PRODUCT HAZARD MODELS IN CARCINOGENIC RISK ASSESSMENT

by

Raymond Douglas Buck

Department of Biostatistics
University of North Carolina at Chapel Hill

Institute of Statistics Mimeo Series No. 1469

October 1984
PRODUCT HAZARD MODELS IN CARCINOGENIC RISK ASSESSMENT

by

Raymond Douglas Buck

A Dissertation submitted to the faculty of The University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Biostatistics.

Chapel Hill
August 1984

Approved by:

Advisor

Reader

Reader

Reader
RAYMOND DOUGLAS BUCK. Product Hazard Models in Carcinogenic Risk Assessment (under the direction of MICHAEL J. SYMONS)

ABSTRACT: One step in the regulation of a potential carcinogen is the extrapolation of the dose response relationship obtained in test animals to levels approximating human exposures. Many of the existing statistical procedures for this low dose extrapolation do not utilize frequently available time to tumor and time to death information. Product hazard survival models are presented as one method for incorporating this information into risk estimation.

All product hazard models used to date for carcinogenic risk assessment have chosen a polynomial for the dose factor in the hazard. Other parsimonious functional dose component forms, which generalize the procedures ignoring time, are described. This generalization technique also allows the pharmacokinetics of the administered and delivered dose relationship to be included directly into the risk estimation.

Estimation techniques using parametric and nonparametric time components are presented. An approximate likelihood method for estimating the time to tumor distribution when tumors are observable only at death is derived. Product hazard models with dose components corresponding to three common quantal response models are applied to both experimental and simulated time to response data.

A long-term study of inhalation exposure to formaldehyde for rats is analyzed using both administered dose and a measure of the dose delivered to the cancer target site. These data show a one to two order of magnitude decrease for both risk estimates and their confidence bounds at low doses, when the delivered dose measure is employed.
A large simulated data base, previously used for comparing other time to response modeling strategies, is also analyzed using the same dose component models. Summaries are provided of the differences in estimated virtually safe doses which result from the inclusion of time, the use of different time endpoints and dose components, and parametric versus nonparametric time components. Comparisons are also made with the conclusions from the original analyses. Estimated virtually safe doses using time are not substantially different from corresponding estimates ignoring time, and depending upon the dose component model, time endpoint analyzed, and estimation technique employed, they may, in fact, be farther from the true virtually safe dose.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>v</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>vi</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>viii</td>
</tr>
<tr>
<td>I.  INTRODUCTION AND REVIEW OF THE LITERATURE</td>
<td></td>
</tr>
<tr>
<td>1.1 Introduction</td>
<td>1</td>
</tr>
<tr>
<td>1.2 Quantal Response Procedures</td>
<td>3</td>
</tr>
<tr>
<td>1.2.1 Mathematical Models</td>
<td>4</td>
</tr>
<tr>
<td>1.2.2 Incorporating Background Responses</td>
<td>6</td>
</tr>
<tr>
<td>1.2.3 Risk Estimates</td>
<td>7</td>
</tr>
<tr>
<td>1.2.4 Estimation</td>
<td>10</td>
</tr>
<tr>
<td>1.3 Quantal Response Difficulties and the Need for Time Information</td>
<td>12</td>
</tr>
<tr>
<td>1.3.1 Quantal Response Difficulties</td>
<td>13</td>
</tr>
<tr>
<td>1.3.2 Specific Arguments for Including Time</td>
<td>16</td>
</tr>
<tr>
<td>1.4 Incorporating Time in Risk Assessment</td>
<td>19</td>
</tr>
<tr>
<td>1.4.1 Time to Response Models</td>
<td>19</td>
</tr>
<tr>
<td>1.4.2 Time Related Risk Estimates</td>
<td>25</td>
</tr>
<tr>
<td>1.5 Review of &quot;A Comparison of Statistical Methods for Low Dose Extrapolation Utilizing Time to Tumor Data&quot;</td>
<td>27</td>
</tr>
<tr>
<td>1.6 Outline of Subsequent Chapters</td>
<td>32</td>
</tr>
<tr>
<td>II. PRODUCT HAZARD MODELS FOR TIME TO RESPONSE TOXICITY DATA USING PARAMETRIC TIME</td>
<td></td>
</tr>
<tr>
<td>2.1 Introduction</td>
<td>34</td>
</tr>
<tr>
<td>2.2 Product Hazard Likelihood Construction</td>
<td>35</td>
</tr>
<tr>
<td>2.3 General Forms for the Dose Component in the Product Hazard Model</td>
<td>39</td>
</tr>
<tr>
<td>2.3.1 Arguments for General Forms</td>
<td>40</td>
</tr>
<tr>
<td>2.3.2 Quantal Response Model Generalizations</td>
<td>41</td>
</tr>
<tr>
<td>2.3.3 Incorporation of Pharmacokinetics in the Product Hazard Model</td>
<td>44</td>
</tr>
<tr>
<td>2.3.4 Incorporation of Background Responses</td>
<td>48</td>
</tr>
<tr>
<td>2.4 Estimation of Model Parameters</td>
<td>51</td>
</tr>
<tr>
<td>2.5 Goodness of Fit Procedures</td>
<td>56</td>
</tr>
<tr>
<td>2.5.1 A Generalization of the Probit, Logit, and Weibull Models</td>
<td>57</td>
</tr>
<tr>
<td>2.5.2 Graphical Techniques</td>
<td>58</td>
</tr>
</tbody>
</table>
# TABLE OF CONTENTS (continued)

