact leads to incorrect predictions at higher dose levels, undermining confidence in the experiment.

The next examples show how much more difficult it is to work with threshold logistic models than it is to work with linear logistic models. With linear models, all the data could be put into two places and the correct model would be chosen (if there were no error). For example, if we know we have a linear model and the points $x=10$ and $x=40$ yield the values $y=100$ and $y=400$, then we know the underlying model must be $y=10x$. However, if we have a threshold logistic model with the same points there are countless possibilities as to what the underlying model might be. Three easy possibilities are that there is no threshold and the baseline value of y is some value less than 100, another possibility is that the baseline is 100 and that there is a knee at $x=10$ and the slope goes gradually up to 400 at $x=40$, the third possibility is that there is a threshold until $x=30$ and then there is a quick jump to 400 at $x=40$. It is very important that the data be distributed evenly in a threshold logistic model so that all the aspects of the curve can be properly estimated. Failure to do so can result in incorrectly

estimated models. The following three examples show how dynamic this type of modeling can be.

Graph 3.2.3



The top line is the true relationship of the data. The bottom line is the fitted model.

Example 3

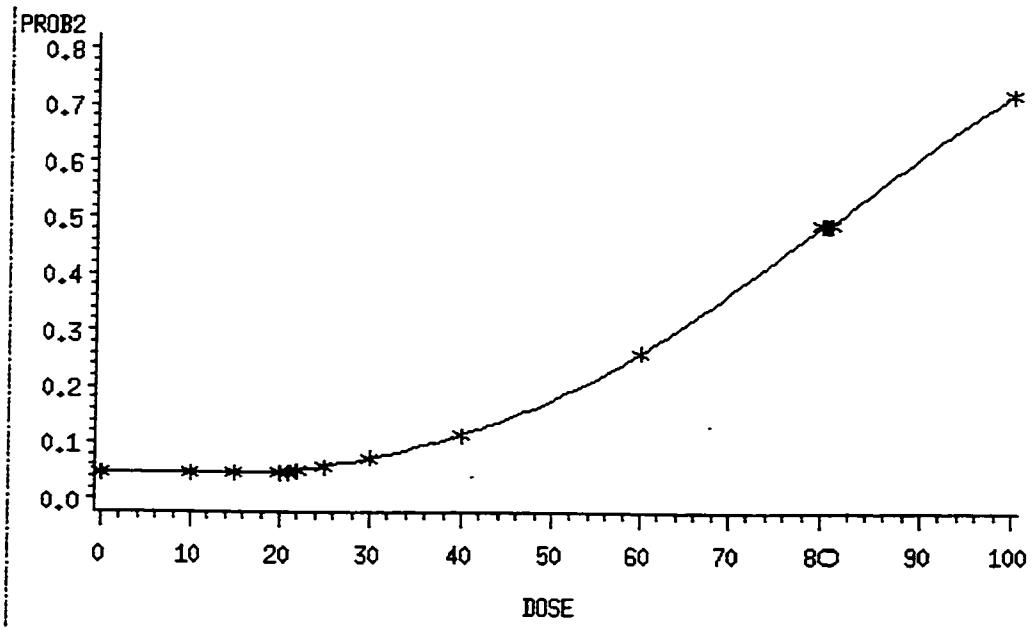
It is known that there is a knee around 21, so the researcher puts a lot of animals as controls (to accurately find the baseline cancer rate), another large group at 21 (to make sure it is the same as the base line) and then evenly spaces out the remaining animals up to 100. The animals are distributed as follows: 100 at 0 and 21 units, and 75 at 40, 60, 80, and 100 units.

The model that is selected by the program is:

$$prob(y = 1 | dose) = \frac{1}{1 + e^{-(-3+0.45knee37-0.4knee39)}}$$

knee37 is significant at the 0.05 level (0.0368)and *knee39* is significant at 0.10 level (0.0682). This model suffers from overfit. The model overestimates the threshold then must compensate using two variables to correct for it.

Graph 3.2.4



The graph shows the fitted model is identical to the true relationship in the data.

Example 4

The experimenter knows that there is a knee somewhere around 21, and tried to adjust accordingly. The animals are distributed accordingly; 0 and 100 units get 40 animals each, 42 animals are assigned to each of the following dosage: 10, 15, 20, 21, 22, 25, 30, 40, 60, 80 units. This fairly equal spacing results in the following model:

$$prob(y=1|dose)=\frac{1}{1+e^{-(-3+0.05*knee21)}}$$

The p value of *knee21* is 0.0001. Although this data fits the model perfectly, in order to reject the null hypothesis that there is no threshold it must be tested against the model using only dose a dose effect. The result of this test only has a p value of 0.67684, so we are unable to reject the null hypothesis.

Example 5

The experimenter believes there a knee in the response, but has no prior knowledge of anything (other than then the MTD at 100). So the animals are evenly space 84 at 0 and 100 units and 83 at 20, 40, 60, and 80 units. This also yields the model

$$prob(y=1|dose)=\frac{1}{1+e^{-(0.05knee21)}}$$

and the *knee21* effect has a p value of 0.0001. At face value this distribution seems to have the same effect as the distribution in example 4, the difference of the two being the p value. The p value in this example is only 0.57466, not nearly close enough to be significant but better than example 4.

Conclusion

The previous two examples have shown that even when the animals are properly distributed across dose levels, the number of animals required can be very high and therefore render analysis of small groups ineffective. With the distribution of example 5, it would required 2094 animals to obtain a significance of $p=0.099502$. To get a significance with $p<0.2$ it took 1500 animals ($p=0.19148$) and to get $p<0.05$ it took 2730 ($p=0.049368$).

This section demonstrates the necessity for evenly distributed groups over the dose range. Without this, the model focuses it decision making too strongly on one area of the curve over another. This in turn, causes the model to be inappropriate for the regions of the curve that are not well represented in the distribution of the animals.

Chapter 4

Data Analysis

4.1 Data

Entrance Criteria

Data from 22 experiments were provided by the Institute for Low Dose Radiation. The data sets were comprised of 8 rat data sets, 6 beagle, 6 mice, 1 human, and one other (marine worms).

Entrance criteria for this thesis focused on maintaining a certain level of homogeneity. For this reason data collected on humans was not included in the study because of competing mortality and imprecise measurements of radiation dosing. Experiments which focused only on fatal cancer or liver cancer were excluded as well. Fatal cancer studies and cancer incidence studies capture very different information and cannot be interpreted in the same fashion as studies which capture incidence rates. The liver cancer studies were excluded after literature review showed that beagles were only prone to developing liver cancer if they survived the period in which the majority of beagles were developing lung cancer (Weller (1995)). This gave an accurate result of the number of liver cancers but not an accurate representation of the cancer incidence in the

beagle population. Several of the experiments were dropped because they contained the same data as other experiments in other studies. This happened when there were different papers published using interim data and then final data sets. The worm experiment was dropped because it was study of the reproductive performance which, needless to say, is far from the scope of this analysis. One experiment was excluded because it excluded animals that had bone cancer in their limbs. Another experiment was dropped because it contained only two data points.

Resume of Data

After excluding experiments which did not fit the entrance criteria there was data from 6 experiments left, one of the experiments studied 5 different radio-nucleotides so it could be considered to be 5 different data sets. Three of the studies dealt with Beagles, 2 mice, and 1 rats. In all, there were 6329 animals, with 969 having developed cancer. Table 4.1.1 summarizes the types of experiments being analyzed, table 4.1.2 summarizes the statistical breakdown of the data sets.

Table 4.1.1 The 6 experiments

Data Set Number	Animal	Number of Animals	Radio-nucleotide	Delivery	Dependent Variable	Independent Variable
1.1-2	Beagles	180	Sr90Cl2 Ra226	single injection	Osteosarcoma	Average dose to skeleton at death
8.31-2	Mice	775	Gamma Fractional Gamma	10 daily exposures	Number of Mice with one or more cancer	Dose Single/Fraction al exposure
10.31-2,10.41-2	Beagles	483	Sr90 injected Sr90	in food, or single inj. or series of injections	Total Sarcomas	Skeletal Dose
24.4	Rats	3157	Pu239O2	inhaled	crude incidence of lung tumours	Lung dose
25.11-41 25.12-42 25.13-43 25.14-44 25.15-45	Mice	1598	Ra226 Pu239 Am241 Cf249 Cf252	single injection	Bone Sarcoma	Average Inj. black/albino male/female
28.52-3	Beagle	136	Pu238O2	inhaled	Bone Tumours Lung Tumours	Dose

Table 4.1.2 Statistical Summary of Data sets

Data Set	Number of dose levels	Minimum in group	Maximum in group	Total number of animals	Minimum dose	Maximum dose
1.1	10	9	38	180	0	117
1.2	9	10	44	164	0	143
8.31	4	94	193	549	0	6
8.32	3	74	78	226	2	6
10.31	8	7	40	239	0	107
10.32	8	12	40	244	0	107
10.41	2	10	15	25	6.7	54.3
10.42	2	10	10	20	6.7	54.3
24.4	12	15	1389	3157	0.002	55.1
25.11	6	11	94	163	0	46.8
25.12	6	11	94	163	0	12.62
25.13	4	11	94	127	0	9.39
25.14	6	10	94	151	0	9
25.15	6	11	94	163	0	18.24
25.21	6	12	87	149	0	39.63
25.22	6	11	87	146	0	8.46
25.23	4	10	87	121	0	12.72
25.24	6	11	87	146	0	10.6
25.25	6	10	87	146	0	211.3
25.31	6	10	60	131	0	45.47
25.32	6	12	60	129	0	13.12
25.33	6	14	60	140	0	14.63
25.34	6	14	60	141	0	16.43
25.35	6	15	60	142	0	20.86
25.41	6	10	58	120	0	56.48
25.42	6	16	58	143	0	6.54
25.43	6	14	58	133	0	12.06
25.44	6	15	50	138	0	16.02
25.45	6	13	58	133	0	19.05
28.52-28.53	6	13	22	116	0.015	6.8

A total of 7 different radio-nucleotides were used: Strontium90 (injected and ingested), Radium226, Plutonium238 and 239, Americium241, Californium249 and Californium252. Radium and Strontium are deposited throughout the bone volume, whereas Plutonium is deposited on the bone surface.

The types of cancers detected in the studies were bone cancer (Osteosarcoma), and lung tumours. These were detected several different ways of detecting (autopsy, radiography, histopathological examination) the cancers listed, although some papers did not list the method used.

Sample Data Set (Data set 10.3)

This section details how data sets were reduced from the style in which they were published to the format used for this thesis.

The following table is from data set from a study by O.G. Raabe (Raabe,1992). Beagles were given food containing Strontium90 from midgestation until 540 days old.

4.1.3 Data as received

dose	#		tot. ingested	median surv.	skeletal dose	f. sarcomas		tot sarcomas		age at onset
level	M	F	kBq	(y)	(Gy)	M	F	M	F	
D00	40	40	0	14.5	0	2	0	2	2	15.3
D05	38	40	370	14.2	0.4	0	0	0	0	-
D10	21	19	1480	13.5	1.2	0	0	0	0	-
D20	33	32	8880	14.4	6.7	0	0	0	0	-
D30	38	34	25900	14.1	22.5	4	0	4	0	13.4
D40	30	35	81400	12.0	50.4	5	5	5	5	11.1
D50	32	32	241000	5.2	80.2	5	12	9	20	7.8
D60	12	7	718000	2.2	107	7	3	13	5	2.3
Total	244	239				24	20	33	32	

Information that was not used in the analysis of the data was removed. Total ingested was removed because the independent variable being used for exposure is skeletal dose. Median survival and age were removed because they are not relevant to the study, and fatal sarcomas were removed because the study is studying incidence of cancer, not the incidence of fatal cancer. Leaving the data set below.

4.1.4 Data as used in analysis

#		skeletal	tot sarcomas	
M	F	dose(Gy)	M	F
40	40	0	2	2
38	40	0.4	0	0
21	19	1.2	0	0
33	32	6.7	0	0
38	34	22.5	4	0
30	35	50.4	5	5
32	32	80.2	9	20
12	7	107	13	5

4.2 Choice of 2 Knee Model Over Others

Data analysis was done using SAS. Three separate logistic regressions were done for each data set. The first logistic regression used only the dose, this was a model linear in dose (in a logistic setting). The second and third logistic regressions were forward analysis with the entry and exit alpha level being 0.15. The second regression forced the model to take at most two explanatory variables and the last took all variables that fit the entrance and exit criteria. Of the 27 data sets analyzed, only 4 (data sets 1.2, 24.4, 25.24, and 28.53) took more than 2 explanatory variables on the 3rd run (see tables in Appendix A). For this reason it is felt that most experiments of low dose radiation can be adequately explained using only two variables.

4.3 Single Run Experiments

In total 31 individual data sets were examined to determine if there was evidence of a threshold effect. The findings can be categorized into five groups. They are: data sets which had **models significantly different from the usual logistic curve** (3), those that had **too little data** (4), data sets which had **too few data points** (13), data sets **with doses that were too low** (7), and data sets which **seemed unlikely to demonstrate a difference even with more data** (4). Each of these groups will be discussed in detail.

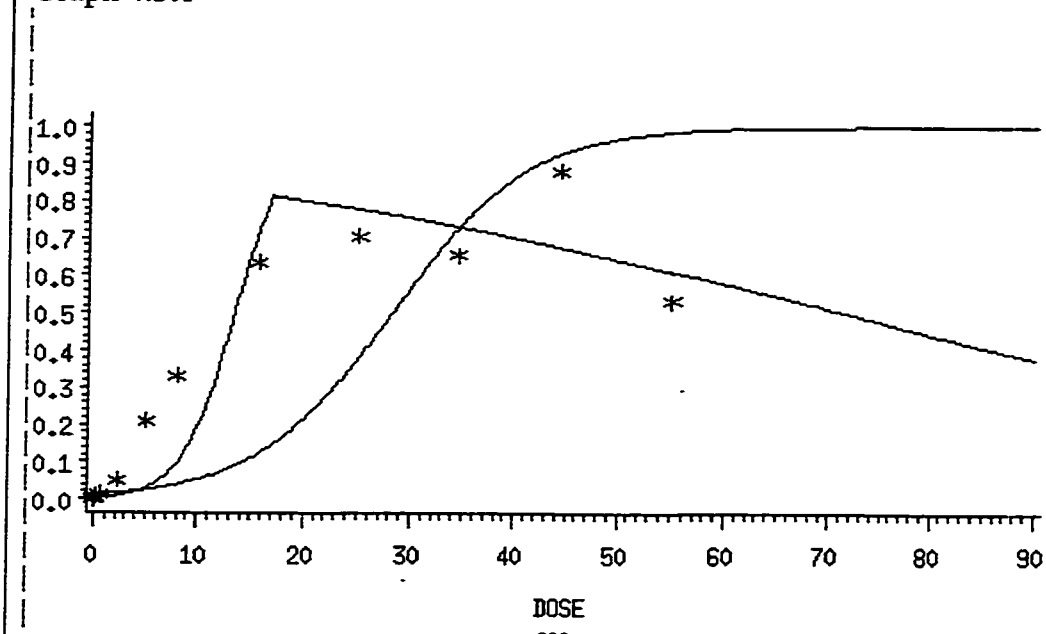
4.3.1 Data sets which had models significantly different than the usual logistic curve.

Analysis showed that three of the data sets had models which were significantly different from the usual logistic model. All three data sets have evidence that the MTD has been exceeded. In such cases, and with the usual logistic model, the effect of dose will be overestimated for low and high dose, but will underestimate the effect of the middle dose ranges. This occurs because the model is trying to balance the higher incidence of cancer at the middle dose rates and lower incidence of cancer at high rates. In order to do this without using a threshold variable the model must balance between the middle dose effect and the high dose effect. This in turn, makes the radionucleotide look less hazardous than it is for most ranges. The lower cancer rates at higher doses can be the product of at least two different trends occurring. One possibility is that it is just random chance that fewer animals at the higher dose levels got cancer, the other possibility is that the dose is so high that it is toxic and the animal does not survive long enough to get cancer (MTD exceeded).

Despite the model being significantly different than the logistic model, in all three data sets in this subsection it is not due to a threshold effect, rather than it is that the MTD has been exceeded.

Now we look at all three data set analyses:

Graph 4.3.1



Data Set 24.4 (Rats, Lung Tumours, $^{239}PuO_2$) The curved line is the new model, the "S" shaped line is the model using no threshold variables.

Data Set 24.4

Data Set 24.4 is a large data set (3157 rats) that studies the effect of $^{239}PuO_2$ on the development of lung tumours. The best fit model for the data using at most two variables was the following:

$$Prob(y=1|dose)=\frac{1}{1+e^{-(-5.1142+0.4117knee1-0.4386knee17)}} \qquad (4.3.1)$$

$(p=0.0001)$

The model indicates that there is a threshold effect up until a dose of 1 gray and then a MTD effect at dose 17. The test to determine if the two models are significantly different came back highly significant ($p=0.0005$).

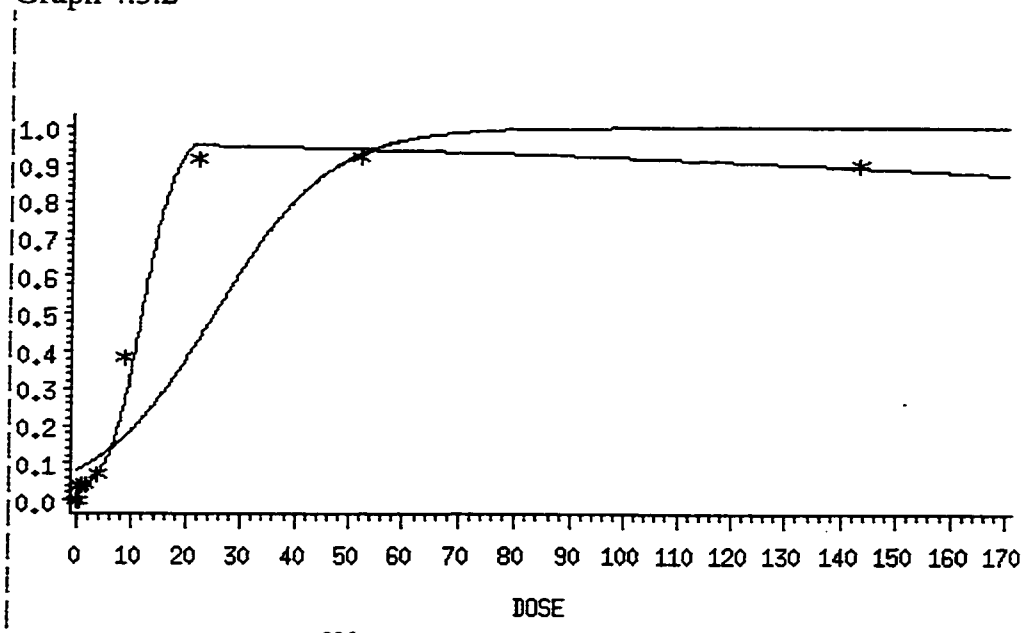
In graph 4.3.1 it looks as though the final data point (at a dose of 55 grays) is having a strong influence on the model. This turns out not to be true. The model excluding the final data point is

$$Prob(y=1|dose)=\frac{1}{1+e^{-(-5.1429+0.3941kneep5-0.4062knee17)}} \qquad (4.3.2)$$

$(p=0.0001)$

So both equations 4.3.1 and 4.3.2 both find a MTD effect at dose of 17. The reason that the last data point does not have a strong effect on the model is that it only contains 15 animals whereas the first two data points contains 2441 animals.

Graph 4.3.2



Data Set 1.2 (Beagles, ^{226}Ra, Osteosarcoma). The curved line is the new model, the "S" shaped line is the model using no threshold variables.

Data Set 1.2

This data set examine the effect of ^{226}Ra had on beagles in the form of osteosarcomas.

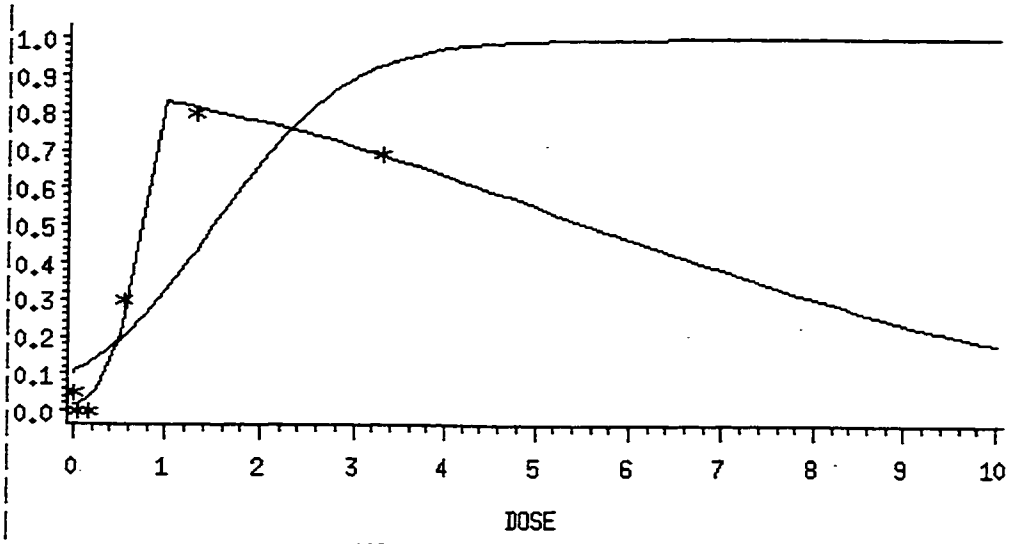
The best fit model using only two variables is:

$$Prob(y=1|dose)=\frac{1}{1+e^{-(-3.7664+0.3222dose-0.3294knee21)}}$$

$(p=0.0001)$

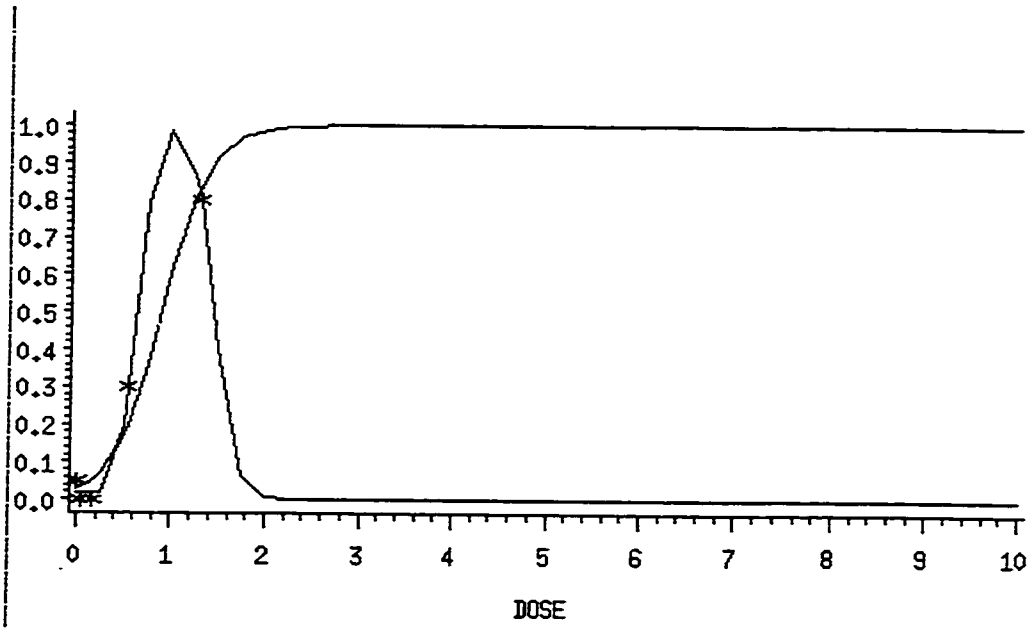
Again, this data set exhibits some evidence of the MTD being exceeded (negative coefficient for the highest knee variable), although in this case it may be more that there is a plateau effect. It appears that roughly the top 8% of beagles are not effected by ^{226}Ra regardless of the level of dose. This leads to the underestimation of the effect of ^{226}Ra at the middle dose range by the usual logistic model as explained earlier in this section. The test to determine if the two models are significantly different came back highly significant ($p < 0.0005$).

Graph 4.3.3



Data Set 28.53 (Beagles, $^{238}PuO_2$, Bone Tumour). The curved line is the new model, the "S" shaped line is the model using no threshold variables.

Graph 4.3.4



Data Set 28.53 (Beagles, $^{238}PuO_2$, Bone Tumour). Model after last data point removed.

Data Set 28.53

As in the first two examples, this data set shows evidence of the MTD being exceeded. The best fit model using only two variables is:

$$Prob(y=1|dose)=\frac{1}{1+e^{-(-4.1891+5.8384kneep01-6.8939knee1)}}$$

$(p=0.0001)$

In looking at graph 4.3.3 it would appear that the MTD at dose of 1 Gray is being generated by the last data point. When the last data point is removed, the model becomes:

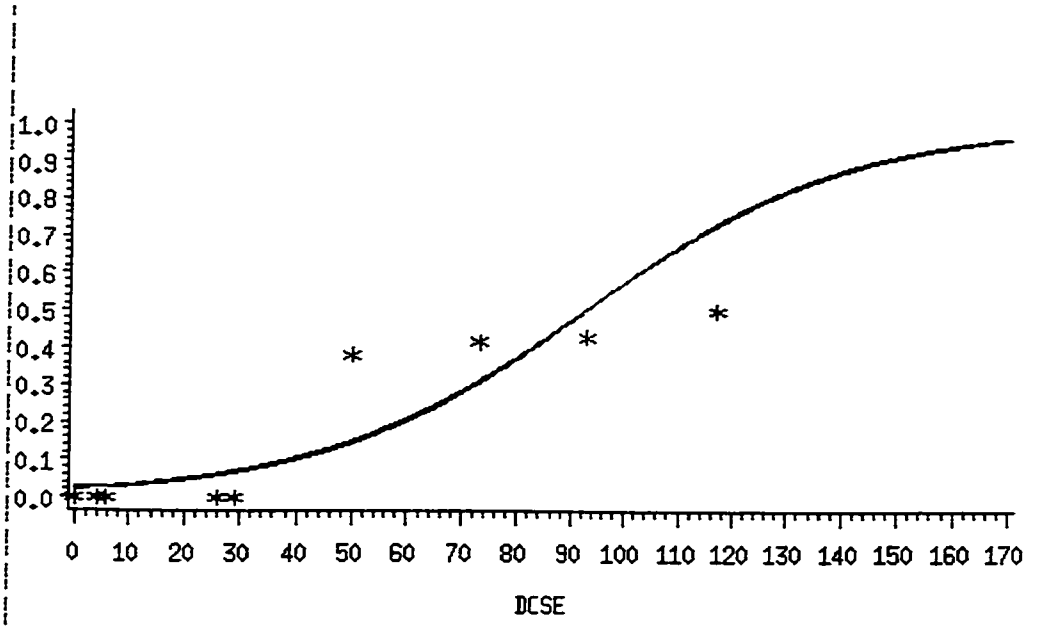
$$Prob(y=1|dose)=\frac{1}{1+e^{-(-4.1271+10.9328kneep25-19.8867knee1)}}$$

$(p=0.0001)$

This also has a drastic MTD effect at dose 1 as can be seen in graph 4.3.4. This model however is not significantly different from the usual logistic model ($p=0.52109$)

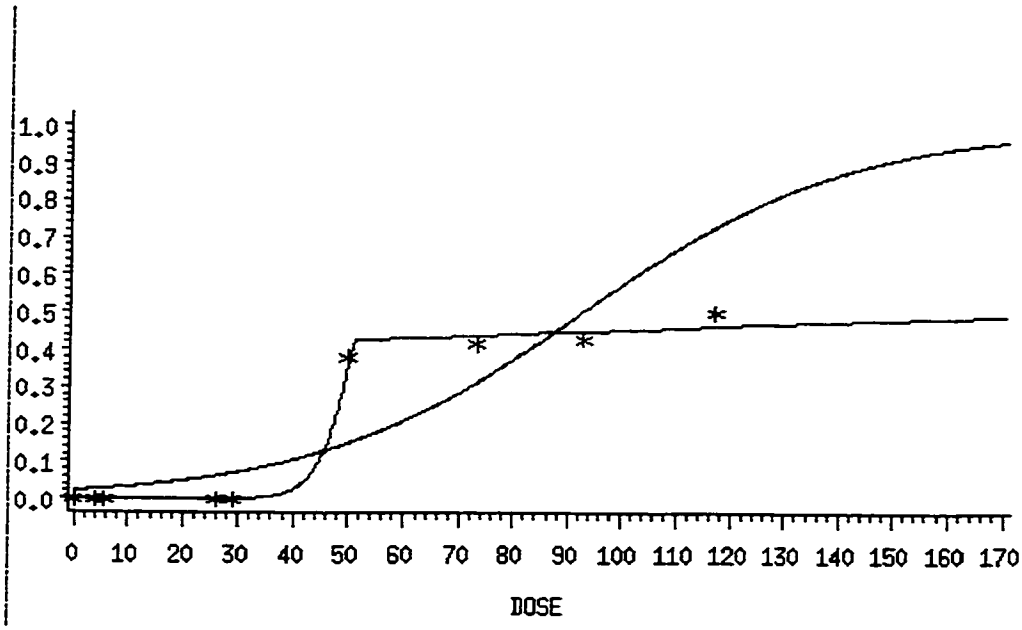
and suffers from not having enough data points to get a good reflection of the underlying distribution of the data.

Graph 4.3.5



Data Set 1.1 (Beagles, $^{90}SrCl_2$, Osteosarcoma). This data set demonstrates the effect of having too few observations in a data set: The algorithm is unable to detect the threshold in the data.

Graph 4.3.6



The model detected if Data Set 1.1 had 478 observations instead of 239.

4.3.2 Data Sets with Too few Data

Data Set 1.1.

Data set 1.1 is a nearly perfect example of the difficulty in studying low dose radiation. Despite the fact that the points clearly follow a model other than the usual logistic model, it is impossible to detect because there were only 239 animals in the study. The model attained was:

$$Prob(y=1|dose)=\frac{1}{1+e^{-(-3.4866+0.0417knee9)}}$$

$(p=0.0001)$

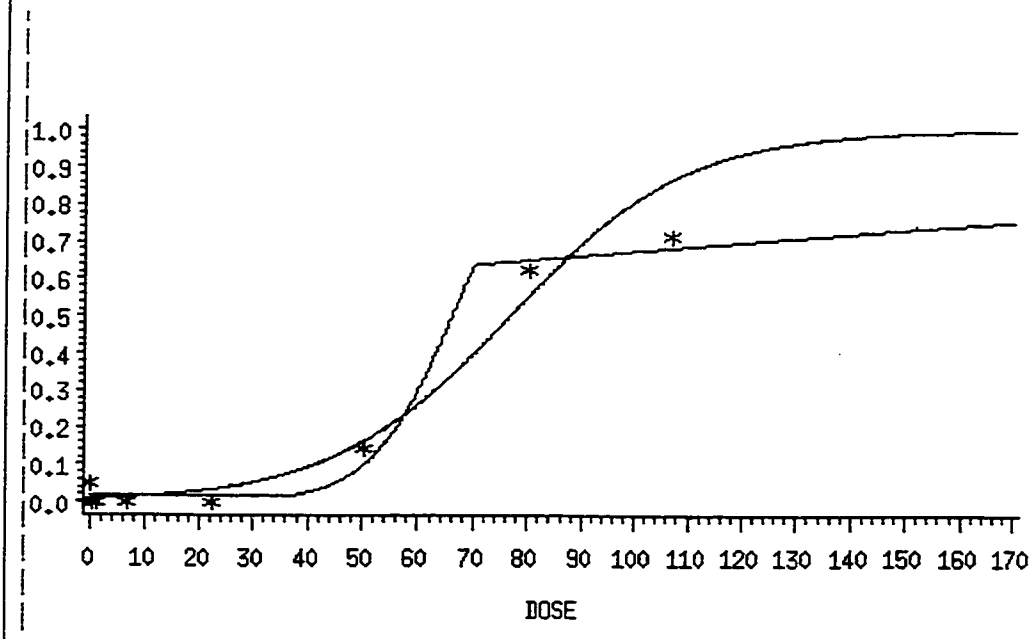
When the number of observations is doubled we get the following model (which can be seen in graph 4.3.6.):

$$Prob(y=1|dose)=\frac{1}{1+e^{-(-12.8931+0.3001knee9-0.2980knee51)}}$$

$(p=0.0001)$

The model is also highly significantly different from the usual logistic model ($p = 0.0001$). This model shows a threshold until a dose of approximately 30 Grays and has a dose effect lower than the usual logistic model up until a value of approximate 50 Grays. Unfortunately for this study only 82 observations were used below a dose level of 26 Grays so it is impossible to get a good measure for the baseline cancer rate. This is reflected in the intercept of -12.8931 which translates to a cancer rate of 1 per 397,560 beagles. This number is a poor estimate of the baseline cancer rate, but without a substantially higher control group (and groups closer to a dose of 0) it is impossible to do any better.

Graph 4.3.7



Data Set 10.31 (Female Beagles, ^{90}Sr, Sarcoma). This data set demonstrates the effect of having too few observations: the model is different, but not significant.

Data Set 10.31

Data set 10.31 also uses beagles and Strontium90, it also shows a threshold up to a value of approximately 30 and a lower than usual logistic model cancer rate up until a dose of approximately 50. Unfortunately, this data set also contains too few data to detect

a difference in the model. In this experiment only 232 beagles were used. The model detected was the following:

$$Prob(y=1|dose)=\frac{1}{1+e^{-(-4.0430+0.1396knee37-0.1340knee70)}}$$

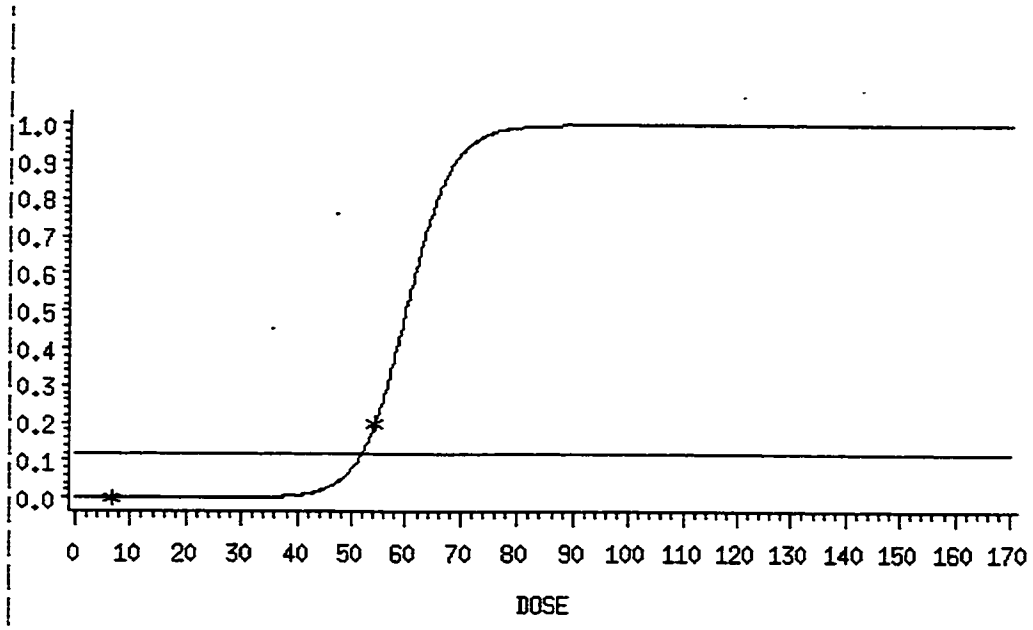
$(p=0.0001)$

The result of the test for significance between this model and the usual logistic model is only $p=0.447$, if we use 2.9 times as many observations (673) the significance between the two models would have risen to $p=0.09705$. It can be noted as well, that the baseline cancer rate in this experiment is on 1 per 60 beagles. This result is due to the two cases of cancer in the control group.

These previous two data sets give good examples of how not using large enough data sets can hamper the search for a threshold in the data. These two datasets will be looked at together in the combined analysis section (Section 4.4).

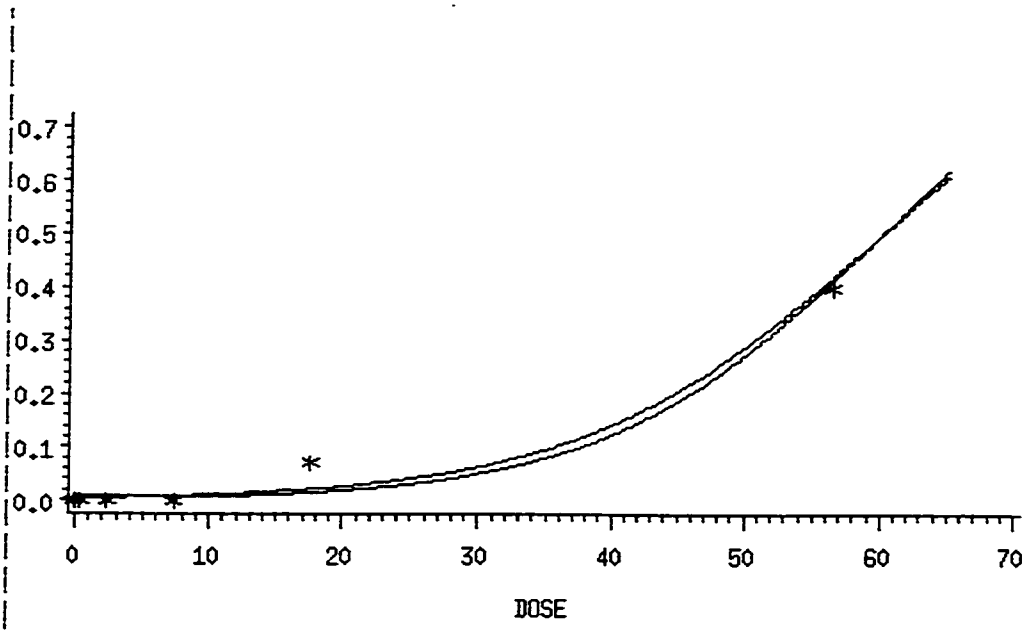
4.3.3 Data Sets with too few points

Graph 4.3.8



Data Set 10.41 (female beagles, ^{226}Ra, Osteosarcoma). This data set has too few points to be analyzed properly

Graph 4.3.9



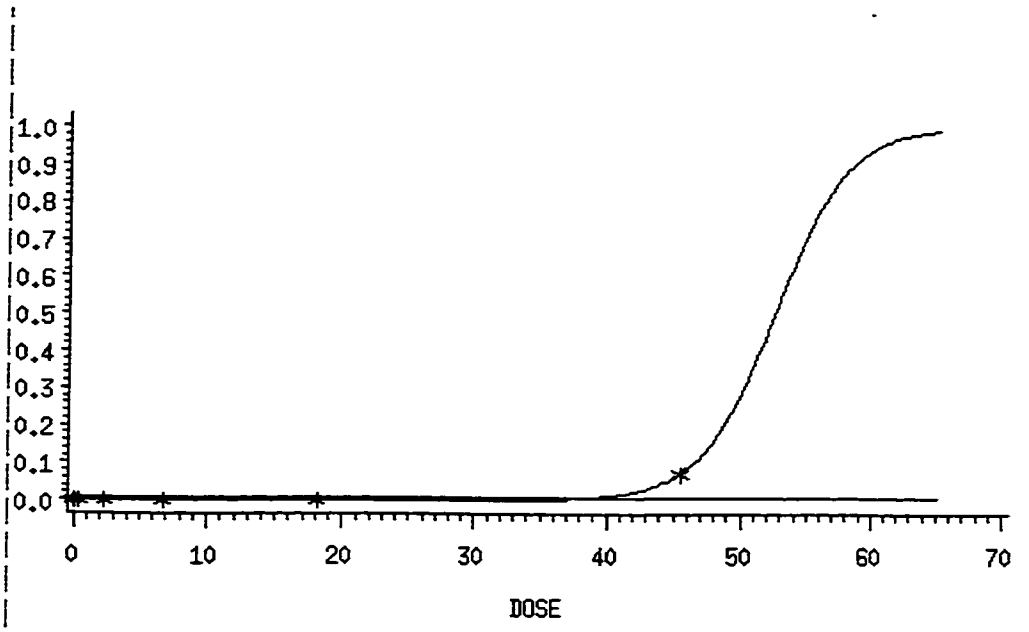
Data set 25.41 (female albino mice, ^{226}Ra, bone sarcomas) this data set lacks observations in the critical region from 20 Grays to 55 Grays.

Data Set 10.41

Four of the datasets presented had too few data points to analyze properly. Some, like data set 10.41 had so few data points that there was no possible way to analyze the data. The reason for retaining this kind of dataset is that they may become useful in the combined analysis section of the research. Others like data set 25.41 had data points missing in critical areas, the experiment has no observations between the range of 20 Grays and 55 Grays. Without this information it is impossible to determine if there is a threshold between these two points.

4.3.4 Data Sets with doses that are too low

Graph 4.3.10



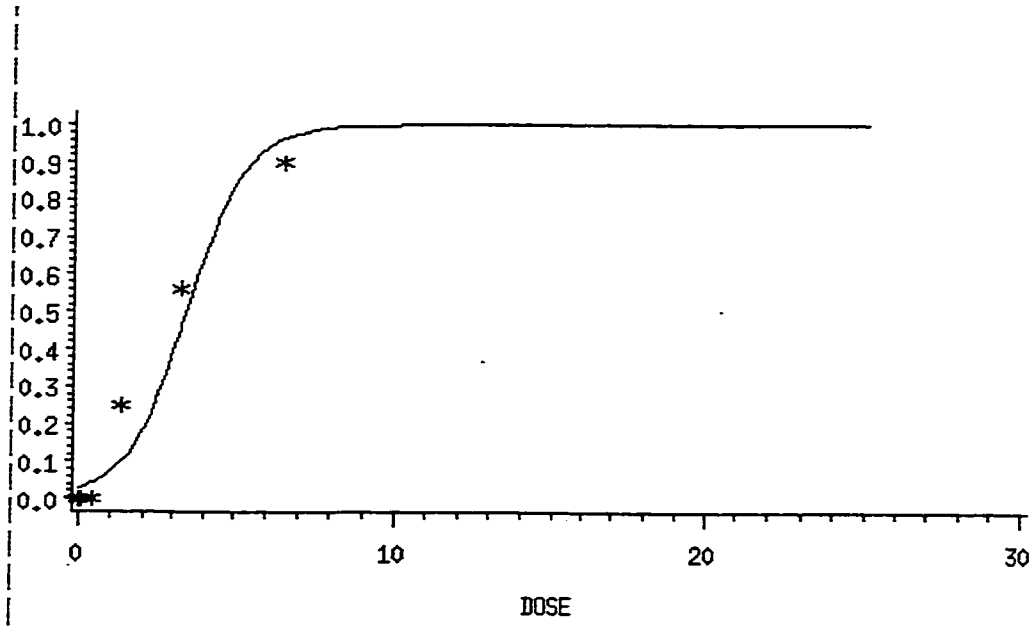
Data Set 25.31 (male albino mice, ^{226}Ra, bone sarcoma). This data set failed to use a dose high enough to effect any of the groups.

Data set 25.31

As discussed in section 3.3, if the range of dose used is too low the model will not be able to detect the difference. This occurred in 7 of the data sets. These data sets quite often suffer from two flaws, one is the dose is not high enough, the other is the small number of observations used in the study. It is possible that the dose level is high enough but that the sample taken is so small that not a true representation of the effect of the radionucleotide is witnessed. This last flaw will also hamper with combined analysis of the data.

4.3.5 Data Sets with No Evidence of a Threshold

Graph 4.3.11



Data set 25.42 (female albino mice, ^{239}Pu, bone sarcomas). This data set exhibits no evidence of a threshold.

Data set 25.42.

Some data sets exhibited no detectable threshold effect and from a visual inspection of the data it appeared there was no chance of there ever being a detectable threshold in the data set. Data set 25.42 is a good example of such a data set. At a dose of 1.32 there is already a 25% cancer rate. It does not appear the there is a threshold in this data set. Of the 4 data sets that appear not to have a threshold 2 are ^{239}Pu and the other two are listed only as Gamma radiation. This does not conclude that there is a threshold effect in the other 28 data sets, rather that there is no reason to believe that these 4 data sets do have a threshold effect.

4.3.6 Conclusion

For the most part, the reason the data sets had difficulty detecting thresholds was due to the relatively small number of animals in each experiment. The only experiment that had enough animals (24.4) had them so badly placed that it is difficult to make any kind of conclusion about the statistical results. The problem of having too few animals in each

data set is partially rectified by performing a combined analysis on the data sets. The results of which can be seen in the next section.