## III. ANALYSIS OF TIME TO RESPONSE TOXICITY DATA USING PRODUCT HAZARD MODELS WITH PARAMETRIC TIME

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Introduction</td>
<td>60</td>
</tr>
<tr>
<td>3.2 CIIT Formaldehyde Data</td>
<td>62</td>
</tr>
<tr>
<td>3.2.1 Parametric Analyses Using Administered Dose Measures</td>
<td>63</td>
</tr>
<tr>
<td>3.2.2 Parametric Analyses Using Delivered Dose Measures</td>
<td>71</td>
</tr>
<tr>
<td>3.3 Krewski et al. (1983) Simulated Data Base</td>
<td>79</td>
</tr>
<tr>
<td>3.3.1 Construction of the Data Base</td>
<td>79</td>
</tr>
<tr>
<td>3.3.2 Analyses of the Data</td>
<td>81</td>
</tr>
<tr>
<td>3.3.3 Comparison Across Time Endpoints</td>
<td>86</td>
</tr>
<tr>
<td>3.3.4 Comparison Among Dose Components</td>
<td>88</td>
</tr>
<tr>
<td>3.3.5 Comparison of Time to Response and Quantal Response Models</td>
<td>88</td>
</tr>
<tr>
<td>3.3.6 Variation Between Replicates</td>
<td>94</td>
</tr>
</tbody>
</table>

## IV. PRODUCT HAZARD MODELS FOR TIME TO RESPONSE TOXICITY DATA USING NONPARAMETRIC TIME

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1 Introduction</td>
<td>98</td>
</tr>
<tr>
<td>4.2 Estimation Techniques When Exact Times are Known</td>
<td>100</td>
</tr>
<tr>
<td>4.2.1 Approximation Method</td>
<td>100</td>
</tr>
<tr>
<td>4.2.2 Partial Likelihood Method</td>
<td>103</td>
</tr>
<tr>
<td>4.2.3 Marginal Likelihood Approach</td>
<td>107</td>
</tr>
<tr>
<td>4.2.4 Hazard and Survival Function Estimation</td>
<td>109</td>
</tr>
<tr>
<td>4.2.5 Discrete Time Model Estimation</td>
<td>111</td>
</tr>
<tr>
<td>4.3 Estimation Techniques When Exact Times are Unknown</td>
<td>112</td>
</tr>
<tr>
<td>4.4 Likelihood Construction for Bioassay Data</td>
<td>117</td>
</tr>
<tr>
<td>4.4.1 Approximation Method with Exact Response Times Known</td>
<td>117</td>
</tr>
<tr>
<td>4.4.2 Approximation Method with Exact Response Times Unknown</td>
<td>120</td>
</tr>
</tbody>
</table>

## V. ANALYSIS OF TIME TO RESPONSE TOXICITY DATA USING PRODUCT HAZARD MODELS WITH NONPARAMETRIC TIME

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1 Introduction</td>
<td>122</td>
</tr>
<tr>
<td>5.2 Differences Due to Survival Function Estimators</td>
<td>123</td>
</tr>
<tr>
<td>5.3 Comparison of Parametric and Nonparametric Time Components</td>
<td>124</td>
</tr>
<tr>
<td>5.4 Comparison of Dose Components and Time Endpoints</td>
<td>130</td>
</tr>
<tr>
<td>5.5 Comparison of Time to Response and Quantal Response Models</td>
<td>131</td>
</tr>
</tbody>
</table>
TABLE OF CONTENTS (continued)

VI. PROPERTIES OF THE VIRTUALLY SAFE DOSE

6.1 Comparison of Time to Response and Quantal Response Virtually Safe Doses

6.2 Distribution of Quantal Response Virtually Safe Doses
   6.2.1 Small Sample Properties of the VSD
   6.2.2 Bimodality of Log(VSD) Distribution

6.3 Confidence Bounds for the Virtually Safe Dose
   6.3.1 Confidence Bounds Methods
   6.3.2 Transformations to Achieve Normality

VII. SUMMARY AND SUGGESTIONS FOR FUTURE RESEARCH

7.1 An Overview
7.2 Nonproportional Hazard Survival Models
7.3 Other Functional Forms for Time
7.4 Problems with Regard to Time Lag Parameters
7.5 Pharmacokinetics Models for Time to Response Data
7.6 Consideration of Other Time Endpoints and Risk Estimates

BIBLIOGRAPHY

APPENDIX
ACKNOWLEDGEMENTS

This research has provided me the opportunity to work closely with my advisor, Dr. Michael J. Symons; his guidance and encouragement are gratefully acknowledged. I have also worked closely with Dr. Thomas B. Starr at the Chemical Industry Institute of Toxicology; his advice and insights into risk assessment issues have been freely offered and are deeply appreciated. In addition, I also extend my thanks to the other members of my committee, Dr. James Gibson, Dr. David Hoel, Dr. Larry Kupper, Dr. Kerry Lee, and Dr. Dana Quade. Special thanks to Dr. Daniel Krewski at Health and Welfare Canada for providing the simulated data base analyzed in this dissertation.

Support for this research and most of my graduate study in biostatistics was provided through the pre-doctoral fellowship program at the Chemical Industry Institute of Toxicology in Research Triangle Park, N. C. I have enjoyed being associated with such an excellent group of scientists for the past three years. All analyses presented herein were performed on their computer, and their formaldehyde data set provided my first exposure to risk assessment.