4.4 Combined Analysis

Disclaimer

Before beginning this section it is important to note that the regrouping of datasets was done on the basis of what seemed to make sense. At each step the reasons for why the data sets were combined will be noted. This section is more to demonstrate the effect of combining data sets for the purpose of combined analysis rather than being able to conclusively say whether radionucleotides have a threshold effect in cancer development. The reader is therefore left on their own to draw conclusions on the acceptability of the results from those meta analyses.

Background

Meta analysis is a solution to the problem of not having enough data in one data set. There are various different methods of doing a meta analysis, one of which is combined analysis. Combined analysis is the analysis of many different data sets with similar characteristics that does not give different weights to different data sets. It considers the regrouping of data sets to form one big data set. Methods like these allow for the results of many small studies to be grouped together in order to get a stronger model. As discussed in section 3.3, the amount of data required for threshold analysis can require more data than a single experiment can provide. It then becomes necessary to do combined analysis. The downside to combined analysis is that there will be variation between the data sets, i.e. an experiment run in place A at time A will quite often not get the same results as an experiment run at place B at time B. Due to the fact that these experiments are quite often not large in size, there can be large discrepancies in their baseline characteristics, such as the cancer rate in the control group. When the radiation is held to 0, one would expect the underlying cancer rate to be the same. This does not always happen.

Despite its drawbacks, combined analysis is still a very powerful tool for detecting hard to detect trends in data sets where several experiments have been done in roughly the same manner. A further discussion on meta analysis can be found in *Statistical Methods for Meta Analysis* (Hedges and Olkin 1985).

Regrouping of Data Sets

Careful consideration was taken in selecting the data sets to be included in this thesis so that the overall design of the experiment was homogeneous enough that the only factor in comparing data sets would be the type of animal or the radionucleotide.

In total 13 new amalgamated data sets were created. The following is a discussion on the criteria by which the data sets were merged.

The first 6 new data sets were merged from data set 25. Groups were collapsed based on sex and albino/black. Therefore what used to be 4 separate analyses for each radionucleotide is now one. This created 5 new data sets. The 6th was created by merging the ^{249}Cf data set with the ^{252}Cf data set to determine if the combined data set could detect an overall effect from Californium.

Data sets 10.31 and 10.32 were merged, the only difference between these two data sets was sex. The same was done for data sets 10.41 and 10.42. These two new data sets were further combined to see if an analysis could be done when merging data sets coming from ingested and injected Strontium.

Data sets 8.31 and 8.32 were merged, the only difference between these two data sets was that one was administered by injection where as the other was ingested through food.

Data sets 10.31, 10.32, 10.41, 10.42, and 1.1 were then merged. The difference between the two data sets is that the 10 series of data sets used ^{90}Sr, whereas data set 1.1 used $^{90}SrCl_2$. This new data set was then combined with data set 1.2. Data set 1.2 used ^{226}Ra, these were combined since they both had the same effect on bone material, i.e. they are deposited throughout the bone volume whereas Plutonium is deposited on the bone surface.

Data sets 1.1 and 10.31 were analyzed together because they both had roughly the same response rate to the radiation, but both data sets were too small to get a significant result. Table 4.4.1 is a summary of the new data sets.

Table 4.4.1

Data Sets	Animal	Radionucleotide	Outcome	Assumptions
25.11, 25.21, 25.31 and 25.41	mice	^{226}Ra	bone sarcomas	male/female and albino/black mice are effected the same way.
25.12, 25.22, 25.32 and 25.42	mice	^{239}Pu	bone sarcomas	male/female and albino/black mice are effected the same way.
25.13, 25.23, 25.33 and 25.43	mice	^{241}Am	bone sarcomas	male/female and albino/black mice are effected the same way.
25.14, 25.24, 25.34 and 25.44	mice	^{249}Cf	bone sarcomas	male/female and albino/black mice are effected the same way.
25.15, 25.25, 25.35 and 25.45	mice	^{252}Cf	bone sarcomas	male/female and albino/black mice are effected the same way.
25.14, 25.24, 25.34, 25.44, 25.15, 25.25, 25.35 and 25.45	mice	^{249}Cf and ^{252}Cf	bone sarcomas	male/female and albino/black mice are effected the same way by Californium 249 and 252.
10.31 and 10.32	beagles	^{90}Sr	Sarcoma	male/female beagles effected the same.
10.41 and 10.42	beagles	injected 90Sr	Sarcoma	male/female beagles effected the same.
10.31, 10.32, 10.41 and 10.42	beagles	^{90}Sr and injected ^{90}Sr	Sarcoma	injected and ingested 90Sr has same effect.
1.1, 10.31, 10.32, 10.41 and 10.42	beagles	^{90}Sr and $^{90}SrCl_2$	Sarcoma	^{90}Sr and $^{90}SrCl_2$ has same effect on beagles.
1.2, 1.1, 10.31, 10.32, 10.41 and 10.42	beagles	^{226}Ra and ^{90}Sr	Sarcoma	226Ra and 90Sr has the same effect on beagles.
8.31 and 8.32	black mice	Gamma and Fractional Gamma	Cancer	Gamma and Fractional Gamma has same effect
1.1 and 10.31	beagles	$^{90}SrCl_2$ and ^{90}Sr	Sarcoma	^{90}Sr and $^{90}SrCl_2$ has same effect on beagles.

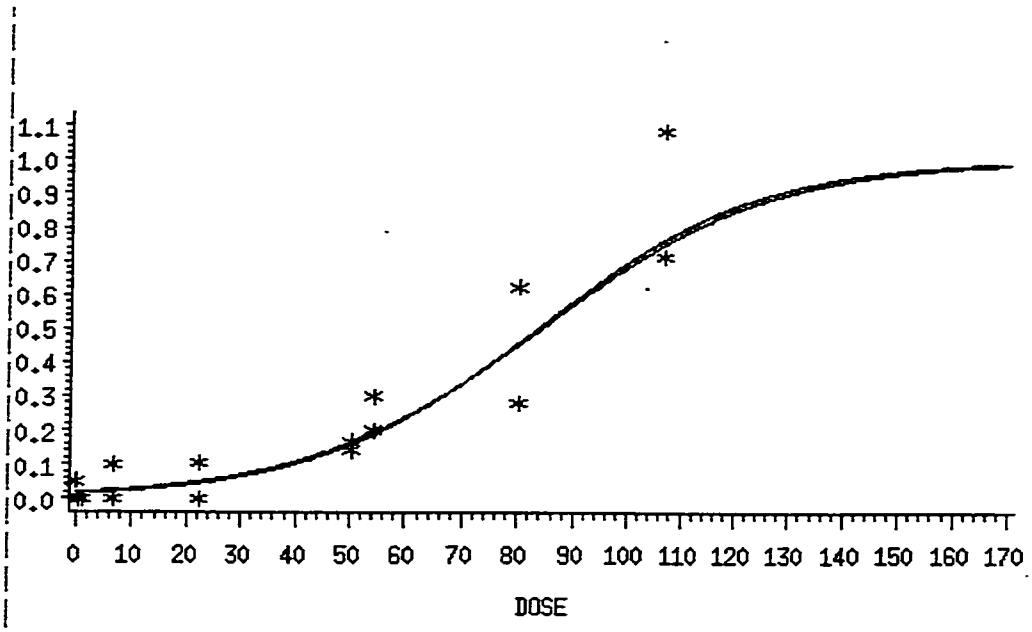
Results

The combined analysis was conducted by combining the data sets and considering them as one larger data set, as opposed to other meta analysis methods (i.e. weighted estimates by error, etc).

The results of the combined analysis can be categorized into four groups: **no threshold** (2), **too much scatter** (9), **too little data** (1), and **threshold achieved** (1).

With the exception of "too much scatter", these are the same groupings as the single run analyses (it replaced the "dose to low" group which was no longer needed after the regrouping). The "threshold achieved" data set came back significant ($p = 0.017$), all but two of the too much scatter came back significant. The two that came back with a significance outside of the 0.1 level had p-values of 0.166 and 0.287.

Graph 4.4.1



The combination of data sets 10.31, 10.32, 10.41, and 10.42. No evidence of a threshold effect.

Two data sets showed no threshold effect. They were the data sets that combined 10.31 and 10.32 and the data set which combined the data sets 10.31, 10.32, 10.41, and 10.42. As an example, the combination of data sets 10.31, 10.32, 10.41 and 10.42 yielded the following model:

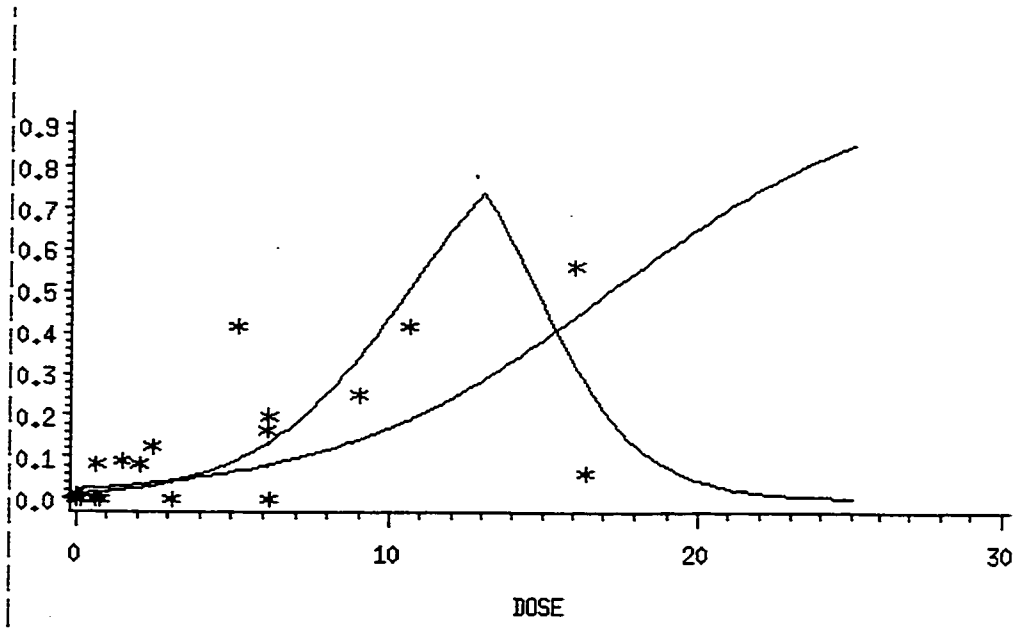
$$Prob(y = 1 | dose) = \frac{1}{1 + e^{-(-3.8285 + 0.05 knee7)}}$$

($p = 0.0001$)

This model actually came back worse than the model that does not include a threshold variable. This is due to the nature in which variables are picked in a forward selection logistic regression. Variable *knee7* was selected before the variable *dose*. Once *knee7* was in the model, the variable *dose* had no improving qualities for the model so it was not selected.

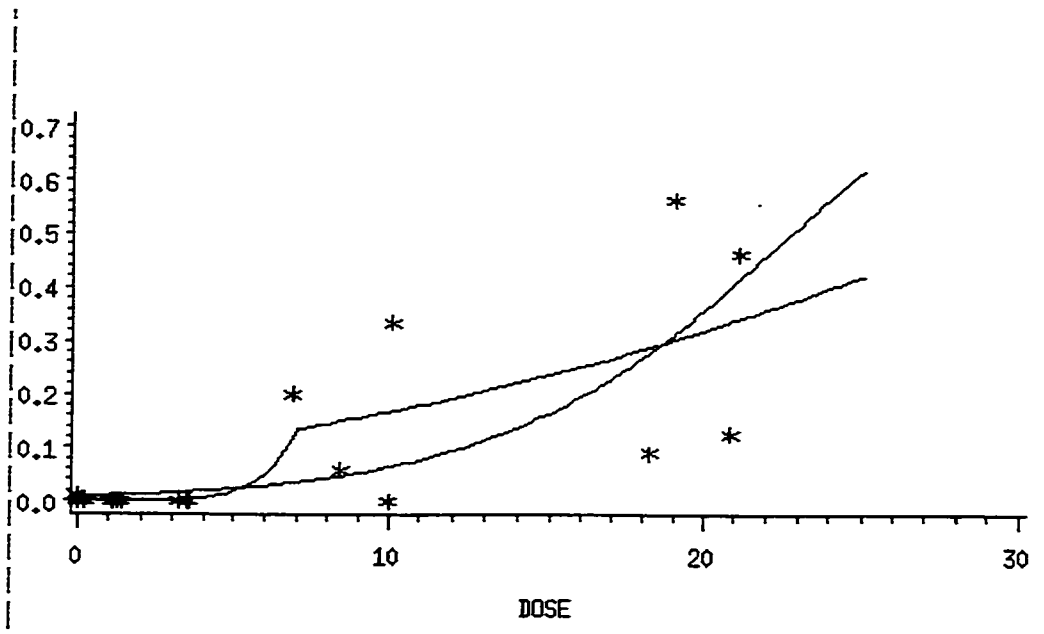
The fact that the model found no evidence of a threshold from these data does not mean there is no threshold from this radionucleotide, it simply means with the experiments conducted there was no evidence. If further data had been collected from between the doses of 30 and 50 it could feasibly have resulted in very low cancer rates until dose 50 and then a jump up to the 20% cancer rate that shows up in the data at doses that high.

Graph 4.4.2



The combinations of data sets 25.14, 25.24, 25.34, and 25.44

Graph 4.4.3



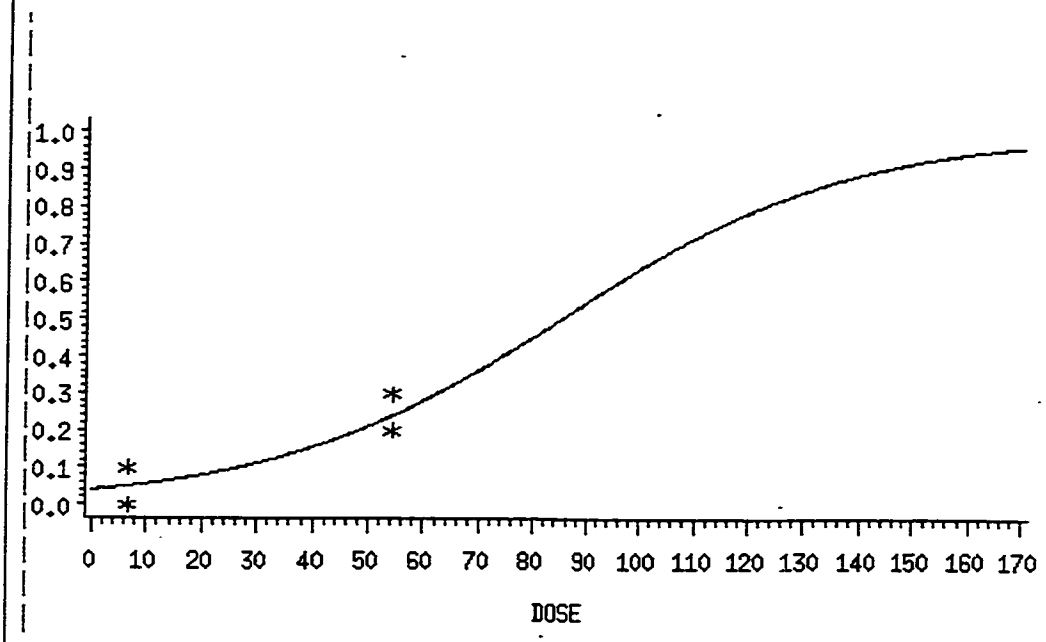
The combination of data sets 25.15, 25.25, 25.35, and 25.45

Most of the combined data sets showed too much scatter to be able to conclude anything about underlying patterns in the data. A total of 9 of the 13 combined analysis had this problem. There are many reasons why experiments run by at different times by different people may fail to produce results that are close to the same (which is need for good combined analysis). Some problems may include: back ground radiation levels, the genealogy of the animals used, or different methods in the way that the experiment was conducted. Background radiation levels can change the amount of radiation that a subject receives, this in turn would change what dosing group the subject should be listed as. The genealogy of the animal could have one group of animals coming from a family that is not very susceptible to cancer whereas another group may come from a family with weak immune systems and are therefore more susceptible to cancer. There are probably many different ways that experiments can be conducted which can slightly effect the outcome of the combined analysis.

Two examples of this problem are the combination of data sets 25.14, 25.24, 25.34, and 25.44 and data sets 25.15, 25.25, 25.35, and 25.45. The first group used Californium249 and the second used Californium252. As can be seen in graphs 4.4.2 and 4.4.3 there is a lot of scatter throughout the data.

When looking at graph 4.4.2 it looks as though the bottom right most data point may be causing the MTD effect in the model, but even with that data point removed the same effect is noticed. If we remove the upper right most data point the model comes out the same as the usual knee model (no threshold and no MTD effect).

Graph 4.4.4

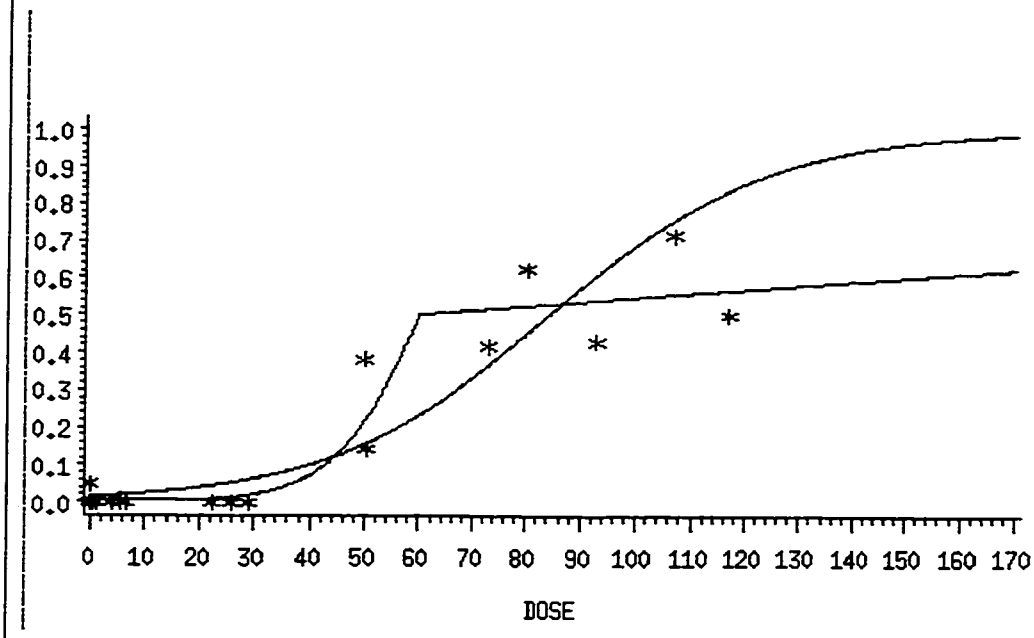


The combination of data sets 10.41 and 10.42.

Finally, there was one combined data set which still had too few data points in it. It was the combination of data sets 10.41 and 10.42. This combination regrouped male and female beagles which had Strontium injected into them rather than have it ingested through food.

Data set with threshold

Graph 4.4.5



The combination of data sets 1.1 and 10.31. Evidence of threshold effect up to a dose of 30.

The data set which combined data sets 1.1 and 10.31 came back with a model that was significantly different from the usual logistic model ($p = 0.017$) and appeared to have a threshold effect. The model of the data was:

$$Prob(y = 1 | dose) = \frac{1}{1 + e^{-(-4.9655 + 1.274\,knee21 - 0.1229\,knee60)}}$$

($p = 0.0001$)

This model looked at the effect of Strontium90 on osteosarcoma in beagles. Section 4.5 gives the details from the complete model diagnostic to demonstrate exactly what information can be extracted from the model.

4.5 Residual Analysis

The following section is the full residual analysis of the combined analysis of data set 1.1 and 10.31. The test statistics are the same as those explained in section 2.2. The order is the same as the example in section 2.3.

Output For Testing The Model

Model Fitting Information and Testing Global Null Hypothesis BETA=0

Criterion	Intercept Only	Intercept and Covariates	Chi-Square for Covariates
AIC	349.748	211.561	.
SC	353.785	223.675	.
-2 LOG L	347.748	205.561	142.186 with 2 DF (p=0.0001)
Score	.	.	144.164 with 2 DF (p=0.0001)

Both the -2LOG L and the Score test show that the model explains a significant amount of variation from the mean: both are significant at the $\alpha = 0.0001$ level. The AIC and SC criteria could be used to compare this model to other logistic models on the same data set.

Output For Testing The Variables

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr> Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-4.9655	0.6588	56.8088	0.0001	.	.
KNEE21	1	0.1274	0.0215	35.1911	0.0001	1.898196	1.136
KNEE60	1	-0.1229	0.0297	17.0867	0.0001	-0.860834	0.884

Both variables, *knee21* and *knee60* are significant at the $\alpha = 0.0001$ level. The positive estimate for *knee21* means that as dose increases so does the incidence of cancer and as can be seen from the Odds Ratio. It increases by 13.6% for each unit increase in

dose. The negative parameter estimate of *knee60* indicates that an increase in dose now results in a decrease in cancer incidence for dose greater than 60. From the Odds Ratio we can calculate that a one unit increase in dose reduces the amount of cancer by 11.6% over the previous estimate. This, of course is coupled with the *knee21* estimate so it actually works as a buffer to slow down the effect of *knee21* at doses above 60.

Output for testing the Goodness of Fit

Hosmer and Lemeshow Goodness-of-Fit Test

		EVENT		NO EVENT	
Group	Total	Observed	Expected	Observed	Expected
1	213	2	1.48	211	211.52
2	47	0	0.45	47	46.55
3	37	8	4.91	29	32.09
4	35	5	7.98	30	27.02
5	56	30	29.13	26	26.87
6	31	16	17.06	15	13.94

Goodness-of-fit Statistic = 4.5377 with 4 DF (p=0.3381)

The Hosmer and Lemeshow goodness of fit has as null hypothesis that the model is well fit. Had the p value of the Goodness-of-fit statistic been below $p = 0.05$ then we would have been able to reject. This says that statistically speaking, the model is a good fit of the data or at least there is no strong evidence against the idea. The model is very close to the actual observed number of cancers in each category (this can be seen by comparing the "observed" versus "expected" values in the table).

Case Numbers

For the remainder of the analysis the case numbers correspond to the following data:

Case Number	*Experiment*	*Animal*	*Radionucleotide*	*Outcome*	*Number*	*Dose*	*# of fatal cancers*
1	*1.1*	*Beagle*	*Sr90Cl2*	*Osteosar*	*13*	*0*	*0*
2	*1.1*	*Beagle*	*Sr90Cl2*	*Osteosar*	*22*	*0*	*0*
3	*10.31*	*female Beagle*	*Sr90*	*Sarcoma*	*40*	*0*	*2*
4	*10.31*	*female Beagle*	*Sr90*	*Sarcoma*	*40*	*0.4*	*0*
5	*10.31*	*female Beagle*	*Sr90*	*Sarcoma*	*19*	*1.2*	*0*
6	*1.1*	*Beagle*	*Sr90Cl2*	*Osteosar*	*38*	*3.8*	*0*
7	*1.1*	*Beagle*	*Sr90Cl2*	*Osteosar*	*9*	*5.7*	*0*
8	*10.31*	*female Beagle*	*Sr90*	*Sarcoma*	*32*	*6.7*	*0*
9	*10.31*	*female Beagle*	*Sr90*	*Sarcoma*	*34*	*22.5*	*0*
10	*1.1*	*Beagle*	*Sr90Cl2*	*Osteosar*	*13*	*26*	*0*
11	*1.1*	*Beagle*	*Sr90Cl2*	*Osteosar*	*16*	*29*	*0*
12	*1.1*	*Beagle*	*Sr90Cl2*	*Osteosar*	*21*	*50*	*8*
13	*10.31*	*female Beagle*	*Sr90*	*Sarcoma*	*35*	*50.4*	*5*
14	*1.1*	*Beagle*	*Sr90Cl2*	*Osteosar*	*24*	*73*	*10*
15	*10.31*	*female Beagle*	*Sr90*	*Sarcoma*	*32*	*80.2*	*20*
16	*1.1*	*Beagle*	*Sr90Cl2*	*Osteosar*	*14*	*93*	*6*
17	*10.31*	*female Beagle*	*Sr90*	*Sarcoma*	*7*	*107*	*5*
18	*1.1*	*Beagle*	*Sr90Cl2*	*Osteosar*	*10*	*117*	*5*

Output For Covariate Pattern Analysis

Case Number	*Covariates KNEE21*	*KNEE60*	*Pearson Residual Value*	*Deviance Residual Value*
1	*0*	*0*	*-0.3011*	*-0.4251*
2	*0*	*0*	*-0.3917*	*-0.553*
3	*0*	*0*	*3.2847*	*2.1299*
4	*0*	*0*	*-0.5282*	*-0.7457*
5	*0*	*0*	*-0.364*	*-0.5139*
6	*0*	*0*	*-0.5148*	*-0.7268*
7	*0*	*0*	*-0.2505*	*-0.3537*
8	*0*	*0*	*-0.4724*	*-0.667*
9	*1.5*	*0*	*-0.5358*	*-0.7561*
10	*5*	*0*	*-0.4141*	*-0.5837*
11	*8*	*0*	*-0.5561*	*-0.7827*
12	*29*	*0*	*1.7924*	*1.6761*
13	*29.4*	*0*	*-1.2006*	*-1.2657*
14	*52*	*13*	*-0.9691*	*-0.9703*
15	*59.2*	*20.2*	*1.1481*	*1.1558*
16	*72*	*33*	*-0.8215*	*-0.8202*
17	*86*	*47*	*0.8547*	*0.8733*
18	*96*	*57*	*-0.4134*	*-0.4117*

With the exception of the 3rd case, all the data fit well within the (-2,+2) range that is standard for residuals. The 3rd case is the data from data set 10.31 and had a 5% (2/40) cancer rate despite having a dose of 0. This is partially a problem of having such a small data set. The natural cancer rate is not 0% but because cases 1 and 2 are so small they failed to detect any naturally occurring cancer so case 3 looks like an outlier when it is probably closer to the actual baseline cancer rate. A pattern emerges in the last 5 cases, the residuals oscillate from negative to positive. Normally a pattern in the residuals is a great concern, but in this case it is because the last 5 data point alternate from data set 1.1 to data set 10.31. The dose effect is slightly lower in experiment 1.1 so the values are all lower than those of experiment 10.31, this leads to the pattern of negative and positive residuals.

	INTERCPT Dfbeta	*KNEE21 Dfbeta*	*KNEE60 Dfbeta*
1	*-0.0617*	*0.0574*	*-0.0486*
2	*-0.1074*	*0.0999*	*-0.0847*
3	*1.289*	*-1.1982*	*1.016*
4	*-0.2073*	*0.1927*	*-0.1634*
5	*-0.0919*	*0.0854*	*-0.0724*
6	*-0.1956*	*0.1818*	*-0.1542*
7	*-0.0422*	*0.0392*	*-0.0333*
8	*-0.1614*	*0.1501*	*-0.1272*
9	*-0.2015*	*0.1859*	*-0.1567*
10	*-0.0998*	*0.0902*	*-0.0747*
11	*-0.1638*	*0.1445*	*-0.1173*
12	*0.3445*	*0.0452*	*-0.2906*
13	*-0.3377*	*-0.0896*	*0.3545*
14	*0.2556*	*-0.4806*	*0.5*
15	*-0.2353*	*0.4424*	*-0.3677*
16	*0.01*	*-0.0189*	*-0.0833*
17	*0.0621*	*-0.1168*	*0.2541*
18	*-0.1045*	*0.1964*	*-0.3645*

The results of the Dfbeta analysis shows that no case (except possibly the 3rd) is having a strong effect on the parameter estimate for any of the variables. This is a good sign, showing that the animals were well distributed in these experiments. Had all the

animals been in only a few of the cases then all the weight could have been associated to those points and it would have been reflected in either extreme (negative or positive) Dfbeta values.

	C	CBAR
1	0.00381	0.00366
2	0.0115	0.0108
3	1.6615	1.4631
4	0.043	0.0378
5	0.00845	0.00797
6	0.0383	0.0339
7	0.00178	0.00173
8	0.0261	0.0236
9	0.0406	0.0361
10	0.01	0.00949
11	0.0272	0.0252
12	1.1007	0.8668
13	1.3109	0.8314
14	0.5993	0.4155
15	0.8836	0.6055
16	0.1977	0.1598
17	0.2588	0.2026
18	0.3771	0.1824

C and CBAR are closely related to the Dfbetas, so it is not surprising that the C and CBAR analysis gives nearly the same results as the Dfbeta analysis. The 3rd case has the strongest influence on the model. However, this analysis also shows that cases 12 and 13 are also having an effect on the parameter estimates. This may be in part due to the fact that their dose levels are so close (50 to 50.4) that the removal of one of them would have an increased effect on the model (allowing the model to approach the other point more closely).

	DIFDEV	DIFCHISQ
1	0.00366	0.0943
2	0.0108	0.1642
3	1.4631	12.2522
4	0.0378	0.3168
5	0.00797	0.1405
6	0.0339	0.299
7	0.00173	0.0645
8	0.0236	0.2468
9	0.0361	0.3232
10	0.00949	0.1809
11	0.0252	0.3344
12	0.8668	4.0796
13	0.8314	2.2727
14	0.4155	1.3546
15	0.6055	1.9235
16	0.1598	0.8346
17	0.2026	0.9332
18	0.1824	0.3533

The DIFDEV and DIFCHISQ analysis shows the effect that each case is having on the Deviance Residuals and the χ^2 residuals, in this case we are looking for large numbers. These numbers represent the change in the two deviance types when the observation is removed. Again, case 3 shows to be the case that has the greatest effect on the residuals, this time cases 12 through 15 also have a stronger effect on the DIFCHISQ than do most of the other cases. This is, however, still quite a good fit, recall the example in section 2.3 with only had 2 values below 2.09 for the DIFCHISQ value.

Conclusion

The fit on this data set is very good. With the exception of a few points the residuals for all the points are well within reasonable levels, and even the few that are slightly higher are not that bad. The reason the one point looks so poorly fit is due to the lack of animals in the control groups, had the control groups had larger sizes and therefore better estimates of the baseline cancer rate, the worst point would most likely have been well fit.

Chapter 5

Experimental Design and Sample Size

5.1 Simulation

In order to determine how well the test statistic is able to detect a threshold in the data, simulations must be run. Theoretical development of this can be quite difficult due to the number of parameters involved and the nonlinear effect we seek to detect. It therefore becomes easier to use simulation to explore the power of the statistic. These simulations will determine over what range of parameters (dose, baseline cancer rate, knee, sample size) that the test statistic will meet the standard rates of success ($\alpha = 0.05$, $\beta = 0.3$). The simulations must attempt to satisfy two conditions, the first that the simulations are general enough that researchers can properly understand the potential future use of the statistic and secondly that the test statistic give an accurate enough description of what is happening with datasets being examined in this thesis. This second condition is very important, without it no results can be properly justified.

The simulations for the alpha and beta significance levels are each done in separate ways. The alpha testing uses simulated data sets which do not have a threshold (see equation 2.4.1) and the test is then used to determine if the statistic finds a threshold or not. In other words we are trying to determine the number of times a test comes back with a false positive, i.e. saying there is a threshold when none truly exists.

The simulation for the beta significance level is the exact opposite. Here we generate data sets that include a threshold (see equation 2.4.2) and determine the number of times that the statistic fails to detect the threshold in the data. This gives us the number of false negatives.

Alpha Level Testing

A total of approximately 3800[1] simulations were run. With $\alpha = 0.1$ only 3 incorrectly determined that there was a threshold in the data when there was none, with $\alpha = 0.05$ no model was incorrectly identified as having a threshold. The test statistic very rarely returns a false positive, this means that if the results produced from a data set show that there is a threshold in the data it is very unlikely that the result is due to random error in the data rather that there is indeed a threshold in the data.

The method in which the simulation was carried out was as follows:

1) A dummy data set was created. It had 6 levels of dose (0, 16, 32, 48, 60, 78) and had varying numbers of animals in each (100, 40, 40, 40, 40, 40 respectively).

2) The model for cancer rate was set to be from the following relation:

$$Prob(y = 1 | dose) = \frac{1}{1 + e^{-(-1.3 - 0.3y + (0.025x)dose)}}$$

Y ranged from 0 to 9 and x ranged from 0 to 19. This means that the intercept (baseline cancer rate) ranged from -1.3 to -4 and the parameter for dose effect ranged from 0 to 0.475[2].

---

[1] A very small number of data sets had no variation in their response (i.e. all the values were the same). This happens when doses are very high or doses are very low and the cancer rate is very low. SAS didn't calculate the error rates for these data sets.

[2] The combination dose=0 with baseline cancer rate=-2.8 to -4 and dose=0.25 with baseline cancer rate=-2.8 to -4 was omitted This meant that there were 190 different models tested instead of 200.

3) From each of the 190 combinations a further 20 data sets were simulated using a binomial distribution with $p = prob(y = 1 | dose)$.

4) The testing algorithm was used to determine if a threshold effect was detected in each data set.

Beta Level Testing

Beta level testing is carried out almost identically as alpha testing except that a threshold is included in the data set and the algorithm is determined to be incorrect if it fails to detect the threshold at either $\alpha = 0.1$ or $\alpha = 0.05$ (depending on the level of certainty required). The procedure is considered "good" if it correctly detects the threshold 70% of the time.

The method in which the simulation was carried out was as follows:

1) A dummy data set was created. It had 6 levels of dose (0, 16, 32, 48, 60, 78) and had varying numbers of animals in each (100, 40, 40, 40, 40, 40 respectively).

2) The model for cancer rate was set to be from the following relation:

$$Prob(y = 1 | dose) = \begin{cases} \dfrac{1}{1 + e^{-(-1.3 - 0.3y + (0.025x)(knee - dose))}} & if\ knee > dose \\ \dfrac{1}{1 + e^{-(-1.3 - 0.3y)}} & if\ knee < dose \end{cases}$$

y ranged from 0 to 9 and x ranged from 0 to 19. This means that the intercept (baseline cancer rate) ranged from -1.3 to -4 and the parameter for dose effect ranged from 0 to 0.475[3].

3) From each of the 190 combinations a further 20 data sets were simulated using a binomial distribution with $p = prob(y = 1 | dose)$.

[3] The combination dose=0 with baseline cancer rate=-2.8 to -4 and dose=0.25 with baseline cancer rate=-2.8 to -4 was omitted This meant that there were 190 different models tested instead of 200.

4) This was repeated for a population of 300, 1500 (5 times the animals in each group), and 3000 (10 times the animals in each group).

5) The testing algorithm was used to determine if a threshold effect was present in the data.

The analysis of the beta error rate is slightly more difficult than that of the alpha error rate, since for starters there is the extra part to step two. It must include the relation between the threshold and the dose effect, this can vary and must have a different simulation for each different possible threshold.

The results of all 114000 simulations can be seen in Appendix B. The main results are that for an experiment with 300 animals it is only at very high thresholds (around 40) is the model capable of detecting a significance difference in the model and even then with very poor results (i.e. much less than $\beta = 0.3$).

With 1500 and 3000 animals the results also show that it was very hard to detect the threshold at low threshold points. When 1500 animals were used the threshold only started to have acceptable levels of false negatives at dose thresholds of 42. When 3000 animals were used it only started have acceptable levels of false negatives at a dose threshold of 34. Tables 5.1.1 and 5.1.2 show that the middle dose levels had the best results for being able to detect a threshold in the data.

Table 5.1.1 Results of simulations with Animals=1500 and Knee=42. Each cell had 20 simulations and a cell marked with "." represents 0 of the simulations had a threshold detected at $\alpha = 0.05$.

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	1	1	2	2	3	4
0.1	.	1	2	2	2	3	5	5	5	6
0.125	2	3	2	4	5	5	7	9	8	10
0.15	3	2	5	5	6	8	12	14	13	13
0.175	2	5	6	8	11	12	14	13	13	14
0.2	5	6	6	9	12	13	14	14	12	9
0.225	5	9	9	11	12	12	14	14	12	10
0.25	X	X	X	X	X	14	14	12	10	8
0.275	8	10	11	14	15	13	12	10	5	4
0.3	9	11	12	13	13	10	8	8	5	2
0.325	8	12	12	11	11	10	6	3	1	.
0.35	9	10	10	10	7	6	3	1	.	.
0.375	8	9	8	7	5	2	.	.	.	.
0.4	8	7	6	3	1	.	.	.	.	.
0.425	7	5	3	.	.	.	.	.	.	.
0.45	4	3	.	.	.	.	.	.	.	.
0.475	1	.	.	.	.	.	.	.	.	.

Table 5.1.2 Results of simulations with Animals=3000 and Knee=34. Each cell had 20 simulations and a cell marked with "." represents 0 of the simulations had a threshold detected at $\alpha = 0.05$

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	1
0.075	.	.	.	.	2	2	2	3	4	5
0.1	1	2	3	3	3	5	5	5	7	7
0.125	3	3	4	5	5	8	9	9	10	9
0.15	3	5	5	7	9	12	12	14	13	12
0.175	4	6	8	11	13	14	15	14	13	9
0.2	6	9	10	12	13	14	14	13	10	9
0.225	9	10	12	12	13	13	11	10	9	5
0.25	X	X	X	X	X	11	10	8	4	2
0.275	10	12	13	12	11	9	7	4	1	.
0.3	10	12	11	10	8	5	3	.	.	.
0.325	9	9	9	6	3	1	1	.	.	.
0.35	8	8	4	5	3	.	.	.	.	.
0.375	4	5	3	1	.	.	.	.	.	.
0.4	3	3	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

The result from the simulations show that the algorithm is not very good at detecting thresholds in the data. This is due to the nature of the threshold. At low doses it can be a very subtle effect due to random error affecting the data. It is possible with a few randomly occuring extra cases of cancer in a low dose group for the threshold effect to missed completely.

The results of the simulations indicate that for this type of study a very large number of animals must be used in order to be able to say that when the algorithm fails to detect a threshold in a data set this actually represents a true absence of a threshold. Even for fairly large experiments, it may be that the algorithm was not powerful enough to detect it. Without increasing the number of animals used it will be difficult to make conclusions about a negative result, i.e. is there no threshold or was the algorithm unable to detect it.

5.2 Number of Animals

It can be seen that if the animals are put into groups as in each simulation, it will require a vast number of animals to accurately determine if a negative result actually reflects a lack of a threshold and not just the inability of the algorithm to detect it.

In Table 5.1.2 we see that even with 3000 animals and a high knee (dose of 34 units), the beta error rate is still too high. It requires a much larger number to be able to reduce where the algorithm can detect a knee.

In section 3.2 it was shown that a data set with a dose parameter of 0.05 needed over 2700 animals to be able to detect a knee at dose 21 without there even being any random error added to the data. Had data been sampled from a binomial distribution instead of using the expected value (i.e. including for the randomness of cancer rates) it would have required a much larger number of animals than the 2730 animals mentioned.

The conclusion that can be drawn from all this analysis of the algorithm is that the threshold at a low dose is a phenomenon which is very hard to detect. It may be only a very slight deviation from what would be expected if the was no threshold in cancer incidence from the radionucleotide.

5.3 Experimental Design

One of the most important results of this thesis is to show that the current data sets available in this field are inadequate for the task demanded. There are several design issues that can be improved for future studies in this field. Some will lead to a reduction in the need for animals, others will help in pinpointing the location of the threshold.

This thesis has shown that the analysis of these types of experiments can be very difficult to undertake due to the subtle effect of a low dose threshold. Experimenters should take great care in determining if this type of experiment is necessary for them to achieve the results they wish to determine. Once a decision has been made to do this type of experiment care should also be taken to ensure that the minimum number of animals required should be used. This should be done to minimize the use of animals for testing.

There are 7 recommendations to be made: **sample size, equal spacing of data points, equal allocation of animals to data points, gradual increases in dose, avoiding MTD, including more explanatory variables in the data sets,** and **keeping track of both incidence and mortality.**

5.2.1 Sample Size

The reason that several of the data sets that apparently exhibited evidence of a threshold failed to show one existed statistically was that they contained too few animals. A low dose threshold is a very fine property of a data set which can easily be distorted by random behaviour. These very slight changes in empirical cancer rates causes the true threshold to be clouded behind random fluctuations in cancer rates. Increasing the number of animals in the study gives a better estimate of the cancer rates at each dose level.

For example, if an experiment was run with 100 animals in each group and for a dose of X the cancer rate was 30% we would have 30 animals with cancer, but due to variation in reaction we may get a few more or a few less. This would cause the cancer rate to look like it was around 30% but not exactly. If the same experiment was done with 10 animals and there was a one more or less cancer than expected the cancer rate would appear to be somewhere between 20 and 40%. In a more extreme case where none of the animals had cancer, it would look as though the cancer rate for that group was 0%. Each dose level below the threshold should have the same cancer rate, since the hypothesis is that dose has no effect on cancer below the threshold. With the random noise affecting each group the cancer rates will increase and decrease. It is important that all the groups below the threshold have a fairly stable cancer incidence rate. If the point before the threshold has a random increase over the group before it, it will look like the threshold is at that point rather than at the true threshold.

With an increase in the number of animals, the statistical power of the test also increases. It was seen in Section 4.3.2 that doubling the number of animals in the experiment would have resulted in the conclusion that a threshold did exist when none was detected with the lower number of animals. The power of the algorithm relies heavily on the number of animals used. Section 5.1 shows how important those numbers are.

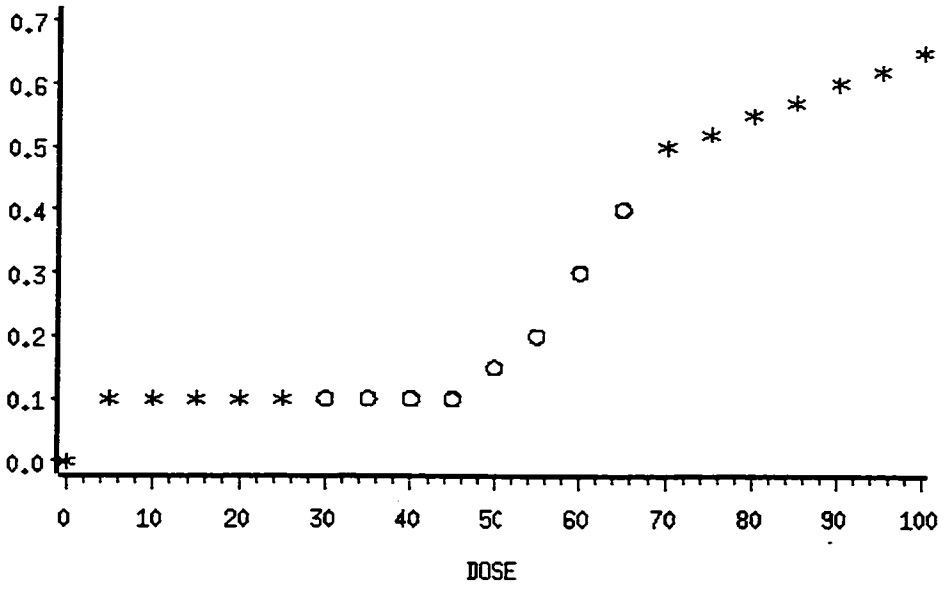
One should not interpret this as a recommendation to attempt larger experiments. In view of the small effects being sought, and the large numbers of animals that would be required, a strong argument would be required to justify subjecting animals to radiation.