I wish to thank my wife, Janice, for her love and support which allowed me to complete this research. I deeply appreciate the unending love, support, and encouragement of my parents throughout my studies. A final thanks to my son, Jonathan, whose presence reminds me that there are more important things in this life than dissertations.
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1.1</td>
<td>Mathematical Models and their Low-Dose Behavior in the Case of Zero or Independent Background</td>
<td>11</td>
</tr>
<tr>
<td>Table 1.2</td>
<td>Summary of Main Comparisons Made in Analyzing the Simulated Data Base</td>
<td>29</td>
</tr>
<tr>
<td>Table 3.1</td>
<td>Formaldehyde - Time to Death with Tumor Analysis Parameter Estimates and Goodness of Fit Statistics</td>
<td>66</td>
</tr>
<tr>
<td>Table 3.2</td>
<td>Formaldehyde - Unobservable Time to Tumor Analysis Parameter Estimates and goodness of Fit Statistics</td>
<td>67</td>
</tr>
<tr>
<td>Table 3.3</td>
<td>Formaldehyde - Estimated Virtually Safe Doses for Risk = 1/1,000,000 at 24 Months</td>
<td>68</td>
</tr>
<tr>
<td>Table 3.4</td>
<td>Absolute Concentrations of Covalently Bound [14C]Formaldehyde in Respiratory Mucosal DNA of Fischer-344 Rats</td>
<td>73</td>
</tr>
<tr>
<td>Table 3.5</td>
<td>Maximum Likelihood Estimates of Risk Based on Administered Dose (A) and Delivered Dose (D) at Selected Ambient Air Formaldehyde Concentrations for Unobservable Time to Tumor Analysis</td>
<td>76</td>
</tr>
<tr>
<td>Table 3.6</td>
<td>Upper 95% Confidence Bounds on Risk Based on Administered Dose (A) and Delivered Dose (D) at Selected Ambient Air Formaldehyde Concentrations for Unobservable Time to Tumor Analysis</td>
<td>76</td>
</tr>
<tr>
<td>Table 3.7</td>
<td>Maximum Likelihood Estimates of Risk Based on Administered Dose (A) and Delivered Dose (D) at Selected Ambient Air Formaldehyde Concentrations for Time to Death with Tumor Analysis</td>
<td>77</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------------------------------------------------------------</td>
<td>---</td>
</tr>
<tr>
<td>Table 3.8</td>
<td>Upper 95% Confidence Bounds on Risk Based on Administered Dose (A) and Delivered Dose (D) at Selected Ambient Air Formaldehyde Concentrations for Time to Death with Tumor Analysis</td>
<td>77</td>
</tr>
<tr>
<td>Table 3.9</td>
<td>Ratios of Risk Estimates Based on Administered Dose to Risk Estimates Based on Delivered Dose at Selected Ambient Air Formaldehyde Concentrations for Unobservable Time to Tumor Analysis</td>
<td>78</td>
</tr>
<tr>
<td>Table 3.10</td>
<td>Ratios of Risk Estimates Based on Administered Dose to Risk Estimates Based on Delivered Dose at Selected Ambient Air Formaldehyde Concentrations for Time to Death with Tumor Analysis</td>
<td>78</td>
</tr>
<tr>
<td>Table 3.11</td>
<td>Estimated Virtually Safe Doses for Risk of 1/1,000,000 at 900 Days by Dose Component and Time Endpoint Analysis - Experiment</td>
<td>82</td>
</tr>
<tr>
<td>Figure 1.1</td>
<td>Linearity, Sublinearity, and Supralinearity at Low Doses</td>
<td>9</td>
</tr>
<tr>
<td>Figure 2.1</td>
<td>A Simple Pharmacokinetic Model for the Metabolic Fate of Some Carcinogens</td>
<td>45</td>
</tr>
<tr>
<td>Figure 3.1</td>
<td>Kaplan-Meier Estimate of Time to Death with Tumor Distribution for Formaldehyde</td>
<td>64</td>
</tr>
<tr>
<td>Figure 3.2</td>
<td>Estimated Time to Death with Tumor Distribution for Formaldehyde from Logit Dose - Weibull Time Model</td>
<td>70</td>
</tr>
<tr>
<td>Figure 3.3</td>
<td>Estimated Time to Tumor Distribution for Formaldehyde from Logit Dose - Weibull Time Model</td>
<td>70</td>
</tr>
<tr>
<td>Figure 3.5</td>
<td>Frequency Distribution of the Values of $\log_{10}[\frac{\text{VSD}<em>{\text{Model}}}{\text{VSD}</em>{\text{True}}}]$ from Time to Death with Tumor Analyses using Probit, Logit, and Weibull Dose and Weibull Time Components (t=900 days)</td>
<td>84</td>
</tr>
<tr>
<td>Figure 3.6</td>
<td>Frequency Distribution of the Values of $\log_{10}[\frac{\text{VSD}<em>{\text{Model}}}{\text{VSD}</em>{\text{True}}}]$ from Unobservable Time to Tumor Analyses using Probit, Logit, and Weibull Dose and Weibull Time Components (t=900 days)</td>
<td>85</td>
</tr>
<tr>
<td>Figure 3.7</td>
<td>Frequency Distribution of the Values of $\log_{10}[\frac{\text{VSD}<em>{\text{Model}}}{\text{VSD}</em>{\text{True}}}]$ from Probit, Logit, and Weibull Quantal Response Models (t=900 days)</td>
<td>89</td>
</tr>
</tbody>
</table>
LIST OF FIGURES (continued)

Figure 3.8  Frequency Distribution of Differences in Values of $\log_{10}[VSD_{\text{Model}}/VSD_{\text{True}}]$ from Time to Death with Tumor Analyses using Weibull Time Components and Quantal Response Models for Probit, Logit, and Weibull Dose Components (t=900 days) 91

Figure 3.9  Frequency Distribution of Differences in Values of $\log_{10}[VSD_{\text{Model}}/VSD_{\text{True}}]$ from Unobservable Time to Tumor Analyses using Weibull Time Components and Quantal Response Models for Probit, Logit, and Weibull Dose Components (t=900 days) 92

Figure 3.10 Frequency Distribution of Differences between Replicates in Values of $\log_{10}[VSD_{\text{Model}}/VSD_{\text{True}}]$ from Time to Death with Tumor Analyses using Probit, Logit, and Weibull Dose and Weibull Time Components (t=900 days) 95

Figure 3.11 Frequency Distribution of Differences between Replicates in Values of $\log_{10}[VSD_{\text{Model}}/VSD_{\text{True}}]$ from Unobservable Time to Tumor Analyses using Probit, Logit, and Weibull Dose and Weibull Time Components (t=900 days) 96

Figure 5.1  Estimated Cumulative Hazard Function for Time to Death with Tumor using Weibull Dose and Time Components for Replicate 1 of Experiment 1 125
LIST OF FIGURES (continued)

Figure 5.2  Estimated Survival Functions for Time to Death with Tumor using Weibull Dose and Time Components for Replicate 1 of Experiment 1  125