5.2.2 Equal Spacing Of Data Points

If data points are equally spaced over all doses from 0 up to the MTD, it is easier to model the entire dose-response behaviour of the radionucleotide. When gaps arise, especially near the threshold point, it is difficult, if not impossible to determine what effect the radionucleotide is having on cancer rates. Graphs 5.3.1 and 5.3.2 show what can happen when there is a gap in the dose groups. The asterisks represent the data measured in a fictitious experiment, the hollow circles represent two possible representations of what may be happening between the doses 25 and 70. One model shows a threshold at 25,

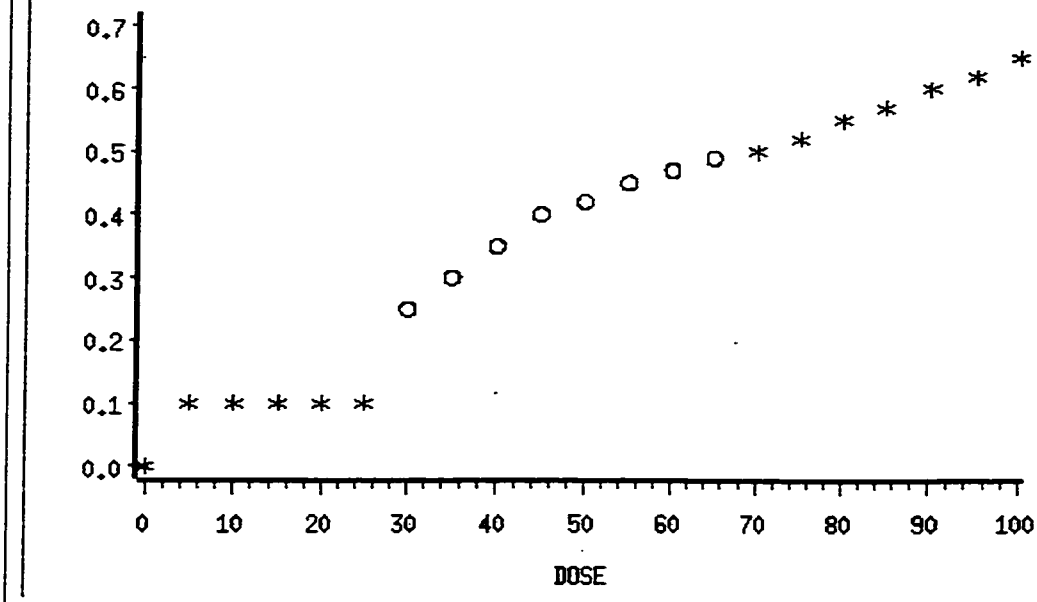
the other at 50. Without evenly spaced doses it is impossible to conclude which is correct. The algorithm will attempt to fit the data using only the first 6 and last 7 points, making the model susceptible to being improperly fit.

Graph 5.3.1



"*" Represent data points, circles are a possible interpolation.

Graph 5.3.2



"*" Represent data points, circles are another possible interpolation.

5.2.3 Equal Allocation Of Animals To Data Points

If animals are not equally allocated to each dose range the model will favor the dose range with the most animals. This happens because the algorithm is trying to best fit the model by the weight of the data points. If one region of dosing has more animals than the others the algorithm will focus on fitting that region more than other regions with less animals.

Data set 24.4 is a perfect example of this. It had 3157 animals in the experiment, enough to run a very good statistical analysis. Unfortunately, 2441 of the animals were in the lowest two dose points, leaving only 716 animals for the other dose levels. This meant nearly all of the statistical power of the algorithm went into fitting the first two points. Since the animals were allocated in that fashion it almost did not matter what was happening with the other higher dose data points, certainly not something as subtle as a

threshold in the data. Had these animals been better spread out the dose-response model could have been analyzed much better.

5.2.4 Gradual Increases In Dose

For the most part the experiments were well designed with respect to gradually increasing the dose. It could be seen in the studies with Plutonium that the mortality rate jumped as soon as the radionucleotide was introduced. This makes it hard to detect a threshold, although it is unlikely that one would exist since the increase in cancer was so immediate.

The opposite can also be a problem as discussed in section 3.2 example 2. In that example it was demonstrated that if the dose was increased too gradually no animals would be left for higher doses and therefore no dose effect would be noticed. If all the animals are at very low doses (below, at, or just above the threshold) it would be impossible for the algorithm to detect a change due to higher doses.

5.2.5 Avoiding MTD

There are several reasons to avoid exceeding the maximally tolerated dose. First, it is cruel to the animals and reduces the ability to detect a low dose threshold. In a perfectly designed experiment the dose levels approach the MTD but never achieve it or exceed it. This leaves the model more power to detect a threshold at lower doses. For data approaching the MTD we must estimate 2 thresholds (upper and lower). This is more difficult. When the MTD is exceed it correctly shows that the incidence of cancer is decreased, but this effect is due to the animals dying of radiation sickness before they had a chance to develop cancer. This in turn makes the model of cancer look like high doses have a protective effect. They do, but only because of competing mortality.

5.2.6 Including More Explanatory Variables in the Data Set

Including more explanatory variables in the data sets could give researchers more data to work with in attempting to explain the results of an experiment. The analysis in this thesis only used the variable *dose*. It is quite possible that there was more that could have been used to explain the results of the experiments. The inclusion of these variables could

allow experimenters to get more accurate results using less data and explain certain characteristics of the data set that could not be explained without the variables being present.

5.2.7 Keeping Track Of Both Incidence And Mortality

Keeping track of both incidence and mortality does not affect the analysis of the data from an experiment, but it does allow for twice as many researchers to be able to use the data. Some experimenters may be interested in doing incidence studies while others are interested in mortality. If for every study both sets of records are kept then both experiments would be able to use the data. Therefore fewer animals needed to be used and can then be used to increase the sample size of other experiments.

Chapter 6

Conclusion

A threshold at low doses of the dose response to radiation is a difficult phenomenon to observe. Although it may appear to be present from an "eyeballing" of the data, statistically it is much harder to prove. Random fluctuations in empirical cancer rates play a serious role in making the threshold hard, or impossible, to detect.

Researchers in this field have based a lot of their work on anecdotal human evidence where dose rates can not easily be measured due to the daily intake of radiation from nature. Human data also has the problem of competing mortality. Proving that there does indeed exist a threshold from low doses of radiation is going to take a great deal of animals in a very well controlled experiment. To add to their difficulties, radiation researchers before them have instilled a fear of radiation in to the public which will cast even more doubt on any positive findings researchers may observe.

This thesis proposes one method for determining a threshold in the data, but it requires great numbers of animals to be able to obtain statistically dependable results. This may make the exection of this method difficult to justify. It is also evident that if a threshold effect exists, it implies that the radiation effect just above the threshold is stronger than that estimated under the Linear Non Threshold Hypothesis.

Appendix A

Data Analysis for Knee Models

The following tables show the results of allowing the model to take as many variables as were found significant (potentially overfitting) versus allowing a maximum of two variables.

The details of this analysis are given in Section 4.2. An entry of "same" means that the model was the same as the model which forced at most 2 variables, an entry of "none" means that none of the variables were significant at the 0.15 level.

Results for data sets with Strontium			
Data Set		At most 2 Explanatory Variables	No Restriction
1.1	AIC score	99.726	Same
	Variables included	Knee9 Knee51	Same

Results for data sets with Gamma Radiation			
Data Set		Only 2 Explanatory Variables	No Restriction
8.31	AIC score	-	-
	Variables	None	None

	included		
8.32	AIC score	-	-
	Variables included	None	None
Results for data sets with Radium			
Data Set		Only 2 Explanatory Variables	No Restriction
1.2	AIC score	83.852	73.159
	Variables included	Dose Knee70	Dose Knee70 Knee21
25.11	AIC score	32.526	Same
	Variables included	Knee21	Same
25.21	AIC score	36.248	Same
	Variables included	Kneep5 Knee19	Same
25.31	AIC score	11.205	Same
	Variables included	Knee19	Same
25.41	AIC score	26.668	Same
	Variables included	Knee9 Knee13	Same

Results for data sets with Plutonium			
Data Set		Only 2 Explanatory Variables	No Restriction
24.4	AIC score	350.852	341.089
	Variables included	Dose Knee7	Dose Knee7 Kneep25 Knee45
28.52	AIC score	126.708	Same
	Variables included	Knee9	Same
28.53	AIC score	76.598	77.083
	Variables included	Dose Knee1	Dose Knee1 Kneep01
25.12	AIC score	36.836	Same
	Variables included	Knee1 Knee7	Same
25.22	AIC score	49.595	Same
	Variables	Dose	Same

	included	Kneep01	
25.32	AIC score	24.295	Same
	Variables included	Knee1 Knee5	Same
25.42	AIC score	58.981	Same
	Variables included	Dose Knee1	Same

Results for data sets with Americium			
Data Set		Only 2 Explanatory Variables	No Restriction
25.13	AIC score	-	-
	Variables included	None	None
25.23	AIC score	40.487	Same
	Variables included	Dose Knee3	Same
25.33	AIC score	25.781	Same
	Variables included	Knee7 Kneep5	Same
25.43	AIC score	45.599	Same
	Variables included	Dose Knee1	Same

Results for data sets with Californium			
Data Set		Only 2 Explanatory Variables	No Restriction
25.14	AIC score	37.215	Same
	Variables included		Same
25.15	AIC score	10.702	Same
	Variables included	Knee11	Same
25.24	AIC score	55.228	54.467
	Variables included	Dose Knee3	Dose Knee3 Kneep5
25.25	AIC score	39.221	Same
	Variables included	Knee1 Knee11	Same
25.34	AIC score	11.481	Same
	Variables included	Knee7	Same
25.35	AIC score	25.663	Same

	Variables included	Knee1 Knee9	Same
25.44	AIC score	55.968	Same
	Variables included	Kneep01 Knee3	Same
25.45	AIC score	42.943	Same
	Variables included	Knee3 Knee7	Same

Appendix B

Tables of Beta Error Simulations

The following tables are the results of running simulation programs to determine the number of times (out of 20) the algorithm was able to detect the presence of a threshold.

This corresponds to Section 5.1 Simulation. The entries that should be marked "0" are marked "." for the facility of the reader. The entries marked "X" did not have simulations performed.

POP=300 KNEE=10

TABLE OF DOSING BY BASELINE

DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	.	.	.
0.1	.	.	.	.	.	.	.	.	.	.
0.125	.	.	.	.	.	.	.	.	.	.
0.15	.	.	.	.	.	.	.	.	.	.
0.175	.	.	.	.	.	.	.	.	.	.
0.2	.	.	.	.	.	.	.	.	.	.
0.225	.	.	.	.	.	.	.	.	.	.
0.25	X	X	X	X	X	.	.	.	.	.
0.275	.	.	.	.	.	.	.	.	.	.
0.3	.	.	.	.	.	.	.	.	.	.
0.325	.	.	.	.	.	.	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=300 KNEE=14

TABLE OF DOSING BY BASELINE

DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	.	.	.
0.1	.	.	.	.	.	.	.	.	.	.
0.125	.	.	.	.	.	.	.	.	.	.
0.15	.	.	.	.	.	.	.	.	.	.
0.175	.	.	.	.	.	.	.	.	.	.
0.2	.	.	.	.	.	.	.	.	.	.
0.225	.	.	.	.	.	.	.	.	.	.
0.25	X	X	X	X	X	.	.	.	.	.
0.275	.	.	.	.	.	.	.	.	.	.
0.3	.	.	.	.	.	.	.	.	.	.
0.325	.	.	.	.	.	.	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=300 KNEE=18

TABLE OF DOSING BY BASELINE

DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	.	.	.
0.1	.	.	.	.	.	.	.	.	.	.
0.125	.	.	.	.	.	.	.	.	.	.
0.15	.	.	.	.	.	.	.	.	.	.
0.175	.	.	.	.	.	.	.	.	.	.
0.2	.	.	.	.	.	.	.	.	.	.
0.225	.	.	.	.	.	.	.	.	.	.
0.25	X	X	X	X	X	.	.	.	.	.
0.275	.	.	.	.	.	.	.	.	.	.
0.3	.	.	.	.	.	.	.	.	.	.
0.325	.	.	.	.	.	.	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=300 KNEE=22

TABLE OF DOSING BY BASELINE

DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	.	.	.
0.1	.	.	.	.	.	.	.	.	.	.
0.125	.	.	.	.	.	.	.	.	.	.
0.15	1	.	.	.	.	.	.	1	1	.
0.175	.	.	.	.	.	.	.	.	.	.
0.2	.	.	.	.	.	.	.	.	.	.
0.225	.	.	.	.	.	.	.	.	.	.
0.25	X	X	X	X	X	.	.	.	.	.
0.275	.	.	.	.	.	.	.	.	.	.
0.3	.	.	.	.	.	.	.	.	.	.
0.325	.	.	.	.	.	.	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=300 KNEE=26

TABLE OF DOSING BY BASELINE

DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	.	.	.
0.1	.	.	.	.	.	.	.	.	.	.
0.125	.	.	.	.	.	.	.	.	.	.
0.15	1	1	.	.	.	.	.	.	1	1
0.175	.	.	.	.	.	.	.	1	.	1
0.2	.	.	.	.	.	.	.	1	.	.
0.225	.	.	.	.	.	.	.	.	.	.
0.25	X	X	X	X	X	.	.	.	.	.
0.275	.	.	.	.	.	.	.	.	.	.
0.3	.	.	.	.	.	.	.	.	.	.
0.325	.	.	.	.	.	.	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=300 KNEE=30

TABLE OF DOSING BY BASELINE

DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	.	.	.
0.1	.	.	.	.	.	.	.	.	.	.
0.125	.	.	.	.	.	.	.	.	.	2
0.15	.	1	.	.	.	.	.	.	2	1
0.175	1	.	.	.	.	.	.	1	1	.
0.2	.	.	.	.	.	.	.	1	1	.
0.225	.	.	.	.	.	.	1	.	.	.
0.25	X	X	X	X	X	.	.	.	.	.
0.275	.	.	.	.	.	.	.	.	.	.
0.3	.	.	.	.	.	.	.	.	.	.
0.325	.	.	.	.	.	.	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=300 KNEE=34

TABLE OF DOSING BY BASELINE

DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	.	.	.
0.1	.	.	.	.	.	.	.	.	.	.
0.125	.	.	.	.	.	.	.	.	.	.
0.15	.	1	1	.	.	.	.	.	.	3
0.175	.	.	.	.	.	.	.	.	2	2
0.2	.	.	.	.	.	.	.	2	2	1
0.225	.	.	.	.	.	.	1	1	1	.
0.25	X	X	X	X	X	.	1	.	.	.
0.275	.	.	.	.	.	.	.	.	.	.
0.3	.	.	.	.	.	.	.	.	.	.
0.325	.	.	.	.	.	.	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=300 KNEE=38

TABLE OF DOSING BY BASELINE

DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	.	.	.
0.1	.	.	.	.	.	.	.	.	.	.
0.125	.	.	.	2	.	.	.	.	.	.
0.15	.	1	1	1	.	.	.	.	.	3
0.175	1	.	1	.	.	.	.	.	.	3
0.2	.	.	.	.	.	.	1	.	3	2
0.225	.	.	.	.	.	.	.	2	1	1
0.25	X	X	X	X	X	.	1	2	1	.
0.275	.	.	.	.	.	.	1	.	.	.
0.3	.	.	.	.	.	.	.	.	.	.
0.325	.	.	.	.	.	.	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=300 KNEE=42

TABLE OF DOSING BY BASELINE
DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	.	.	.
0.1	.	.	.	.	.	.	.	.	.	.
0.125	.	.	.	.	.	.	.	.	.	.
0.15	.	.	2	1	.	.	.	.	.	.
0.175	1	2	1	1	.	.	.	.	.	3
0.2	1	.	.	.	.	.	.	1	.	3
0.225	.	.	.	.	.	1	1	.	3	2
0.25	X	X	X	X	X	1	.	2	3	2
0.275	.	.	.	.	1	.	.	2	1	.
0.3	.	.	.	.	.	.	1	1	.	.
0.325	.	.	.	.	.	1	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=300 KNEE=46

TABLE OF DOSING BY BASELINE
DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	.	.	.
0.1	.	.	.	.	.	.	.	.	.	.
0.125	.	.	.	.	.	.	.	.	.	.
0.15	.	.	3	2	.	.	.	.	1	.
0.175	1	1	2	1	.	.	.	.	.	1
0.2	1	.	.	.	.	.	1	1	1	4
0.225	.	.	.	.	1	2	1	1	1	3
0.25	X	X	X	X	X	1	2	.	3	3
0.275	.	.	.	.	2	1	1	3	3	2
0.3	.	.	.	1	1	.	.	2	2	1
0.325	.	1	1	.	.	.	2	1	1	.
0.35	1	.	.	.	.	.	1	.	.	.
0.375	.	.	.	.	.	1	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=1500 KNEE=10

TABLE OF DOSING BY BASELINE
DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	.	.	.
0.1	.	.	.	.	.	.	.	.	.	.
0.125	.	.	.	.	.	.	.	.	.	.
0.15	.	.	.	.	.	.	.	.	.	.
0.175	.	.	.	.	.	.	.	.	.	.
0.2	.	.	.	.	.	.	.	.	.	.
0.225	.	.	.	.	.	.	.	.	.	.
0.25	X	X	X	X	X	.	.	.	.	.
0.275	.	.	.	.	.	.	.	.	.	.
0.3	.	.	.	.	.	.	.	.	.	.
0.325	.	.	.	.	.	.	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=1500 KNEE=14

TABLE OF DOSING BY BASELINE
DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	.	.	.
0.1	.	.	.	.	.	.	.	.	.	.
0.125	.	.	.	.	.	.	.	.	.	.
0.15	.	.	.	.	.	.	.	.	.	.
0.175	.	.	.	.	.	.	.	.	.	.
0.2	.	.	.	.	.	.	.	.	.	.
0.225	.	.	.	.	.	.	.	.	.	.
0.25	X	X	X	X	X	.	.	.	.	.
0.275	.	.	.	.	.	.	.	.	.	.
0.3	.	.	.	.	.	.	.	.	.	.
0.325	.	.	.	.	.	.	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=1500 KNEE=18

TABLE OF DOSING BY BASELINE
DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	.	.	.
0.1	.	.	.	.	.	.	.	.	1	1
0.125	.	.	.	.	.	1	1	1	.	.
0.15	.	1	.	1	.	.	.	.	.	.
0.175	.	.	.	.	.	.	.	.	.	.
0.2	.	.	.	.	.	.	.	.	.	.
0.225	.	.	.	.	.	.	.	.	.	.
0.25	X	X	X	X	X	.	.	.	.	.
0.275	.	.	.	.	.	.	.	.	.	.
0.3	.	.	.	.	.	.	.	.	.	.
0.325	.	.	.	.	.	.	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=1500 KNEE=22

TABLE OF DOSING BY BASELINE
DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	.	.	.
0.1	.	.	.	.	.	1	1	1	1	1
0.125	.	.	.	1	1	1	1	2	1	.
0.15	1	1	1	1	1	1	.	.	.	.
0.175	1	1	.	.	.	.	.	.	.	.
0.2	.	.	.	.	.	.	.	.	.	.
0.225	.	.	.	.	.	.	.	.	.	.
0.25	X	X	X	X	X	.	.	.	.	.
0.275	.	.	.	.	.	.	.	.	.	.
0.3	.	.	.	.	.	.	.	.	.	.
0.325	.	.	.	.	.	.	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=1500 KNEE=26

TABLE OF DOSING BY BASELINE

DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	.	.	1
0.1	.	.	.	.	.	1	1	1	1	1
0.125	.	1	1	1	1	1	1	1	2	1
0.15	1	1	1	1	1	1	1	1	.	.
0.175	1	1	1	1	1	1	1	1	.	.
0.2	1	1	1	2	1	1	.	.	.	.
0.225	1	1	1	.	.	.	.	.	.	.
0.25	X	X	X	X	X	.	.	.	.	.
0.275	.	.	.	.	.	.	.	.	.	.
0.3	.	.	.	.	.	.	.	.	.	.
0.325	.	.	.	.	.	.	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=1500 KNEE=30

TABLE OF DOSING BY BASELINE

DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	1	1	1
0.1	.	.	.	.	1	1	1	1	1	2
0.125	.	2	1	1	1	1	2	3	4	2
0.15	1	1	1	2	2	2	2	2	2	1
0.175	1	1	2	2	2	2	2	2	2	1
0.2	1	1	2	2	3	2	2	1	1	.
0.225	2	2	2	2	2	2	1	.	.	.
0.25	X	X	X	X	X	.	.	.	.	.
0.275	3	3	1	1	.	.	.	.	.	.
0.3	2	.	1	.	.	.	.	.	.	.
0.325	1	.	.	.	.	.	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=1500 KNEE=34

TABLE OF DOSING BY BASELINE

DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	1	1	1
0.1	.	.	.	1	1	1	1	1	3	4
0.125	1	1	2	1	1	3	4	3	4	4
0.15	1	1	2	2	4	4	4	3	3	2
0.175	1	1	3	2	2	3	4	3	3	2
0.2	2	3	3	3	3	4	3	2	2	2
0.225	3	3	3	3	4	4	2	3	2	1
0.25	X	X	X	X	X	4	3	2	.	.
0.275	4	4	5	5	3	3	.	1	.	.
0.3	4	5	4	3	1	1	.	.	.	.
0.325	5	3	2	1	.	.	.	.	.	.
0.35	3	2	1	.	.	.	.	.	.	.
0.375	3	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=1500 KNEE=38

TABLE OF DOSING BY BASELINE

DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	1	1	1	2	1
0.1	.	.	1	1	1	2	4	5	5	4
0.125	1	1	2	3	4	5	5	5	5	4
0.15	1	1	3	5	4	6	7	7	7	3
0.175	2	4	5	5	5	6	8	8	7	5
0.2	2	3	3	7	9	9	9	9	5	4
0.225	3	4	8	8	9	10	9	9	6	3
0.25	X	X	X	X	X	10	8	3	3	1
0.275	7	8	9	9	9	6	5	3	1	1
0.3	8	8	8	7	6	3	4	2	.	.
0.325	7	7	7	4	4	3	1	.	.	.
0.35	7	5	6	5	2	.	.	.	.	.
0.375	6	5	3	1	.	.	.	.	.	.
0.4	4	3	.	.	.	.	.	.	.	.
0.425	1	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=1500 KNEE=42

TABLE OF DOSING BY BASELINE

DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	1	1	2	2	3	4
0.1	.	1	2	2	2	3	5	5	5	6
0.125	2	3	2	4	5	5	7	9	8	10
0.15	3	2	5	5	6	8	12	14	13	13
0.175	2	5	6	8	11	12	14	13	13	14
0.2	5	6	6	9	12	13	14	14	12	9
0.225	5	9	9	11	12	12	14	14	12	10
0.25	X	X	X	X	X	14	14	12	10	8
0.275	8	10	11	14	15	13	12	10	5	4
0.3	9	11	12	13	13	10	8	8	5	2
0.325	8	12	12	11	11	10	6	3	1	.
0.35	9	10	10	10	7	6	3	1	.	.
0.375	8	9	8	7	5	2	.	.	.	.
0.4	8	7	6	3	1	.	.	.	.	.
0.425	7	5	3	.	.	.	.	.	.	.
0.45	4	3	.	.	.	.	.	.	.	.
0.475	1	.	.	.	.	.	.	.	.	.