Figure 5.3  Frequency Distribution of the Values of $\log_{10}[\text{VSD}_{\text{Model}}/\text{VSD}_{\text{True}}]$ from Time to Death with Tumor Analyses using Probit, Logit, and Weibull Dose and Nonparametric Time Components ($t=900$ days)  127

Figure 5.4  Frequency Distribution of the Values of $\log_{10}[\hat{\text{VSD}}_{\text{Model}}/\text{VSD}_{\text{True}}]$ from Unobservable Time to Tumor Analyses using Probit, Logit, and Weibull Dose and Nonparametric Time Components ($t=900$ days)  128

Figure 5.5  Frequency Distribution of Differences in Values of $\log_{10}[\text{VSD}_{\text{Model}}/\text{VSD}_{\text{True}}]$ from Time to Death with Tumor Analyses using Nonparametric Time Components and Quantal Response Models for Probit, Logit, and Weibull Dose Components ($t=900$ days)  132

Figure 5.6  Frequency Distribution of Differences in Values of $\log_{10}[\hat{\text{VSD}}_{\text{Model}}/\text{VSD}_{\text{True}}]$ from Unobservable Time to Tumor Analyses using Nonparametric Time Components and Quantal Response Models for Probit, Logit, and Weibull Dose Components ($t=900$ days)  133
LIST OF FIGURES (continued)

Figure 6.1  Asymptotic and Simulated Densities of Parameter Alpha from Probit Model using Formaldehyde Data  141

Figure 6.2  Asymptotic and Simulated Densities of Parameter Beta from Probit Model using Formaldehyde Data  141

Figure 6.3  Asymptotic and Simulated Densities of VSD from Probit Model using Formaldehyde Data  142

Figure 6.4  Asymptotic and Simulated Densities of log(VSD) from Probit Model using Formaldehyde Data  142

Figure 6.5  Asymptotic and Simulated Densities of 1/VSD from Probit Model using Formaldehyde Data  142

Figure 6.6  Predicted Logit Quantal Response Model for Dieldrin Data  144

Figure 6.7  Asymptotic and Simulated Densities of Parameter Alpha from Logit Model using Dieldrin Data  145

Figure 6.8  Asymptotic and Simulated Densities of Parameter Beta from Logit Model using Dieldrin Data  145

Figure 6.9  Asymptotic and Simulated Densities of Parameter Gamma from Logit Model using Dieldrin Data  145

Figure 6.10 Asymptotic and Simulated Densities of VSD from Logit Model using Dieldrin Data  146
LIST OF FIGURES (continued)

Figure 6.11  Asymptotic and Simulated Densities of log(VSD)
             from Logit Model using Dieldrin Data 146

Figure 6.12  Asymptotic and Simulated Densities of l/VSD
             from Logit Model using Dieldrin Data 146

Figure 6.13  Regions Determining Bimodality of (a+U)/(b+V)
             for Independent Standard Normal Variables U and V 149
CHAPTER I
INTRODUCTION AND REVIEW OF THE LITERATURE

1.1. Introduction

As part of the process for determining the proper regulatory policy for compounds which are known or suspected chemical carcinogens, it is frequently necessary to estimate long term human cancer risk at low levels of exposure using the results from animal experiments. Using enough animals to directly measure increases in cancer risk on the order of 1/100,000 or 1/100,000,000 is impractical. Because of the necessity to effectively establish a dose response relationship with relatively few animals, bioassays are conducted with doses chosen so as to produce lesions or tumors in an appreciable proportion of the animals. For example, Sontag et al. (1977) report that the typical cancer bioassay sponsored by the National Cancer Institute is conducted using fifty animals of each sex at each of three dose levels for a period of time approximately equal to the lifetime of the animal.

Making a risk assessment for man based upon these animal data involves two fundamental problems. The first, the low dose extrapolation problem, is the extrapolation of the dose response relationship obtained in the test animals to levels approximating human exposures. This is the basic concern of the research below. The second problem is that of converting an acceptable dose level for the species under test to an acceptable level for man. This species conversion problem is not considered in
this dissertation; however, the interested reader will find many of the relevant issues in this area discussed in reports by Hoel et al. (1975), the Food Safety Council (1978, 1980), and the National Academy of Sciences (1977). Krewski and Brown (1981) have prepared an excellent guide to the statistical literature on carcinogenic risk assessment which also includes a summary of these and other risk assessment issues.

Many of the existing statistical procedures for low dose extrapolation are applicable only to quantal response toxicity data, and do not utilize frequently available time information. This information includes times to tumor as well as times to death either 1) from tumor, 2) by scheduled sacrifice, or 3) some other cause such as natural mortality. With this additional information, several possible response times are of interest. The focus of this research is on techniques for incorporating this time to response data into quantitative risk assessment. Of particular interest are potential differences in estimates of risk which could result from the inclusion of time.

This thesis considers a methodology for incorporating time into low dose extrapolation using product hazard survival models; that is, models in which the instantaneous conditional probability of an event $\lambda(t;d)$, known as the hazard function, at time $t$ for an animal receiving dose $d$, is a product of a function of time $\lambda_0(t)$ and a function of dose $g(d)$. Symbolically,

$$\lambda(t;d) = \lambda_0(t) g(d).  \quad (1.1)$$

Hartley and Sielken (1977), Crump (1978), Dafer et al. (1980), and Crump et al. (1981) have all considered this type of model for quantitative
risk assessment and low dose extrapolation. All of these authors choose $g(d)$ to be a polynomial, but differ in the forms selected for $\lambda_0(t)$.

This model and other specific methods for incorporating time information are discussed further in Section 1.4. In Section 1.2 a summary is given of the usual techniques for handling the low dose extrapolation problem. These techniques do not use time explicitly, however. Difficulties which arise when using these quantal response methods and arguments for including time are considered in Section 1.3. Section 1.5 contains a review of a large comparative study of different analysis techniques for time to response data. The chapter concludes with an outline of the material to be presented in subsequent chapters.