POP=1500 KNEE=46

TABLE OF DOSING BY BASELINE

DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	2	1	2	3	3	5	5
0.1	.	2	3	3	3	5	5	6	10	11
0.125	3	2	3	5	6	9	11	15	15	15
0.15	3	4	5	7	11	15	16	17	16	16
0.175	3	7	8	12	15	16	17	17	17	15
0.2	6	8	10	14	15	18	18	19	18	16
0.225	7	10	12	16	17	18	19	18	17	15
0.25	X	X	X	X	X	19	19	17	17	13
0.275	10	14	16	17	17	19	17	16	15	12
0.3	13	15	16	18	18	17	17	16	11	9
0.325	15	15	16	17	17	17	14	12	8	4
0.35	15	16	16	17	16	14	12	6	5	1
0.375	15	15	16	14	14	10	8	5	1	.
0.4	15	14	14	12	9	9	3	1	.	.
0.425	12	12	10	10	9	3	.	.	.	.
0.45	10	10	11	6	2	.	.	.	.	.
0.475	10	8	4	2	.	.	.	.	.	.

POP=3000 KNEE=10

TABLE OF DOSING BY BASELINE

DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	.	.	.
0.1	.	.	.	.	.	.	.	.	.	.
0.125	.	.	.	.	.	.	.	.	.	.
0.15	.	.	.	.	.	.	.	.	.	.
0.175	.	.	.	.	.	.	.	.	.	.
0.2	.	.	.	.	.	.	.	.	.	.
0.225	.	.	.	.	.	.	.	.	.	.
0.25	X	X	X	X	X	.	.	.	.	.
0.275	.	.	.	.	.	.	.	.	.	.
0.3	.	.	.	.	.	.	.	.	.	.
0.325	.	.	.	.	.	.	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=3000 KNEE=14

TABLE OF DOSING BY BASELINE

DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	.	.	.
0.1	.	.	.	.	.	.	.	.	.	.
0.125	.	.	.	.	.	.	.	.	.	.
0.15	.	.	.	.	.	.	.	.	.	.
0.175	.	.	.	.	.	.	.	.	.	.
0.2	.	.	.	.	.	.	.	.	.	.
0.225	.	.	.	.	.	.	.	.	.	.
0.25	X	X	X	X	X	.	.	.	.	.
0.275	.	.	.	.	.	.	.	.	.	.
0.3	.	.	.	.	.	.	.	.	.	.
0.325	.	.	.	.	.	.	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=3000 KNEE=18

TABLE OF DOSING BY BASELINE

DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	.	.	.
0.1	.	.	.	.	.	.	.	1	1	1
0.125	.	.	.	1	1	1	1	1	1	3
0.15	.	1	1	1	1	2	1	.	.	.
0.175	.	1	1	1	.	.	.	.	.	.
0.2	.	.	.	.	.	.	.	.	.	.
0.225	.	.	.	.	.	.	.	.	.	.
0.25	X	X	X	X	X	.	.	.	.	.
0.275	.	.	.	.	.	.	.	.	.	.
0.3	.	.	.	.	.	.	.	.	.	.
0.325	.	.	.	.	.	.	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=3000 KNEE=22

TABLE OF DOSING BY BASELINE

DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	.	.	.	1
0.1	.	.	.	.	1	1	1	1	1	1
0.125	.	1	1	1	1	1	1	2	1	1
0.15	1	1	1	1	1	2	2	1	1	.
0.175	1	1	1	2	1	1	1	.	.	.
0.2	1	1	1	2	2	.	.	.	.	.
0.225	1	2	1	1	.	.	.	.	.	.
0.25	X	X	X	X	X	.	.	.	.	.
0.275	.	.	.	.	.	.	.	.	.	.
0.3	.	.	.	.	.	.	.	.	.	.
0.325	.	.	.	.	.	.	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=3000 KNEE=26

TABLE OF DOSING BY BASELINE
DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1 .6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	.	1	1	1	1
0.1	.	.	.	.	1	1	1	1	1	2
0.125	.	2	1	1	2	3	3	4	3	4
0.15	1	1	1	2	3	4	4	5	2	2
0.175	1	2	3	3	2	2	2	2	2	2
0.2	2	2	3	3	3	2	2	2	1	.
0.225	3	3	3	3	2	2	2	.	.	.
0.25	X	X	X	X	X	1	.	.	.	.
0.275	3	3	3	1	.	.	.	.	.	.
0.3	3	1	.	.	.	.	.	.	.	.
0.325	.	.	.	.	.	.	.	.	.	.
0.35	.	.	.	.	.	.	.	.	.	.
0.375	.	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=3000 KNEE=30

TABLE OF DOSING BY BASELINE
DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	.
0.075	.	.	.	.	.	1	1	1	1	2
0.1	.	.	1	2	2	3	5	5	5	5
0.125	2	2	2	3	5	5	5	5	5	5
0.15	2	3	3	5	5	6	6	7	6	5
0.175	2	5	5	6	7	7	6	6	4	3
0.2	5	4	6	7	8	9	7	4	3	2
0.225	4	6	9	9	9	9	4	2	2	.
0.25	X	X	X	X	X	5	3	2	.	.
0.275	7	8	7	5	3	3	2	.	.	.
0.3	6	7	4	3	3	.	.	.	.	.
0.325	5	3	3	.	.	.	.	.	.	.
0.35	3	.	1	.	.	.	.	.	.	.
0.375	1	.	.	.	.	.	.	.	.	.
0.4	.	.	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=3000 KNEE=34

TABLE OF DOSING BY BASELINE
DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	.	.	1
0.075	.	.	.	.	2	2	2	3	4	5
0.1	1	2	3	3	3	5	5	5	7	7
0.125	3	3	4	5	5	8	9	9	10	9
0.15	3	5	5	7	9	12	12	14	13	12
0.175	4	6	8	11	13	14	15	14	13	9
0.2	6	9	10	12	13	14	14	13	10	9
0.225	9	10	12	12	13	13	11	10	9	5
0.25	X	X	X	X	X	11	10	8	4	2
0.275	10	12	13	12	11	9	7	4	1	.
0.3	10	12	11	10	8	5	3	.	.	.
0.325	9	9	9	6	3	1	1	.	.	.
0.35	8	8	4	5	3	.	.	.	.	.
0.375	4	5	3	1	.	.	.	.	.	.
0.4	3	3	.	.	.	.	.	.	.	.
0.425	.	.	.	.	.	.	.	.	.	.
0.45	.	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=3000 KNEE=38

TABLE OF DOSING BY BASELINE
DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	.	1	1	1
0.075	.	.	.	2	3	3	3	5	5	5
0.1	1	3	3	3	6	6	11	13	13	13
0.125	3	4	5	7	9	15	16	16	17	16
0.15	4	7	8	13	15	16	17	17	17	16
0.175	7	9	12	15	17	19	19	19	18	16
0.2	10	12	16	18	18	19	19	18	17	14
0.225	11	13	16	18	18	20	19	16	16	13
0.25	X	X	X	X	X	19	17	16	13	10
0.275	15	16	17	18	18	17	15	12	9	3
0.3	16	16	16	17	17	14	11	7	5	3
0.325	16	16	16	16	12	10	8	5	1	.
0.35	15	15	15	12	10	6	3	.	.	.
0.375	12	12	10	6	5	2	.	.	.	.
0.4	10	8	6	3	.	.	.	.	.	.
0.425	7	4	2	.	.	.	.	.	.	.
0.45	3	.	.	.	.	.	.	.	.	.
0.475	.	.	.	.	.	.	.	.	.	.

POP=3000 KNEE=42

TABLE OF DOSING BY BASELINE
DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	.	1	3	3	3
0.075	.	.	2	3	3	4	4	7	14	14
0.1	3	3	3	4	9	12	18	19	19	19
0.125	3	6	8	11	17	18	20	20	20	20
0.15	6	8	15	18	20	20	20	20	20	20
0.175	9	13	17	19	20	20	20	20	20	20
0.2	11	17	18	20	20	20	20	20	20	20
0.225	16	18	20	20	20	20	20	20	20	19
0.25	X	X	X	X	X	20	20	20	20	17
0.275	18	20	20	20	20	20	20	20	18	15
0.3	20	20	20	20	20	20	20	19	14	9
0.325	20	20	20	20	20	20	17	12	10	6
0.35	20	20	20	20	19	17	12	9	5	1
0.375	20	20	19	19	16	12	7	4	.	.
0.4	17	18	16	15	10	8	3	.	.	.
0.425	15	16	12	9	7	1	.	.	.	.
0.45	12	10	9	3	.	.	.	.	.	.
0.475	10	6	2	.	.	.	.	.	.	.

POP=3000 KNEE=46

TABLE OF DOSING BY BASELINE
DOSING BASELINE

Frequency	-4	-3.7	-3.4	-3.1	-2.8	-2.5	-2.2	-1.9	-1.6	-1.3
0	X	X	X	X	X	.	.	.	.	.
0.025	.	.	.	.	.	.	.	.	.	.
0.05	.	.	.	.	.	3	3	3	4	3
0.075	.	3	3	3	3	6	10	15	17	18
0.1	3	3	5	8	13	19	20	20	20	20
0.125	4	8	13	19	20	20	20	20	20	20
0.15	9	16	20	20	20	20	20	20	20	20
0.175	13	19	20	20	20	20	20	20	20	20
0.2	16	19	20	20	20	20	20	20	20	20
0.225	18	20	20	20	20	20	20	20	20	20
0.25	X	X	X	X	X	20	20	20	20	20
0.275	20	20	20	20	20	20	20	20	20	20
0.3	20	20	20	20	20	20	20	20	20	20
0.325	20	20	20	20	20	20	20	20	20	15
0.35	20	20	20	20	20	20	20	20	18	12
0.375	20	20	20	20	20	20	20	17	12	7
0.4	20	20	20	20	20	20	16	10	8	1
0.425	20	20	20	20	20	15	12	6	1	.
0.45	20	20	20	18	14	12	4	.	.	.
0.475	20	19	16	14	11	3	.	.	.	.

Appendix C

SAS Program for Beta Error Simulation

The following program was used to model the Alpha and Beta error rates. To modify the program to calculate Alpha error rates all that is necessary is the removal of the Knee variable from the simulation. The results of these simulations can be seen in Section 5.1 Simulation and Appendix C Tables of Beta Error Simulations.

```
data newdata;
input expmnt dose num;
cards;
1 0 500
1 16 200
1 32 200
1 48 200
1 60 200
1 78 200
;
run;
data table; run;

%macro looping(baseline,doseeff,knee,random,code);

data loopdata; set newdata;          /**CONSTRUCION OF THE MODELED DATA**/
if dose>&knee then prob1=1/(1+exp(-((&baseline)+(&doseeff)*(dose-&knee))));
if dose=<&knee then prob1=1/(1+exp(-((&baseline)+(0)*dose)));
if prob1=0 then prob1=0.0000000001;
if prob1=1 then prob1=0.9999999999;
result=ranbin(&random,num,prob1);    /**SAMPLES FROM BINARY TO SIMULATE RANDOM
                                                CHANGES IN CANCER RATES**/

run;
data loopdata; set loopdata;
ratio=result/num;
knee1=0;knee3=0;knee5=0;knee7=0;knee9=0;kneep5=0;kneep25=0;kneep01=0;
knee11=0;knee13=0;knee15=0;knee17=0;knee19=0;knee21=0;knee23=0;knee25=0;
knee27=0;knee29=0;knee31=0;knee33=0;knee35=0;knee37=0;knee39=0;
knee41=0;knee43=0;knee45=0;knee47=0;knee49=0;knee51=0;knee53=0;
knee60=0;knee70=0;knee80=0;knee90=0;knee100=0;knee110=0;knee120=0;knee140=0;
if dose>60 then knee60=dose-60;
if dose>70 then knee70=dose-70;
if dose>80 then knee80=dose-80;
if dose>90 then knee90=dose-90;
if dose>100 then knee100=dose-100;
if dose>110 then knee110=dose-110;
if dose>120 then knee120=dose-120;
if dose>140 then knee140=dose-140;
if dose>1 then knee1=dose-1;
if dose>3 then knee3=dose-3;
if dose>5 then knee5=dose-5;
if dose>7 then knee7=dose-7;
if dose>9 then knee9=dose-9;
if dose>11 then knee11=dose-11;
if dose>13 then knee13=dose-13;
if dose>15 then knee15=dose-15;
if dose>17 then knee17=dose-17;
if dose>19 then knee19=dose-19;
if dose>0.5 then kneep5=dose-0.5;
if dose>21 then knee21=dose-21;
if dose>23 then knee23=dose-23;
if dose>25 then knee25=dose-25;
if dose>27 then knee27=dose-27;
```

```
 if dose>29 then knee29=dose-29;
 if dose>31 then knee31=dose-31;
 if dose>33 then knee33=dose-33;
 if dose>35 then knee35=dose-35;
 if dose>37 then knee37=dose-37;
 if dose>39 then knee39=dose-39;
 if dose>41 then knee41=dose-41;
 if dose>43 then knee43=dose-43;
 if dose>45 then knee45=dose-45;
 if dose>47 then knee47=dose-47;
 if dose>51 then knee51=dose-51;
 if dose>53 then knee53=dose-53;
 if dose>49 then knee49=dose-49;
 if dose>0.25 then kneep25=dose-0.25;
 if dose>0.01 then kneep01=dose-0.01;
 run;
 proc sort data=loopdata;
 by expmnt;
 run;

 data bigout;
 run;
 data newdata1; set loopdata;
 run;
 proc logistic data=newdata1 noprint outest=out1;      /**LOGISTIC REGRESSION**/
 model result/num=dose;
 output out=newdata1 predicted=upred;
 run;

 proc logistic data=newdata1 noprint outest=out3;     /**KNEE LOGISTIC REGRESSION**/
 model result/num=dose knee1 knee3 knee5 knee7 knee9 kneep5 kneep25 kneep01
   knee11 knee13 knee15 knee17 knee19
   knee21 knee23 knee25 knee27 knee29
   knee31 knee33 knee35 knee37 knee39
   knee41 knee43 knee45 knee47 knee49
   knee51 knee53
   knee60 knee70 knee80 knee90 knee100 knee110 knee120 knee140
/stepwise slentry=0.15 slstay=0.15 selection=forward stop=2;
output out=newdata1 predicted=kpred;
run;

proc sort data=loopdata;
by expmnt;
run;


data out1; set out1;
expmnt=1; line="u";
run;
data out3; set out3;
expmnt=1; line="k";
run;

data results; set out1  out3;          /**COMPARISON OF THE TWO MODELS**/
```

```
uresult=lag1(_LNLIKE_);
if line="k" then chiku=_LNLIKE_-uresult;
run;


data bigout; set bigout results;
run;

data prefinal; set bigout;
where line="k";
ident=&dtemp;
run;

data final; set prefinal final;       /**COUNTING THE NUMBER OF SIGNIFICANT DIFFERENCES**/
if probchi(chiku,2)>=0.90 then k90u&code=1;
if probchi(chiku,2)>=0.95 then k95u&code=1;
pku=1-probchi(chiku,2);
run;
/*
proc datasets;
delete out1 out3 loopdata bigout results;
run;*/
%mend;


%macro toloop;
%do x=0 %to 9;    /*dose effect*/       /**GENERATING THE MODELS**/
 %do y=0 %to 4;  /*base line*/ /**THESE WERE CHANGED **/
                                  /**TO PRODUCE THE DIFFERENT MODELS**/
  %do z=0 %to 9;    /*knee*/
   data final; run;

   %let dtemp=%eval(%eval(&z)*100+%eval(&x)*10+%eval(&y));


   %do w=1 %to 20;    /*SEED*/
     %let btemp=-1.3-0.3*%eval(&y);
     %let ctemp=0.25+0.025*%eval(&x);
     %let etemp=10+4*%eval(&z);
     %looping(&btemp,&ctemp,&z,&w,&dtemp); /*(baseline,doseeff,knee,random,code)*/
   %end;
  data final; set final;
  if pku=. then delete;
  run;

  proc summary data=final sum;
  var k90u&dtemp k95u&dtemp;       /**SAVING THE RESULTS**/
  id ident;
  output out=line sum=totalu90 totalu95;
  run;
  data table; set table line;
  run;
  %end;
%end;
```

```
%end;
%mend;
%toloop;


quit;

proc print data=table;          /**OUTPUTING THE RESULTS**/
run;
```

Appendix D

SAS Program for Knee Logistic Models

The following program modeled the data using the Knee Logistic Regression model. It was used for both the single run experiments and the combined analysis. The results from this program can be seen in section 4.2 Choice of 2 Knee Model Over Others, 4.3 Single Run Experiments, and 4.4 Combined Analysis.

```
data datum;
input Expmnt  Species$    Radionuc$   outcome$    num      dose /*Grays*/     result;
cards;
1.1    Beagle      Sr90Cl2     Osteosar    13    0     0
1.1    Beagle      Sr90Cl2     Osteosar    38    3.8   0
1.1    Beagle      Sr90Cl2     Osteosar    13    26    0
1.1    Beagle      Sr90Cl2     Osteosar    24    73    10
1.1    Beagle      Sr90Cl2     Osteosar    10    117   5
1.1    Beagle      Sr90Cl2     Osteosar    22    0     0
1.1    Beagle      Sr90Cl2     Osteosar    9     5.7   0
1.1    Beagle      Sr90Cl2     Osteosar    16    29    0
1.1    Beagle      Sr90Cl2     Osteosar    14    93    6
1.1    Beagle      Sr90Cl2     Osteosar    21    50    8
1.2    Beagle      Ra226       Osteosar    44    0     0
1.2    Beagle      Ra226       Osteosar    10    0.26  0
1.2    Beagle      Ra226       Osteosar    25    0.75  1
1.2    Beagle      Ra226       Osteosar    23    1.6   1
1.2    Beagle      Ra226       Osteosar    14    3.7   1
1.2    Beagle      Ra226       Osteosar    13    8.7   5
1.2    Beagle      Ra226       Osteosar    12    22    11
1.2    Beagle      Ra226       Osteosar    13    52    12
1.2    Beagle      Ra226       Osteosar    10    143   9
8.31   BlbMice     Gamma       Cancer      193   0     120
8.31   BlbMice     Gamma       Cancer      149   2     97
8.31   BlbMice     Gamma       Cancer      94    4     55
8.31   BlbMice     Gamma       Cancer      113   6     64
8.32   BlbMice     Gammafr     Cancer      74    2     48
8.32   BlbMice     Gammafr     Cancer      74    4     50
8.32   BlbMice     Gammafr     Cancer      78    6     50
10.31  fBeagle     Sr90        Sarcoma     40    0     2
10.31  fBeagle     Sr90        Sarcoma     40    0.4   0
10.31  fBeagle     Sr90        Sarcoma     19    1.2   0
10.31  fBeagle     Sr90        Sarcoma     32    6.7   0
10.31  fBeagle     Sr90        Sarcoma     34    22.5  0
10.31  fBeagle     Sr90        Sarcoma     35    50.4  5
10.31  fBeagle     Sr90        Sarcoma     32    80.2  20
10.31  fBeagle     Sr90        Sarcoma     7     107   5
10.32  mBeagle     Sr90        Sarcoma     40    0     2
10.32  mBeagle     Sr90        Sarcoma     38    0.4   0
10.32  mBeagle     Sr90        Sarcoma     21    1.2   0
10.32  mBeagle     Sr90        Sarcoma     33    6.7   0
10.32  mBeagle     Sr90        Sarcoma     38    22.5  4
10.32  mBeagle     Sr90        Sarcoma     30    50.4  5
10.32  mBeagle     Sr90        Sarcoma     32    80.2  9
10.32  mBeagle     Sr90        Sarcoma     12    107   13
10.41  fBeagle     Sr90inj     Sarcoma     10    6.7   0
10.41  fBeagle     Sr90inj     Sarcoma     15    54.3  3
10.42  mBeagle     Sr90inj     Sarcoma     10    6.7   1
10.42  mBeagle     Sr90inj     Sarcoma     10    54.3  3
24.4   rat         Pu239O2     LungTum     15    55.1  8
24.4   rat         Pu239O2     LungTum     17    44.4  15
24.4   rat         Pu239O2     LungTum     32    34.5  21
24.4   rat         Pu239O2     LungTum     17    25.1  12
24.4   rat         Pu239O2     LungTum     33    15.7  21
```

24.4	rat	Pu239O2	LungTum	18	7.99	6
24.4	rat	Pu239O2	LungTum	38	5.03	8
24.4	rat	Pu239O2	LungTum	58	2.32	3
24.4	rat	Pu239O2	LungTum	145	0.62	2
24.4	rat	Pu239O2	LungTum	343	0.19	3
24.4	rat	Pu239O2	LungTum	1389	0.06	1
24.4	rat	Pu239O2	LungTum	1052	0.002	2
25.11	mblkmice	Ra226	bonesarc	12	46.8	6
25.11	mblkmice	Ra226	bonesarc	11	19.67	0
25.11	mblkmice	Ra226	bonesarc	12	7.35	1
25.11	mblkmice	Ra226	bonesarc	12	2.56	0
25.11	mblkmice	Ra226	bonesarc	12	0.4	0
25.12	mblkmice	Pu239	bonesarc	13	12.62	7
25.12	mblkmice	Pu239	bonesarc	11	5.32	3
25.12	mblkmice	Pu239	bonesarc	12	1.62	0
25.12	mblkmice	Pu239	bonesarc	11	0.67	0
25.12	mblkmice	Pu239	bonesarc	12	0.1	0
25.13	mblkmice	Am241	bonesarc	11	9.39	0
25.13	mblkmice	Am241	bonesarc	11	4.57	1
25.13	mblkmice	Am241	bonesarc	11	1.7	0
25.14	mblkmice	Cf249	bonesarc	12	9	3
25.14	mblkmice	Cf249	bonesarc	12	6.12	2
25.14	mblkmice	Cf249	bonesarc	12	2.08	1
25.14	mblkmice	Cf249	bonesarc	10	0.64	0
25.14	mblkmice	Cf249	bonesarc	11	0.11	0
25.15	mblkmice	Cf252	bonesarc	11	18.24	1
25.15	mblkmice	Cf252	bonesarc	11	9.99	0
25.15	mblkmice	Cf252	bonesarc	13	3.43	0
25.15	mblkmice	Cf252	bonesarc	12	1.27	0
25.15	mblkmice	Cf252	bonesarc	12	0.2	0
25.10	mblkmice	Controls	bonesarc	94	0	0
25.21	fblkmice	Ra226	bonesarc	14	39.63	4
25.21	fblkmice	Ra226	bonesarc	12	18.62	3
25.21	fblkmice	Ra226	bonesarc	12	6.4	0
25.21	fblkmice	Ra226	bonesarc	12	2.32	0
25.21	fblkmice	Ra226	bonesarc	12	0.38	0
25.22	fblkmice	Pu239	bonesarc	12	8.46	11
25.22	fblkmice	Pu239	bonesarc	11	3.79	6
25.22	fblkmice	Pu239	bonesarc	12	1.23	1
25.22	fblkmice	Pu239	bonesarc	12	0.47	1
25.22	fblkmice	Pu239	bonesarc	12	0.06	1
25.23	fblkmice	Am241	bonesarc	12	12.72	3
25.23	fblkmice	Am241	bonesarc	12	5.19	3
25.23	fblkmice	Am241	bonesarc	10	1.76	1
25.24	fblkmice	Cf249	bonesarc	12	10.6	5
25.24	fblkmice	Cf249	bonesarc	12	5.18	5
25.24	fblkmice	Cf249	bonesarc	11	1.5	1
25.24	fblkmice	Cf249	bonesarc	12	0.65	1
25.24	fblkmice	Cf249	bonesarc	12	0.12	0
25.25	fblkmice	Cf252	bonesarc	13	21.13	6
25.25	fblkmice	Cf252	bonesarc	12	10.09	4
25.25	fblkmice	Cf252	bonesarc	12	3.17	0
25.25	fblkmice	Cf252	bonesarc	10	1.1	0
25.25	fblkmice	Cf252	bonesarc	12	0.2	0