1.2. Quantal Response Procedures

Statistical procedures for low dose extrapolation involve the specification of a mathematical model. For this model, the probability of an induced response at dose $d$, $P(d)$, has a particular functional form which is assumed to be strictly increasing for all positive doses $d$. The current mathematical models and the underlying bases for these models are summarized below. Existing techniques for incorporating background responses are also described along with their implications for low dose extrapolation. The account given here closely follows the summary of quantal response models by Krewski and Van Ryzin (1981). Other summaries may be found in articles by the Food Safety Council (1978, 1980), Fishbein (1980), and Gaylor and Shapiro (1979).
1.2.1. Mathematical Models

The mathematical models used for risk assessment purposes are often considered as either tolerance distribution models or mechanistic models. Tolerance distribution models are based upon the concept that each animal in the population has its own tolerance to the test compound. Any dose not exceeding the tolerance of an individual will have no effect, whereas any dose exceeding the tolerance will result in a positive response; for example, the development of a tumor. For these models, the probability of a positive response, \( P(d) \), is the cumulative distribution function of the tolerances in the population. In contrast, mechanistic models are based upon the concept that for each animal a positive response is the result of the random occurrence of one or more biological events. For these models, \( P(d) \) is the probability of achieving the required number of events.

The log tolerance distribution models have been discussed by Chand and Hoel (1974) as one general class of tolerance distribution models. These models are characterized by

\[
P(d) = \begin{cases} 
G(\alpha + \beta \log d) & , d > 0 \\
0 & , d = 0 
\end{cases},
\]

(1.2)

where \( G(x) \) is any standardized cumulative distribution function defined for all real \( x \), and \( \alpha \) and \( \beta \) are unknown parameters with \( \beta \) positive. Best known of these is the probit model, for which the tolerances are assumed to follow a lognormal distribution. Two other frequently used models from this class arise when the log tolerances follow logistic or extreme value distributions; these are the logit and Weibull models respectively.
Symbolically, for the probit model,

\[ P(d) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\alpha + \beta \log d} \exp(-t^2/2) \, dt; \]  

for the logit model,

\[ P(d) = \frac{e^{\alpha} \, d^\beta}{1 + e^{\alpha} \, d^\beta}; \]

and for the Weibull model,

\[ P(d) = 1 - \exp[-e^{\alpha} \, d^\beta]. \]

If the induction of a tumor is the result of the sequential occurrence of \( k \) different random biological events, the \( k \) stage multistage model results. In this mechanistic model, the age specific rate of occurrence of each event is assumed to be a positive linear function of dose.

\[ P(d) = 1 - \exp[-\prod_{i=1}^{k} (a_i + b_i \, d)] \]

\[ = 1 - \exp[-\sum_{i=0}^{k} c_i \, d^i], \]

for constants \( a_i > 0, b_i > 0, \) and \( c_i > 0. \)

The "hit" mechanistic models are derived if responses are induced after the occurrence of one or more of a variety of fundamental biological events at the target site within a specified time interval. If the
The number of hits during this period follows a homogeneous Poisson process and a positive number, $k$, of hits is required to produce a response, then the probability that an animal receiving dose $d$ will respond during the time interval is given by

$$P(d) = 1 - \sum_{i=0}^{k-1} \frac{\exp(-\lambda d)(\lambda d)^i}{i!}$$  \hspace{1cm} (1.8)

$$= \sum_{i=k}^{\infty} \frac{\exp(-\lambda d)(\lambda d)^i}{i!}$$  \hspace{1cm} (1.9)

$$= \frac{1}{\Gamma(k)} \int_{0}^{\lambda d} e^{-u} u^{k-1} du,$$  \hspace{1cm} (1.10)

where $\lambda d$ is the expected number of hits during the interval. The gamma multi-hit model results from using the formulation (1.10) with $k$ not necessarily an integer. Because $1 - \exp(-x)$ is approximately equal to $x$ for $x$ small, the one hit and the one stage model are frequently referred to in the literature as the linear model.

1.2.2. Incorporating Background Response

All models, with the exception of the multistage, presented above have the property that $P(0) = 0$. Because the response of interest may occur spontaneously in control animals, it is necessary to allow for background responses. Two types of parameters have been suggested by Hoel (1980) to quantify the background responses. If the spontaneous and dose-induced responses are assumed to be independent, then the prob-
ability of a response at dose \( d \) of either type is given by

\[
P^*(d) = \gamma + (1 - \gamma) P(d),
\]

where \( 0 \leq \gamma < 1 \) denotes the spontaneous response probability.

If the background is assumed to act in an additive mechanistic fashion, then the background responses may be considered to arise from an effective positive background dose, \( \delta \), and

\[
P^*(d) = P(d + \delta).
\]

A mixed background model, consisting of both independent and additive background components, may also be considered:

\[
P^*(d) = \gamma + (1 - \gamma) P(d + \delta).
\]

1.2.3. Risk Estimates

The primary risk measures used in low dose extrapolation are the excess risk over background and the virtually safe dose. The excess risk at dose \( d \) is defined as

\[
\Pi(d) = P^*(d) - P^*(0),
\]

regardless of the type of background component(s) present in the model.
The virtually safe dose (VSD) corresponding to a given added risk \( \pi \) is that unique dose \( d^* \) satisfying
\[
\Pi(d^*) = \pi. \tag{1.15}
\]

Figure 1.1 is a schematic representing this concept, for three different underlying dose response functions. Estimates of the VSD and its confidence bounds are the usual statistics from the bioassay utilized by regulatory agencies for decisions about acceptable human exposure levels. The VSD was first proposed by Mantel and Bryan (1961) and later extended to include positive background components by Crump, Guess, and Deal (1977).

The added risks \( \pi \), for which estimates of the VSD are desired, are generally very small. Thus one should examine the behavior of the VSD for very small increases in risk. This behavior is most easily derived by studying the low dose behavior of the excess risk. Let
\[
\rho = \lim_{d \to 0^+} \frac{\Pi(d)}{d} \tag{1.16}
\]
\[
= \lim_{d \to 0^+} \Pi'(d). \tag{1.17}
\]

Then \( \Pi(d) \) is
\[
\begin{cases}
\text{sublinear}, & \text{if } \rho = 0 \\
\text{linear}, & \text{if } 0 < \rho < \infty \\
\text{supralinear}, & \text{if } \rho = \infty
\end{cases} \tag{1.18}
\]

These terms are also represented schematically in Figure 1.1.

For additive background models \( \Pi'(0) = P'(\delta) \) and for mixed background models \( \Pi'(0) = (1-\gamma) P'(\delta) \). Since \( \delta > 0 \) and \( P(d) \) is strictly increasing, \( \rho \) is always finite and nonzero. Thus \( \Pi(d) \) is always linear at low doses. For models with at most an independent background, the
FIGURE 1.1  LINEARITY, SUBLINEARITY, AND SUPRALINEARITY AT LOW DOSES
results are not as straightforward, but depend on the other parameters and functional form of the model. The low dose behavior for these models is summarized in Table 1.1, which is adapted from Krewski and Van Ryzin (1981).

If the excess risk is sublinear at low doses, then the corresponding VSD is supralinear at small risk levels; and vice versa. From Table 1.1 and the above derivation we then have that, depending upon the model and the type of background components considered, the VSD is either a linear, sublinear, or supralinear function of the excess risk.

1.2.4. Estimation

Suppose that a total of \( n \) animals is used in a bioassay with the ordered dose levels \( d_1, d_2, \ldots, d_k \) and that \( m_i \) of the \( n_i \) animals at dose \( d_i \) have a positive response to the agent. The model parameters and consequently the excess risk, \( \Pi(d) \), and the VSD, \( d^* \), may then be estimated using maximum likelihood techniques next described:

Assuming that each animal responds independently of every other animal in the experiment, the likelihood of the observed outcome under any model \( P^*(d) = P^*(d; \theta) \) is given by

\[
L(\theta) = \prod_{i=1}^{k} \left( \frac{n_i}{m_i} \right) [P_i^*]^{m_i} [1 - P_i^*]^{(n_i - m_i)} \tag{1.19}
\]

where \( P_i^* = P^*(d_i; \theta) \) and \( \theta \) is an \( r \) dimensional vector of parameters with \( r \leq k \). In most instances, the maximization of \( L(\theta) \) requires the use of iterative numerical procedures.
<table>
<thead>
<tr>
<th>Model</th>
<th>P(d)</th>
<th>Constraints</th>
<th>Sublinear</th>
<th>Linear</th>
<th>Supralinear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probit</td>
<td>$(2\pi)^{-1/2} \int_{-\infty}^{0} e^{-u^2/2} du$</td>
<td>$\beta &gt; 0$</td>
<td>$\beta &gt; 0$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Logit</td>
<td>$\frac{\alpha \beta}{e^{\alpha \beta} + e^{\alpha \beta}}$</td>
<td>$\beta &gt; 0$</td>
<td>$\beta &gt; 1$</td>
<td>$\beta = 1$</td>
<td>$\beta &lt; 1$</td>
</tr>
<tr>
<td>Weibull</td>
<td>$1 - e^{-\alpha d \beta}$</td>
<td>$\beta &gt; 0$</td>
<td>$\beta &gt; 1$</td>
<td>$\beta = 1$</td>
<td>$\beta &lt; 1$</td>
</tr>
<tr>
<td>One-Hit</td>
<td>$1 - e^{-\lambda d}$</td>
<td>$\lambda &gt; 0$</td>
<td>-</td>
<td>$\lambda &gt; 0$</td>
<td>-</td>
</tr>
<tr>
<td>Multi-Hit</td>
<td>$\frac{1}{[\Gamma (k)]} \int_{0}^{\lambda d \beta} u^{-k-1} e^{-u} du$</td>
<td>$\lambda, k &gt; 0$</td>
<td>$k &gt; 1$</td>
<td>$k = 1$</td>
<td>$k &gt; 1$</td>
</tr>
<tr>
<td>Multi-Stage</td>
<td>$1 - e^{-\sum_{i=1}^{k} \beta_i d_i}$</td>
<td>$\beta_i &gt; 0$</td>
<td>$\beta_1 = 0$</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*aAdapted from Krewski and Van Ryzin (1981)*
Under suitable regularity conditions, summarized in Krewski and Van Ryzin (1981),

The maximum likelihood estimator $\hat{\theta}$ is unique with probability one;

$\hat{\theta}$ is a consistent estimator of $\theta$;

$$\sqrt{n} (\hat{\theta} - \theta) \sim N(0, \Sigma^{-1})$$

where $\Sigma = (\sigma_{rs})$ is defined by

$$\sigma_{rs} = \sum_{i=1}^{k} \frac{c_i \theta_r \theta_s}{\frac{\theta_i}{1 - \theta_i}}$$

with $c_i = \lim_{n \to \infty} n_i / n$.

If $\hat{P}^*(d) = P^*(d, \theta)$, then $\hat{\Pi}(d) = \hat{P}^*(d) - \hat{P}^*(0)$ is a consistent estimator of the excess risk, $\Pi(d)$, and the estimated VSD, $d^*$, which satisfies $\pi = \hat{\Pi}(d^*)$ is a consistent estimator of the VSD, $d^*$. As functions of the maximum likelihood estimates, $\hat{\Pi}(d)$, $d^*$, $\log(d^*)$, and $1/d^*$ all have asymptotic normal distributions. This fact may be used to construct asymptotic confidence bounds on the excess risk and VSD.

1.3. Quantal Response Difficulties and the Need for Time Information

In this section, some of the problems which arise with the use of quantal response models are discussed. Specific arguments for including
time in quantitative risk assessment are given. Many of the problems
pointed out for quantal response models are also concerns when time is
explicitly considered.

1.3.1. Quantal Response Difficulties

Since the typical animal bioassay has at most two or three dose
groups above controls and the number of parameters must not exceed the
total number of dose groups, the number of parameters allowed in a given
model is limited. If in fact the number of dose groups equals the number
of parameters, there are no degrees of freedom remaining to perform a
customary chi-squared goodness of fit test. There also may be an identifi-
ability problem for the parameters in certain of the quantal response
models which have mixed background components. Additional computational
and identifiability problems can and do arise for many of the models un-
less the number of positive dose groups at which one obtains a positive
response is two or greater.