25.20	fblkmice	Controls	bonesarc	87	0	1
25.31	malbmice	Ra226	bonesarc	14	45.47	1
25.31	malbmice	Ra226	bonesarc	14	18.12	0
25.31	malbmice	Ra226	bonesarc	18	6.77	0
25.31	malbmice	Ra226	bonesarc	15	2.33	0
25.31	malbmice	Ra226	bonesarc	10	0.39	0
25.32	malbmice	Pu239	bonesarc	12	13.12	2
25.32	malbmice	Pu239	bonesarc	16	4.44	1
25.32	malbmice	Pu239	bonesarc	12	2.04	0
25.32	malbmice	Pu239	bonesarc	16	0.55	0
25.32	malbmice	Pu239	bonesarc	13	0.1	0
25.33	malbmice	Am241	bonesarc	16	14.63	2
25.33	malbmice	Am241	bonesarc	18	5.13	1
25.33	malbmice	Am241	bonesarc	16	1.63	0
25.33	malbmice	Am241	bonesarc	14	0.58	0
25.33	malbmice	Am241	bonesarc	16	0.09	0
25.34	malbmice	Cf249	bonesarc	16	16.42	1
25.34	malbmice	Cf249	bonesarc	20	6.19	0
25.34	malbmice	Cf249	bonesarc	16	3.07	0
25.34	malbmice	Cf249	bonesarc	14	0.59	0
25.34	malbmice	Cf249	bonesarc	15	0.14	0
25.35	malbmice	Cf252	bonesarc	16	20.86	2
25.35	malbmice	Cf252	bonesarc	17	8.44	1
25.35	malbmice	Cf252	bonesarc	17	3.52	0
25.35	malbmice	Cf252	bonesarc	17	1.35	0
25.35	malbmice	Cf252	bonesarc	15	0.24	0
25.30	malbmice	Controls	bonesarc	60	0	0
25.41	falbmice	Ra226	bonesarc	10	56.48	4
25.41	falbmice	Ra226	bonesarc	14	17.59	1
25.41	falbmice	Ra226	bonesarc	11	7.43	0
25.41	falbmice	Ra226	bonesarc	12	2.31	0
25.41	falbmice	Ra226	bonesarc	15	0.37	0
25.42	falbmice	Pu239	bonesarc	20	6.54	18
25.42	falbmice	Pu239	bonesarc	16	3.22	9
25.42	falbmice	Pu239	bonesarc	16	1.32	4
25.42	falbmice	Pu239	bonesarc	17	0.43	0
25.42	falbmice	Pu239	bonesarc	16	0.08	0
25.43	falbmice	Am241	bonesarc	15	12.06	9
25.43	falbmice	Am241	bonesarc	14	5.28	7
25.43	falbmice	Am241	bonesarc	14	1.68	0
25.43	falbmice	Am241	bonesarc	16	0.52	0
25.43	falbmice	Am241	bonesarc	16	0.09	0
25.44	falbmice	Cf241	bonesarc	16	16.02	9
25.44	falbmice	Cf241	bonesarc	15	6.17	3
25.44	falbmice	Cf241	bonesarc	16	2.48	2
25.44	falbmice	Cf241	bonesarc	16	0.79	0
25.44	falbmice	Cf241	bonesarc	17	0.11	0
25.45	falbmice	Cf252	bonesarc	16	19.05	9
25.45	falbmice	Cf252	bonesarc	15	6.89	3
25.45	falbmice	Cf252	bonesarc	15	3.42	0
25.45	falbmice	Cf252	bonesarc	14	1.21	0
25.45	falbmice	Cf252	bonesarc	15	0.02	0
25.40	falbmice	Controls	bonesarc	58	0	0
28.51	Beagle	Pu238O2	LiverTum	20	0.0015	1

```
28.51  Beagle      Pu238O2      LiverTum      21     0.085  1
28.51  Beagle      Pu238O2      LiverTum      22     0.35   3
28.51  Beagle      Pu238O2      LiverTum      20     1.1    3
28.51  Beagle      Pu238O2      LiverTum      20     2.7    0
28.51  Beagle      Pu238O2      LiverTum      13     6.8    0
28.52  Beagle      Pu238O2      LungTum       20     0.0040 1
28.52  Beagle      Pu238O2      LungTum       21     0.0022 9
28.52  Beagle      Pu238O2      LungTum       22     0.096  2
28.52  Beagle      Pu238O2      LungTum       20     3.6    5
28.52  Beagle      Pu238O2      LungTum       20     14     5
28.52  Beagle      Pu238O2      LungTum       13     56     9
28.53  Beagle      Pu238O2      BoneTum       20     0.0071 1
28.53  Beagle      Pu238O2      BoneTum       21     0.041  0
28.53  Beagle      Pu238O2      BoneTum       22     0.17   0
28.53  Beagle      Pu238O2      BoneTum       20     0.55   6
28.53  Beagle      Pu238O2      BoneTum       20     1.3    16
28.53  Beagle      Pu238O2      BoneTum       13     3.3    9
;
run;
```

```
data newdata1; set datum;              /*CREATING THE DATA SET*/
ratio=result/num;
knee1=0;knee3=0;knee5=0;knee7=0;knee9=0;kneep5=0;kneep25=0;kneep01=0;
knee11=0;knee13=0;knee15=0;knee17=0;knee19=0;knee21=0;knee23=0;knee25=0;
knee27=0;knee29=0;knee31=0;knee33=0;knee35=0;knee37=0;knee39=0;
knee41=0;knee43=0;knee45=0;knee47=0;knee49=0;knee51=0;knee53=0;
knee60=0;knee70=0;knee80=0;knee90=0;knee100=0;
if dose>60 then knee60=dose-60;
if dose>70 then knee70=dose-70;
if dose>80 then knee80=dose-80;
if dose>90 then knee90=dose-90;
if dose>100 then knee100=dose-100;
if dose>1 then knee1=dose-1;
if dose>3 then knee3=dose-3;
if dose>5 then knee5=dose-5;
if dose>7 then knee7=dose-7;
if dose>9 then knee9=dose-9;
if dose>11 then knee11=dose-11;
if dose>13 then knee13=dose-13;
if dose>15 then knee15=dose-15;
if dose>17 then knee17=dose-17;
if dose>19 then knee19=dose-19;
if dose>0.5 then kneep5=dose-0.5;
if dose>21 then knee21=dose-21;
if dose>23 then knee23=dose-23;
if dose>25 then knee25=dose-25;
if dose>27 then knee27=dose-27;
if dose>29 then knee29=dose-29;
```

```
if dose>31 then knee31=dose-31;
if dose>33 then knee33=dose-33;
if dose>35 then knee35=dose-35;
if dose>37 then knee37=dose-37;
if dose>39 then knee39=dose-39;
if dose>41 then knee41=dose-41;
if dose>43 then knee43=dose-43;
if dose>45 then knee45=dose-45;
if dose>47 then knee47=dose-47;
if dose>51 then knee51=dose-51;
if dose>53 then knee53=dose-53;
if dose>49 then knee49=dose-49;
if dose>0.25 then kneep25=dose-0.25;
if dose>0.01 then kneep01=dose-0.01;
run;
proc sort; by dose expmnt; run;

data table; line="k"; run;

/***THE FOLLOWING DATA SETS FOUND MORE THAN 2 VARIABLES THAT WERE SIGNIFICANT*****/
/***A "BEST SUBSET ANALYSIS WAS DONE TO DETERMINE THE BEST MODEL USING 2 VARIABLE**/
/***WHICH WAS THEN HARD CODED ***************************************************/

data newdata2; set newdata1;
where expmnt=1.1 or expmnt=1.2 or expmnt=10.31 or expmnt=10.32 or expmnt=10.41 or
expmnt=10.42;
run;
data dummy; do dose= 0 to 170 by .25; output; end; run;
run;
data dummy; set dummy;
knee1=0;knee3=0;knee5=0;knee7=0;knee9=0;kneep5=0;kneep25=0;kneep01=0;
knee11=0;knee13=0;knee15=0;knee17=0;knee19=0;knee21=0;knee23=0;knee25=0;
knee27=0;knee29=0;knee31=0;knee33=0;knee35=0;knee37=0;knee39=0;
knee41=0;knee43=0;knee45=0;knee47=0;knee49=0;knee51=0;knee53=0;
knee60=0;knee70=0;knee80=0;knee90=0;knee100=0;
if dose>60 then knee60=dose-60;
if dose>70 then knee70=dose-70;
if dose>80 then knee80=dose-80;
if dose>90 then knee90=dose-90;
if dose>100 then knee100=dose-100;
if dose>1 then knee1=dose-1;
if dose>3 then knee3=dose-3;
if dose>5 then knee5=dose-5;
if dose>7 then knee7=dose-7;
if dose>9 then knee9=dose-9;
if dose>11 then knee11=dose-11;
if dose>13 then knee13=dose-13;
if dose>15 then knee15=dose-15;
if dose>17 then knee17=dose-17;
if dose>19 then knee19=dose-19;
if dose>0.5 then kneep5=dose-0.5;
if dose>21 then knee21=dose-21;
if dose>23 then knee23=dose-23;
if dose>25 then knee25=dose-25;
```

```
if dose>27 then knee27=dose-27;
if dose>29 then knee29=dose-29;
if dose>31 then knee31=dose-31;
if dose>33 then knee33=dose-33;
if dose>35 then knee35=dose-35;
if dose>37 then knee37=dose-37;
if dose>39 then knee39=dose-39;
if dose>41 then knee41=dose-41;
if dose>43 then knee43=dose-43;
if dose>45 then knee45=dose-45;
if dose>47 then knee47=dose-47;
if dose>51 then knee51=dose-51;
if dose>53 then knee53=dose-53;
if dose>49 then knee49=dose-49;
if dose>0.25 then kneep25=dose-0.25;
if dose>0.01 then kneep01=dose-0.01;
run;
data newdata2; set newdata2 dummy;
run;

proc logistic data=newdata2 outest=out1  noprint;
model result/num=dose;
output out=newdata2 predicted=upred;
run;

proc logistic data=newdata2 outest=out2;
model result/num=knee7 knee9;
output out=newdata2 predicted=kpred;
title "1.1, 1.2, 10.31, 10.32, 10.41, 10.42";
run;

proc sort data=newdata2; by dose; run;
proc gplot data=newdata2;
plot kpred*dose=2 upred*dose=2 ratio*dose=1/overlay;
axis c=black;
symbol1 i=none v=star c=black;
symbol2 i=join;
title "1.1, 1.2, 10.31, 10.32, 10.41, 10.42";
run;


data out1; set out1;
line="u";
run;
data out2; set out2;
line="k";
run;

data results; set out1 out2;
uresult=lag1(_LNLIKE_);
if line="k" then chiku=_LNLIKE_-uresult;
if chiku<0 then signif=999;
signif=probchi(chiku,1);
lbl=110.1234;
```

```
run;

data table; set table results;
where line="k";
run;

proc datasets;
delete out1 out2  results;
run;

/*****************************************************************/
/*****************************************************************/

data newdata2; set newdata1;
where expmnt=25.12 or expmnt=25.10 or expmnt=25.22 or expmnt=25.20 or expmnt=25.32 or
expmnt=25.30 or expmnt=25.42 or expmnt=25.40;

run;
data dummy; do dose= 0 to 25 by .25; output; end; run;
run;
data dummy; set dummy;
knee1=0;knee3=0;knee5=0;knee7=0;knee9=0;kneep5=0;kneep25=0;kneep01=0;
knee11=0;knee13=0;knee15=0;knee17=0;knee19=0;knee21=0;knee23=0;knee25=0;
knee27=0;knee29=0;knee31=0;knee33=0;knee35=0;knee37=0;knee39=0;
knee41=0;knee43=0;knee45=0;knee47=0;knee49=0;knee51=0;knee53=0;
knee60=0;knee70=0;knee80=0;knee90=0;knee100=0;
if dose>60 then knee60=dose-60;
if dose>70 then knee70=dose-70;
if dose>80 then knee80=dose-80;
if dose>90 then knee90=dose-90;
if dose>100 then knee100=dose-100;
if dose>1 then knee1=dose-1;
if dose>3 then knee3=dose-3;
if dose>5 then knee5=dose-5;
if dose>7 then knee7=dose-7;
if dose>9 then knee9=dose-9;
if dose>11 then knee11=dose-11;
if dose>13 then knee13=dose-13;
if dose>15 then knee15=dose-15;
if dose>17 then knee17=dose-17;
if dose>19 then knee19=dose-19;
if dose>0.5 then kneep5=dose-0.5;
if dose>21 then knee21=dose-21;
if dose>23 then knee23=dose-23;
if dose>25 then knee25=dose-25;
if dose>27 then knee27=dose-27;
if dose>29 then knee29=dose-29;
if dose>31 then knee31=dose-31;
if dose>33 then knee33=dose-33;
if dose>35 then knee35=dose-35;
if dose>37 then knee37=dose-37;
if dose>39 then knee39=dose-39;
if dose>41 then knee41=dose-41;
if dose>43 then knee43=dose-43;
```

```
if dose>45 then knee45=dose-45;
if dose>47 then knee47=dose-47;
if dose>51 then knee51=dose-51;
if dose>53 then knee53=dose-53;
if dose>49 then knee49=dose-49;
if dose>0.25 then kneep25=dose-0.25;
if dose>0.01 then kneep01=dose-0.01;
run;
data newdata2; set newdata2 dummy;
run;

proc logistic data=newdata2 outest=out1  noprint;
model result/num=dose;
output out=newdata2 predicted=upred;
run;

proc logistic data=newdata2 outest=out2;
model result/num=kneep5 knee11;
output out=newdata2 predicted=kpred;
title "25.*2";
run;

proc sort data=newdata2; by dose; run;
proc gplot data=newdata2;
plot kpred*dose=2 upred*dose=2 ratio*dose=1/overlay;
axis c=black;
symbol1 i=none v=star c=black;
symbol2 i=join;
title "expmnt =25.*2";
run;


data out1; set out1;
line="u";
run;
data out2; set out2;
line="k";
run;

data results; set out1 out2;
uresult=lag1(_LNLIKE_);
if line="k" then chiku=_LNLIKE_-uresult;
if chiku<0 then signif=999;
signif=probchi(chiku,2);
lbl=25.02;
run;

data table; set table results;
where line="k";
run;

proc datasets;
delete out1 out2  results;
run;
```

```
/*****************************************************************/
/*****************************************************************/

data newdata2; set newdata1;
where expmnt=25.13 or expmnt=25.10 or expmnt=25.23 or expmnt=25.20 or expmnt=25.33 or
expmnt=25.30 or expmnt=25.43 or expmnt=25.40;
run;
data dummy; do dose= 0 to 25 by .25; output; end; run;
run;
data dummy; set dummy;
knee1=0;knee3=0;knee5=0;knee7=0;knee9=0;kneep5=0;kneep25=0;kneep01=0;
knee11=0;knee13=0;knee15=0;knee17=0;knee19=0;knee21=0;knee23=0;knee25=0;
knee27=0;knee29=0;knee31=0;knee33=0;knee35=0;knee37=0;knee39=0;
knee41=0;knee43=0;knee45=0;knee47=0;knee49=0;knee51=0;knee53=0;
knee60=0;knee70=0;knee80=0;knee90=0;knee100=0;
if dose>60 then knee60=dose-60;
if dose>70 then knee70=dose-70;
if dose>80 then knee80=dose-80;
if dose>90 then knee90=dose-90;
if dose>100 then knee100=dose-100;
if dose>1 then knee1=dose-1;
if dose>3 then knee3=dose-3;
if dose>5 then knee5=dose-5;
if dose>7 then knee7=dose-7;
if dose>9 then knee9=dose-9;
if dose>11 then knee11=dose-11;
if dose>13 then knee13=dose-13;
if dose>15 then knee15=dose-15;
if dose>17 then knee17=dose-17;
if dose>19 then knee19=dose-19;
if dose>0.5 then kneep5=dose-0.5;
if dose>21 then knee21=dose-21;
if dose>23 then knee23=dose-23;
if dose>25 then knee25=dose-25;
if dose>27 then knee27=dose-27;
if dose>29 then knee29=dose-29;
if dose>31 then knee31=dose-31;
if dose>33 then knee33=dose-33;
if dose>35 then knee35=dose-35;
if dose>37 then knee37=dose-37;
if dose>39 then knee39=dose-39;
if dose>41 then knee41=dose-41;
if dose>43 then knee43=dose-43;
if dose>45 then knee45=dose-45;
if dose>47 then knee47=dose-47;
if dose>51 then knee51=dose-51;
if dose>53 then knee53=dose-53;
if dose>49 then knee49=dose-49;
if dose>0.25 then kneep25=dose-0.25;
if dose>0.01 then kneep01=dose-0.01;
run;
data newdata2; set newdata2 dummy;
run;
```

```
proc logistic data=newdata2 outest=out1  noprint;
model result/num=dose;
output out=newdata2 predicted=upred;
run;

proc logistic data=newdata2 outest=out2;
model result/num=kneep5 knee13;
output out=newdata2 predicted=kpred;
title "25.*3";
run;

proc sort data=newdata2; by dose; run;
proc gplot data=newdata2;
plot kpred*dose=2 upred*dose=2 ratio*dose=1/overlay;
axis c=black;
symbol1 i=none v=star c=black;
symbol2 i=join;
title "expmnt =25.*3";
run;


data out1; set out1;
line="u";
run;
data out2; set out2;
line="k";
run;

data results; set out1 out2;
uresult=lag1(_LNLIKE_);
if line="k" then chiku=_LNLIKE_-uresult;
if chiku<0 then signif=999;
signif=probchi(chiku,2);
lbl=25.03;
run;

data table; set table results;
where line="k";
run;

proc datasets;
delete out1 out2  results;
run;

/*************************************************************/
/*************************************************************/

data newdata2; set newdata1;
where expmnt=25.14 or expmnt=25.10 or expmnt=25.24 or expmnt=25.20 or expmnt=25.34 or
expmnt=25.30 or expmnt=25.44 or expmnt=25.40;
run;
data dummy; do dose= 0 to 25 by .25; output; end; run;
run;
```

```
data dummy; set dummy;
knee1=0;knee3=0;knee5=0;knee7=0;knee9=0;kneep5=0;kneep25=0;kneep01=0;
knee11=0;knee13=0;knee15=0;knee17=0;knee19=0;knee21=0;knee23=0;knee25=0;
knee27=0;knee29=0;knee31=0;knee33=0;knee35=0;knee37=0;knee39=0;
knee41=0;knee43=0;knee45=0;knee47=0;knee49=0;knee51=0;knee53=0;
knee60=0;knee70=0;knee80=0;knee90=0;knee100=0;
if dose>60 then knee60=dose-60;
if dose>70 then knee70=dose-70;
if dose>80 then knee80=dose-80;
if dose>90 then knee90=dose-90;
if dose>100 then knee100=dose-100;
if dose>1 then knee1=dose-1;
if dose>3 then knee3=dose-3;
if dose>5 then knee5=dose-5;
if dose>7 then knee7=dose-7;
if dose>9 then knee9=dose-9;
if dose>11 then knee11=dose-11;
if dose>13 then knee13=dose-13;
if dose>15 then knee15=dose-15;
if dose>17 then knee17=dose-17;
if dose>19 then knee19=dose-19;
if dose>0.5 then kneep5=dose-0.5;
if dose>21 then knee21=dose-21;
if dose>23 then knee23=dose-23;
if dose>25 then knee25=dose-25;
if dose>27 then knee27=dose-27;
if dose>29 then knee29=dose-29;
if dose>31 then knee31=dose-31;
if dose>33 then knee33=dose-33;
if dose>35 then knee35=dose-35;
if dose>37 then knee37=dose-37;
if dose>39 then knee39=dose-39;
if dose>41 then knee41=dose-41;
if dose>43 then knee43=dose-43;
if dose>45 then knee45=dose-45;
if dose>47 then knee47=dose-47;
if dose>51 then knee51=dose-51;
if dose>53 then knee53=dose-53;
if dose>49 then knee49=dose-49;
if dose>0.25 then kneep25=dose-0.25;
if dose>0.01 then kneep01=dose-0.01;
run;
data newdata2; set newdata2 dummy;
run;

proc logistic data=newdata2 outest=out1  noprint;
model result/num=dose;
output out=newdata2 predicted=upred;
run;

proc logistic data=newdata2 outest=out2;
model result/num=kneep25 knee13;
output out=newdata2 predicted=kpred;
title "25.*4";
```

```
run;

proc sort data=newdata2; by dose; run;
proc gplot data=newdata2;
plot kpred*dose=2 upred*dose=2 ratio*dose=1/overlay;
axis c=black;
symbol1 i=none v=star c=black;
symbol2 i=join;
title "expmnt =25.*4";
run;


data out1; set out1;
line="u";
run;
data out2; set out2;
line="k";
run;

data results; set out1 out2;
uresult=lag1(_LNLIKE_);
if line="k" then chiku=_LNLIKE_-uresult;
if chiku<0 then signif=999;
signif=probchi(chiku,2);
lbl=25.04;
run;

data table; set table results;
where line="k";
run;

proc datasets;
delete out1 out2  results;
run;

/*****************************************************************/
/*****************************************************************/
data newdata2; set newdata1;
where expmnt=24.4;
run;
data dummy; do dose= 0 to 90 by .25; output; end; run;
run;
data dummy; set dummy;
knee1=0;knee3=0;knee5=0;knee7=0;knee9=0;kneep5=0;kneep25=0;kneep01=0;
knee11=0;knee13=0;knee15=0;knee17=0;knee19=0;knee21=0;knee23=0;knee25=0;
knee27=0;knee29=0;knee31=0;knee33=0;knee35=0;knee37=0;knee39=0;
knee41=0;knee43=0;knee45=0;knee47=0;knee49=0;knee51=0;knee53=0;
knee60=0;knee70=0;knee80=0;knee90=0;knee100=0;
if dose>60 then knee60=dose-60;
if dose>70 then knee70=dose-70;
if dose>80 then knee80=dose-80;
if dose>90 then knee90=dose-90;
if dose>100 then knee100=dose-100;
if dose>1 then knee1=dose-1;
```

```
if dose>3 then knee3=dose-3;
if dose>5 then knee5=dose-5;
if dose>7 then knee7=dose-7;
if dose>9 then knee9=dose-9;
if dose>11 then knee11=dose-11;
if dose>13 then knee13=dose-13;
if dose>15 then knee15=dose-15;
if dose>17 then knee17=dose-17;
if dose>19 then knee19=dose-19;
if dose>0.5 then kneep5=dose-0.5;
if dose>21 then knee21=dose-21;
if dose>23 then knee23=dose-23;
if dose>25 then knee25=dose-25;
if dose>27 then knee27=dose-27;
if dose>29 then knee29=dose-29;
if dose>31 then knee31=dose-31;
if dose>33 then knee33=dose-33;
if dose>35 then knee35=dose-35;
if dose>37 then knee37=dose-37;
if dose>39 then knee39=dose-39;
if dose>41 then knee41=dose-41;
if dose>43 then knee43=dose-43;
if dose>45 then knee45=dose-45;
if dose>47 then knee47=dose-47;
if dose>51 then knee51=dose-51;
if dose>53 then knee53=dose-53;
if dose>49 then knee49=dose-49;
if dose>0.25 then kneep25=dose-0.25;
if dose>0.01 then kneep01=dose-0.01;
run;
data newdata2; set newdata2 dummy;
run;

proc logistic data=newdata2 outest=out1  noprint;
model result/num=dose;
output out=newdata2 predicted=upred;
run;

proc logistic data=newdata2 outest=out2;
model result/num=knee1 knee17;
output out=newdata2 predicted=kpred;
title "24.4";
run;

proc sort data=newdata2; by dose; run;
proc gplot data=newdata2;
plot kpred*dose=2 upred*dose=2 ratio*dose=1/overlay;
axis c=black;
symbol1 i=none v=star c=black;
symbol2 i=join;
title "expmnt =24.4";
run;
```

```
data out1; set out1;
line="u";
run;
data out2; set out2;
line="k";
run;

data results; set out1 out2;
uresult=lag1(_LNLIKE_);
if line="k" then chiku=_LNLIKE_-uresult;
if chiku<0 then signif=999;
signif=probchi(chiku,2);
lbl=24.4;
run;

data table; set table results;
where line="k";
run;

proc datasets;
delete out1 out2  results;
run;
/*******************************************************/

data dummy1; do dose= 0 to 25 by .25; expmnt=8.31; output; end; run;   /*THESE DUMMY DATA
SETS WERE CREATED TO HELP WITH GRAPHING*/
data dummy2; do dose= 0 to 25 by .25; expmnt=8.32; output; end; run;
data dummy3a; do dose= 0 to 25 by .25; expmnt=25.12; output; end; run;
data dummy3b; do dose= 0 to 25 by .25; expmnt=25.13; output; end; run;
data dummy3c; do dose= 0 to 25 by .25; expmnt=25.14; output; end; run;
data dummy3d; do dose= 0 to 25 by .25; expmnt=25.15; output; end; run;
data dummy4a; do dose= 0 to 25 by .25; expmnt=25.22; output; end; run;
data dummy4b; do dose= 0 to 25 by .25; expmnt=25.23; output; end; run;
data dummy4c; do dose= 0 to 25 by .25; expmnt=25.24; output; end; run;
data dummy4d; do dose= 0 to 25 by .25; expmnt=25.25; output; end; run;
data dummy5a; do dose= 0 to 25 by .25; expmnt=25.32; output; end; run;
data dummy5b; do dose= 0 to 25 by .25; expmnt=25.33; output; end; run;
data dummy5c; do dose= 0 to 25 by .25; expmnt=25.34; output; end; run;
data dummy5d; do dose= 0 to 25 by .25; expmnt=25.35; output; end; run;
data dummy6a; do dose= 0 to 25 by .25; expmnt=25.42; output; end; run;
data dummy6b; do dose= 0 to 25 by .25; expmnt=25.43; output; end; run;
data dummy6c; do dose= 0 to 25 by .25; expmnt=25.44; output; end; run;
data dummy6d; do dose= 0 to 25 by .25; expmnt=25.45; output; end; run;
data dummy7a; do dose= 0 to 10 by .25; expmnt=28.51; output; end; run;
data dummy7b; do dose= 0 to 10 by .25; expmnt=28.53; output; end; run;
data dummy8a; do dose= 0 to 65 by .25; expmnt=25.11; output; end; run;
data dummy8b; do dose= 0 to 65 by .25; expmnt=25.21; output; end; run;
data dummy8c; do dose= 0 to 65 by .25; expmnt=25.31; output; end; run;
data dummy8d; do dose= 0 to 65 by .25; expmnt=25.41; output; end; run;
data dummy9; do dose= 0 to 65 by .25; expmnt=28.52; output; end; run;
data dummy10a; do dose= 0 to 170 by .25; expmnt=1.1; output; end; run;
data dummy10b; do dose= 0 to 170 by .25; expmnt=1.2; output; end; run;
data dummy11a; do dose= 0 to 170 by .25; expmnt=10.31; output; end; run;
data dummy11b; do dose= 0 to 170 by .25; expmnt=10.32; output; end; run;
```

```
data dummy12a; do dose= 0 to 170 by .25; expmnt=10.41; output; end; run;
data dummy12b; do dose= 0 to 170 by .25; expmnt=10.42; output; end; run;

data dummy; set dummy1 dummy2 dummy3a dummy3b dummy3c dummy3d dummy4a dummy4b
dummy4c dummy4d dummy5a dummy5b dummy5c dummy5d
 dummy6a dummy6b dummy6c dummy6d dummy7a dummy7b dummy8a dummy8b dummy8c dummy8d
dummy9 dummy10a dummy10b dummy11a
 dummy11b dummy12a dummy12b;
run;

%macro godoit(dataset,label);

data newdata2; set newdata1;
where &DATASET;
run;
data dummy; set dummy;
knee1=0;knee3=0;knee5=0;knee7=0;knee9=0;kneep5=0;kneep25=0;kneep01=0;
knee11=0;knee13=0;knee15=0;knee17=0;knee19=0;knee21=0;knee23=0;knee25=0;
knee27=0;knee29=0;knee31=0;knee33=0;knee35=0;knee37=0;knee39=0;
knee41=0;knee43=0;knee45=0;knee47=0;knee49=0;knee51=0;knee53=0;
knee60=0;knee70=0;knee80=0;knee90=0;knee100=0;
if dose>60 then knee60=dose-60;
if dose>70 then knee70=dose-70;
if dose>80 then knee80=dose-80;
if dose>90 then knee90=dose-90;
if dose>100 then knee100=dose-100;
if dose>1 then knee1=dose-1;
if dose>3 then knee3=dose-3;
if dose>5 then knee5=dose-5;
if dose>7 then knee7=dose-7;
if dose>9 then knee9=dose-9;
if dose>11 then knee11=dose-11;
if dose>13 then knee13=dose-13;
if dose>15 then knee15=dose-15;
if dose>17 then knee17=dose-17;
if dose>19 then knee19=dose-19;
if dose>0.5 then kneep5=dose-0.5;
if dose>21 then knee21=dose-21;
if dose>23 then knee23=dose-23;
if dose>25 then knee25=dose-25;
if dose>27 then knee27=dose-27;
if dose>29 then knee29=dose-29;
if dose>31 then knee31=dose-31;
if dose>33 then knee33=dose-33;
if dose>35 then knee35=dose-35;
if dose>37 then knee37=dose-37;
if dose>39 then knee39=dose-39;
if dose>41 then knee41=dose-41;
if dose>43 then knee43=dose-43;
if dose>45 then knee45=dose-45;
if dose>47 then knee47=dose-47;
if dose>51 then knee51=dose-51;
if dose>53 then knee53=dose-53;
if dose>49 then knee49=dose-49;
```

```
if dose>0.25 then kneep25=dose-0.25;
if dose>0.01 then kneep01=dose-0.01;
run;

proc sort data=dummy;
by expmnt;
run;

data dummya; set dummy;
where &DATASET;
run;

data newdata2; set newdata2 dummya;
run;

proc logistic data=newdata2 outest=out1  noprint;    /*LOGISTIC REGRESSION*/
model result/num=dose;
output out=newdata2 predicted=upred;
run;

proc logistic data=newdata2 outest=out2;            /*KNEE LOGISTIC REGRESSION*/
model result/num=dose knee1 knee3 knee5 knee7 knee9 kneep5 kneep25 kneep01
  knee11 knee13 knee15 knee17 knee19
  knee21 knee23 knee25 knee27 knee29
  knee31 knee33 knee35 knee37 knee39
  knee41 knee43 knee45 knee47 knee49
  knee51 knee53
  knee60 knee70 knee80 knee90 knee100
/stepwise slentry=0.15 slstay=0.15 selection=stepwise;
output out=newdata2 predicted=kpred;
title "&LABEL";
run;

proc sort data=newdata2; by dose; run;
proc gplot data=newdata2;                        /*PLOTTING THE GRAPHS*/
plot kpred*dose=2 upred*dose=2 ratio*dose=1/overlay;
axis c=black;
symbol1 i=none v=star c=black;
symbol2 i=join;
title "&LABEL";
run;


data out1; set out1; /*KEEPING TRACK OF THE SIGNIFICANCE COMPARISON OF EACH MODEL*/
line="u";
run;
data out2; set out2;
line="k";
run;

data results; set out1 out2;
uresult=lag1(_LNLIKE_);
if line="k" then chiku=_LNLIKE_-uresult;
if chiku<0 then signif=999;
```

```
if chiku>=0 then signif=probchi(chiku,2);
lbl=&LABEL;
run;

data table; set table results;
where line="k";
run;

proc datasets;
delete out1 out2  results;
run;
%mend;

%godoit((expmnt=1.1),1.1);   /*ALL THE DATA SETS OR COMBINATION OF DATA SETS USED*/
%godoit((expmnt=1.2),1.2);
%godoit((expmnt=8.31),8.31);
%godoit((expmnt=8.32),8.32);
%godoit((expmnt=10.31),10.31);
%godoit((expmnt=10.32),10.32);
%godoit((expmnt=10.41),10.41);
%godoit((expmnt=10.42),10.42);
%godoit((expmnt=28.51),28.51);
%godoit((expmnt=28.52),28.52);
%godoit((expmnt=28.53),28.53);
%godoit((expmnt=25.11 or expmnt=25.10),25.11);
%godoit((expmnt=25.12 or expmnt=25.10),25.12);
%godoit((expmnt=25.13 or expmnt=25.10),25.13);
%godoit((expmnt=25.14 or expmnt=25.10),25.14);
%godoit((expmnt=25.15 or expmnt=25.10),25.15);
%godoit((expmnt=25.21 or expmnt=25.20),25.21);
%godoit((expmnt=25.22 or expmnt=25.20),25.22);
%godoit((expmnt=25.23 or expmnt=25.20),25.23);
%godoit((expmnt=25.24 or expmnt=25.20),25.24);
%godoit((expmnt=25.25 or expmnt=25.20),25.25);
%godoit((expmnt=25.31 or expmnt=25.30),25.31);
%godoit((expmnt=25.32 or expmnt=25.30),25.32);
%godoit((expmnt=25.33 or expmnt=25.30),25.33);
%godoit((expmnt=25.34 or expmnt=25.30),25.34);
%godoit((expmnt=25.35 or expmnt=25.30),25.35);
%godoit((expmnt=25.41 or expmnt=25.40),25.41);
%godoit((expmnt=25.42 or expmnt=25.40),25.42);
%godoit((expmnt=25.43 or expmnt=25.40),25.43);
%godoit((expmnt=25.44 or expmnt=25.40),25.44);
%godoit((expmnt=25.45 or expmnt=25.40),25.45);
%godoit((expmnt=10.31 or expmnt=10.32),10.312);
%godoit((expmnt=10.41 or expmnt=10.42),10.412);
%godoit((expmnt=8.31 or expmnt=8.32),8.312);
%godoit((expmnt=1.1 or expmnt=10.31),11.311);
%godoit((expmnt=10.31 or expmnt=10.32 or expmnt=10.41 or expmnt=10.42),10.3412);
%godoit((expmnt=1.1 or expmnt=10.31 or expmnt=10.32 or expmnt=10.41 or expmnt=10.42),110.3412);
%godoit((expmnt=25.11 or expmnt=25.10 or expmnt=25.21 or expmnt=25.20 or expmnt=25.31 or
expmnt=25.30 or expmnt=25.41 or expmnt=25.40
),25.01);
```

```
%godoit((expmnt=25.15 or expmnt=25.10 or expmnt=25.25 or expmnt=25.20 or expmnt=25.35 or
expmnt=25.30 or expmnt=25.45 or expmnt=25.40
),25.05);
%godoit((expmnt=25.15 or expmnt=25.10 or expmnt=25.25 or expmnt=25.20 or expmnt=25.35 or
expmnt=25.30 or expmnt=25.45 or expmnt=25.40
or expmnt=25.14 or expmnt=25.24 or expmnt=25.34 or expmnt=25.44),25.45);

proc print data=table; var signif;
ID lbl;
run;

quit;
```