In the observable response range, it is almost impossible to dis-
tinguish between the quantal response models fitted with the maximum
likelihood estimates of the parameters, despite the differences in the
functional forms of the models. Usual goodness of fit tests may not
reject the fit of any of these models. Nevertheless, differences are most
apparent in the tails of the fitted models. Munro and Krewski (1981)
demonstrated empirically that, if the underlying dose response curve
itself is sublinear, then the resulting model specific VSDs are ordered
as follows:
One hit < Multistage < Weibull \not\leq Logit \leq Multi-hit < Probit.

If, however, the dose response curve is supralinear, then in general the VSDs are in reverse order:

Probit < Weibull \not\leq Logit \leq Multi-hit < Multistage < One hit.

This is consistent with the theoretical results of Yanagimoto and Hoel (1980), who derived a measure of the heaviness of the tail of a distribution at the origin. These authors demonstrated with this measure that the tails of the models increased in heaviness as follows:

Probit < Logit < Weibull < Multistage,

with the multi-hit model near to the logit or Weibull.

The appropriate manner for incorporating background responses in the quantal response model is another problem that the statistician must address. The fit of a specific model using either an independent or additive background may be equally satisfactory. However, for models with an additive background component, the excess risk is approximately linear at low doses; hence the VSD is essentially linear for small added risks. For models with at most an independent background component, the VSD may be linear, sublinear, or supralinear depending upon the model and its parameter values. Thus another potential difference exists for VSDs depending on the modeling strategy employed.

For these reasons some investigators, for example, Cornfield et al. (1980), have recommended that as many models as possible be fit to the
data and all the corresponding risk estimates and VSDs be considered by regulators. Others, including Mantel et al. (1975) and Gaylor and Kodell (1980), have proposed a single conservative risk estimate. Guess, Crump, and Deal (1977) and still other investigators recommended fitting many models, but also obtaining confidence bounds for the risk estimates. In this instance, the VSDs and their confidence bounds are then to be used for regulatory purposes. These confidence bounds could be constructed from the asymptotic properties of the parameter estimates or by simulation. Further discussion as to the choice of the best quantal response model and which risk quantities should be provided to and/or used by the regulators is beyond the scope of this thesis. However, the statistical and toxicological literatures contain numerous individual arguments for particular approaches to these long standing problems.

While arguments may be given for biological bases of particular quantal response models, these models do not always reflect the laboratory results obtained by the biochemical researcher. In particular, none of these models takes into consideration the extremely complicated processes of distribution, metabolic activation, and detoxification of the chemical agent under study. Scherer and Emmelot (1979) noted that these mechanisms and metabolic processes may increase, decrease, or even remove the potential for tumor formation in the animal. These biological processes are being ignored if one assumes that administered and delivered active dose are proportional. Cornfield (1977) made this important distinction and proposed one of the first nonlinear steady state kinetic models for effective dose.

Gehring et al. (1978) found that, for vinyl chloride exposure in rats, the relationship between air concentration and activated dose
was adequately described by Michaelis-Menten kinetics. Anderson et al. (1980) generalized these results and proposed a general scheme for incorporating pharmacokinetics in the low dose extrapolation problem. Hoel et al. (1983) found that the low dose risk based upon a nonlinear pharmacokinetic model was never greater that the risk predicted by linear kinetics and could be smaller by several orders of magnitude.

While the mechanisms of action of toxic and carcinogenic agents are only partially understood, attempts should be made to choose models which more accurately reflect the known or suspected biology of the situation. When such information is available, it is desirable to incorporate differences between administered and effective doses.

The purpose of this section has not been to criticize the use of quantal response models, but to highlight some of the problems and controversies which arise from their usage. These difficulties, which also arise when both dose and time to response information are available, are more complex with the added time dimension. Some arguments for including time to response in quantitative risk assessment are presented.

1.3.2. Specific Arguments for Including Time

Because of the unscheduled deaths of animals in an experiment due to causes which may or may not be related to the agent under study, some adjustments should be made to obtain the effective number of animals at risk at the end of the study. This difficulty arises because the procedures employed consider only the number of animals with and without tumor at that time. Kodell et al. (1982) and others employ life table
methods to determine these effective numbers. Since the parameter estimates and consequently the risk estimates are dependent on both the number of animals with a positive response and the total number of animals at risk, different methods for obtaining the effective numbers could lead to different risk estimates. The need to estimate the effective number of animals is eliminated with models which incorporate specific times to response.

Numerous kinds of time information are typically available from the animal bioassay. In addition to the necropsy findings for unscheduled deaths, there are frequently planned sacrifice data as well. In order to make effective use of these types of time information and avoid the need for estimating effective numbers of animals, models which utilize both dose and time should be used.

The patterns of ages at which cancers occur is also important in risk assessment. Tumors occurring late in life might be viewed differently from those occurring earlier. Information on early and late occurring tumors can be fully utilized in a time to response model, whereas these tumors are not treated differently for quantal response modeling. Information about late occurring tumors has on occasion been discarded in order to use a quantal response model; for example, see Federal Register (1976).

In lifetime feeding experiments, sometimes the proportion of animals developing a particular tumor increases steadily at lower doses, but levels off or even decreases at the higher doses. A nonlinear dependence of effective dose upon administered dose is one possible explanation for this phenomenon. Alternatively, Wahrendorf (1979) suggested that the animals at higher doses are more likely to die prior to tumor development because of the compound's toxic effects.
Since the quantal response models are strictly increasing functions of dose, the data at the higher doses in this situation are frequently omitted in order to perform the low dose extrapolation. The data at the higher doses can be reasonably accommodated with a proper time to response model.

The most compelling reason for including time is this: by utilizing the available time information, better estimates of potential human risk may result. Hoel (1976) found that other questions relevant to risk assessment, such as tumor incidence rates or the amount of life shortening in a particular age group, could also be answered as least theoretically by time to response models. Thus the incorporation of time information via mathematical modeling should be quite valuable.