Bibliography

Amico, P., Upso, P. Bacher, P. Rehmann, M, Krill, S., Feltus, M.(1996) *Transaction of the American nuclear society and the European nuclear society*. TANSAO, **75**, 1-490.

Burnett, R.T., Ross, W.H., and Krewski, D. (1995). *Nonlinear Random Effects Regression Models*. Environmetrics 6: 85-89.

Draper, Norman, and Smith, Harry. (1981) *Applied Regression Analysis, Second Edition*. John Wiley & Sons, Chichester.

Freedman, D.A., Zeisel, H.(1988) *From Mouse-to-Man: The Quantitative Assessment of Cancer Risks*. Statistical Science, **3** no 1, 3-56.

Gray, R.G., Lafuma, J., Parish, S.E., and Peto, R. (1983) *Lung Tumors and Radon Inhalation in over 2000 rats: Approximate linearity across a wide range of doses and potentiation by tobacco smoke*. Proceedings of the 22nd DOE Life Sciences Symposium: Life-span radiation effects studies in animals: What can they tell us?, R.C. Thompson and J.A. Mahafey eds, Richland WA, US DOE publication CONF-830951. p. 592-607

Gragtmans, N.J., Myers, D.K., Johnson, J. R., Jones, A. R., Johnson, L.D.(1984) *Occurrence of Mammary Tumors in Rats after Exposure to Tritium Beta Rays and 200-kVp X Rays*. Radiation Research, **99**, 636-650.

Hedges, Larry V., and Olkin, Ingram. (1985) *Statisical Methods for Meta Analysis*. Academic Press Inc, Orlando Florida.

Hosmer, David W., and Lemeshow, Stanley. (1989) *Applied Logistic Regression*. John Wiley & Sons, Chichester.

International Centre for Low Dose Radiation Research (1999), *International Symposium on Health Effectrs of Low Doses of Ionizing Radiation: Research Into the New Millennium*, International Centre for Low Dose Radiation Research, Ottawa.

Johnson, J.R., Gragtmans, N.J. Myers, D.K. and Jones, A.R. (1989) *Dose-Rate Effects for Mammary Tumor Development in Female Sprague-Dawley Rats Exposed to X and γ Radiation*. Radiation Research, **118**, 545-558.

Knowles, J.F., Greenwood, L.N.(1997) *A comparison of the effects of long term Beta and gamma irradiation on the reproductive performance of a marine invertabrae Ophryotrocha diadema*. J. Environ, Radoac, **34** no 1, 1-7.

Lundgren, D.L., Haley, P.J., Hahn, F.F., Diel, J.H., Griffith, W.C., and Scott, B.R. (1995) *Pulmonary Carcinogenicity of repeated inhalation exposure of rats to Aerosols of Plutonium Dioxide*. Rad Research, **142**, p39-53.

Ma, R., Krewski, D., and Burnett, R.T., (1999). *Random Effects Cox Models: A Poisson Regression Modelling Approach*. Submitted.

Maisin, J.R., Gerber, G.B., Wambersie, A., Mattelin, G., Lambiet-Collier, M., and Gueulette, J. (1983) *Life-Span shortening and disease incidnece in male BALB/c and C57BL mice after single fractionated d(50)-Be neutron or gamma exposure*. Proceedings of the 22nd DOE Life Sciences Symposium: Life-span radiation effects studies in animals: What can they tell us?, R.C. Thompson and J.A. Mahafey eds, Richland WA, US DOE publication CONF-830951. p. 172-183

Mays, C.W., Spiess, H., Taylor, G.N., Lloyd R.D., Jee, W.S.S., McFarland, Susan S., Taysum, D.H., Brammer, T.W., Brammer, D., and Pollard, T.A.(1973) *Estimated Risk to Human Bone From ^{239}Pu*. The Health Effects of Plutonium. J.W. Press, Salt Lake City.

Mewhinney, J.A., Griffith, W.C., Hahn, F.F., Snipes, M.B., Boecker, B.B., and McClennan, R.O. (1983) Incidence of Bone Cancer in beagles after inhalataion of 90SrCl2 or 238PuO2: *Implications for estimation opf risk to humans*. Proceedings of the 22nd DOE Life Sciences Symposium: Life-span radiation effects studies in animals: What can they tell us?, R.C. Thompson and J.A. Mahafey eds, Richland WA, US DOE publication CONF-830951. p. 535-555

Moolgavkar, S.H., Krewski, D., Ziese, L., Cardis, E., and Moller, H. (1999). *Quantitative Estimation and Prediction of Human cancer Risks*. Internation Agency for Research on Cancer Scientific Publications No. **131**, IARC Press, Lyon.

Morin, M. Masse, R and Lafuma, J. (1990) *Effets cancerogenes de l'irradiation gamma a faible debit de dose*. C.R. Acad. Des Sci., **311**, Serie III. p. 459-466

Morin, M, Masse, R, Lafuma, J. (1983) *An experimental study of fission neutron carcinogenisis*. Proceedings of the 22nd DOE Life Sciences Symposium: Life-span radiation effects studies in animals: What can they tell us?, R.C. Thompson and J.A. Mahafey eds, Richland WA, US DOE publication CONF-830951. p. 184-192

Morlier, Jean-Paul, Morin, Michele, Chameaud, Jean, Masse, Roland, Bottard, Sylvie, and Lafuma, Jacques (1992) *Importance du role du debit de dose sur l'apparition des cancers chez le rat apres inhalation de radon*, C.R. Acad. Sci. Paris. **315** Serie III, p.463-466.

Morlier, J.P. Morin, M., Monchaux, G., Fritch, P., Pineau, J.F., Chameaud, J., Lafuma, J and Masse, R. (1994) *Lung Cancer Incidence After Exposure of Rats to Low Doses of Radon: Influence of Dose Rate*. Radiation Protection Dosimetry. V **56** no 1-4, 93-97.

National Research Council (1999). *Health Effect of Exposure to Radon: BEIR VI*. National Academy Press, Washington, D.C.

Park, J.F., Bushbom, R.L. Dagle, G.E., James, A.C., Watson, C.R., and Weller, R.E.(1997) Biological Effects of Inhaled $^{238}PuO_2$ in Beagles. Radiation Research, 148, 365-381.

Raabe, Otto G., Bulberson, M Roger, White, Russell G., Spangler, William L., Cain, Gary R, Parks, Norris J., and Samuels, Stephen J.(1992) *Comparative Toxicity of Strontium-90 and Radium-226 in Beagle Dogs*. DOE DE-FG03-89ER60914/92.

Radford, I.R. (1994) *p53 status, DNA double-strand break repair profeciency, and radiation response of mouse lymphoid and myeloid cell lines*. Int. J. Radiat. Biol. **66** no. 5, 557-560.

Sanders, C.L., Lauhala, K.E., and Moore, B.G. (1994) *Pacific northwest laboratory report DOE Office of Energy Research low-level 239- PuO^2 life-span studies*. PNL-9000 UC-408, part 1, 21-24.

Sanders, C.L., Lundgren, D.L.(1995) *Pulmonary carcinogenesis in he F344 and Wistar rat after inhalation of Plutonium Dioxide*. Rad. Research, **144**, p73-81.

Sanders, C.L., Sanders, G.A.(1993) *Low-Level $^{239}PuO_2$ Life-Span Studies*.Annual Report: Battelle PNL, p23-30.

SAS Institute Inc.(1996) *SAS/STAT Software: Changes and Enhancements through Release 6.11*, Cary, NC: SAS Institute Inc.

Taylor. Glenn N., Lloyd, Ray D., Mays, Charles W., Angus, Walter, Miller, Scott C., Shabestari, Lorraine, and Hahn, Fletcher F.(1991) *Plutonium or Americium-Induced Liver Tumors and Lesions in Beagles*. Health Physics. **61** no 3. 337-347.

Taylor, G.N., Mays, C.W., Lloyd, R.D., Gardner, P.A., Talbot, L.R., McFarland Susan S, Pollard, T.A., Atherton, D.R., VanMoorhem, Diane, Brammer, D. Brammer T. W., Ayoroa, G. and Taysum, D.H.(1983) *Comparative Toxicity of ^{226}Ra, ^{239}Pu, 241Am, ^{249}Cf, and ^{252}Cf in C57Bl/Do Black and Albino Mice*. Radiation Research, **95**, 584-601.

Thomas, R.G.(1994) The US radium luminisers*: A case for a police of 'below regualtory concern'*. J. Radiol. Prot. **14** no 2. 141-153.

Weller, R.E., Buschbom R.L., Dagle, G.E., Ragan, H.A., and Park, J.F.(1995) *Hepatic Effects of Inhaled Plutonium Dioxde in Beagles*. Radiation Research, **144**, 73-81.

White, R.G., Raabe, O.G., Culberston, M.R., Parks, N.J., Samuels, S.J., and Rosenblatt, L.S.(1994) *Bone Sarcoma Characteristics and Distribution in Beagles Injected with Radium-226*. Radiation Research, **137**, 361-370.