Mathematical modeling is, however, only one way in which time information can be used in carcinogenicity testing. Peto et al. (1980) discussed several other approaches for analyzing data for which tumors are observable only at death. If the tumor type is rapidly lethal and kills its host immediately after onset, life table tests are appropriate. Prevalence type tests are appropriate when the tumor is not lethal. For tumor types which are neither rapidly lethal nor nonlethal, neither of these methods may be valid. Peto (1974) proposed a method for dealing with these intermediate tumor types when cause of death can be determined. Lagakos (1982) examined the biases which can occur with these three methods for various types of tumor data.

Whether one uses mathematical modeling or other techniques, a time to response analysis is of course more complicated than a quantal response analysis because of the additional time dimension. The need for additional data can also make the organization of the experiment more complex. This is especially true when tumor latency periods are long.
Lahl et al. (1981) remarked that while many scientists would like to analyze animal bioassays using the time contributions more effectively, frequently the data are so sparse or collected in such a manner that the time information is essentially lost. Whether these organizational problems can, or should be, overcome depends in part on the effects that time to response may have on the risk assessment.

1.4. Incorporating Time in Risk Assessment

Based upon the above considerations, it is important to study the various approaches which have been considered for modeling time to response data. Recall that depending upon the type of data available and of interest, the time to response may include the actual time to tumor, time to death from tumor, or time to death with tumor present. Whitemore and Keller (1978) gave a review of the major models of carcinogenesis. The extensive summary of the major classes of time to response models provided by Kalbfleisch et al. (1983) is the basis for much of the material presented in Section 1.4.1. In Section 1.4.2. numerous risk estimates which incorporate time are presented.

1.4.1. Time to Response Models

Let $T$ be the time to response and $F(t;d) = \Pr \{ T \leq t; d \}$ be the cumulative distribution function of $T$ at dose $d$. The corresponding hazard
function is defined as

\[ \lambda(t;d) = \lim_{\Delta \to 0} \frac{\Pr \{ T \in (t, t + \Delta) \mid T > t \}}{\Delta} \]  

(1.21)

Consequently,

\[ F(t;d) = 1 - \exp[- \Lambda(t;d)] \]  

(1.22)

where

\[ \Lambda(t;d) = \int_{0}^{t} \lambda(u;d) \, du \]  

(1.23)

is the cumulative hazard.

Thus the hazard function characterizes the distribution of T. In this section some models for F(t;d), or equivalently \( \Lambda(t;d) \), are discussed.

The earliest work that modeled relationships between dose, response, and time to response in animal experiments was primarily observational. Using data from a large number of studies where rats and mice were given high doses of carcinogenic nitrosamines, Druckrey (1967) found that the median time to tumor appeared to decrease as the dose increased. The relationship hypothesized was that

\[ d \, t^n = c; \]  

(1.24)

where \( d \) is the administered dose; \( t \) is the median time to tumor; \( c \) is a constant; and \( n \) is a positive exponent typically near three. Many
investigators hoped that through the use of this relation low doses could be found such that the median time to tumor would be greater than the expected lifetime of the animal; thus exposures at or below these low doses would be virtually without risk.

Albert and Altshuler (1973) expanded upon Druckrey's relation to incorporate distributions of time to response in individual animals into a mathematical model of dose and time. In particular, their model assumes that the time to response $T$ is lognormally distributed. The mean of the distribution satisfies the Druckrey relation (1.24) and the standard deviation is independent of dose. Chand and Hoel (1974) showed that a Weibull distribution for time to response results if the random error term in this same model followed an extreme value rather than normal distribution. Other choices of the time to response distributions and their effects on the distribution of tumors have been considered by Albert and Altshuler (1973).

Both the Weibull time to response model and the Albert-Altshuler model are special cases of the general class of log-linear models. In these models, the logarithm of time to response is a linear combination of functions of dose and a random variable $w$ defined on the entire real line which does not depend on dose. That is,

$$\log T = z' \beta + \sigma w,$$  \hspace{1cm} (1.25)

where $z' = (z_1, \ldots, z_s)$, $\beta' = (\beta_1, \ldots, \beta_s)$, and the components of $z$ are functions of dose alone. If $G(w) = \Pr\{W \leq w\}$ is the distribution function of $w$, then
\[ F(t;d) = G \left( \log t - z' \beta \right) \quad (1.26) \]

By appropriate choice of the error distribution \( G(w) \), different behaviors of the hazard function can be modeled with log-linear models. For example, an increasing hazard might be expected following repeated exposure to low doses of a carcinogen; whereas a decreasing hazard might be more applicable when a single exposure to an acutely toxic agent occurs. The action of a compound with a single exposure which is slowly absorbed could be modeled with a hazard which increases, as a result of exposure, and then decreases, because of absorption or elimination.

For multi-event models, a particular response results from the occurrence of a number of biological events. If \( k \) events are required, then the time to response is \( \max(T_1, T_2, \ldots, T_k) \), where the \( i \)-th event occurs at time \( T_i \). If these events are independent with cumulative hazards \( \Lambda_i(t;d) \) at dose \( d \), then

\[
F(t;d) = \Pr\{T \leq t;d\} = \prod_{i=1}^{k} \Pr\{T_i \leq t;d\} \quad (1.27)
\]

\[
= \prod_{i=1}^{k} \{ 1 - \exp[- \Lambda_i(t;d)] \} \quad (1.28)
\]

\[
\approx \prod_{i=1}^{k} \Lambda_i(t;d) \quad (1.29)
\]

for \( \Lambda_i(t;d) \) small for \( i = 1, \ldots, k \). If the \( T_i \) are exponentially distri-
buted with time independent hazards $\lambda_i(t;d) = \psi_i(d)$, then $\Lambda_i(t;d) = \psi_i(d) \cdot t$, and thus

$$F(t;d) = C(d) t^k$$  \hspace{1cm} (1.30)$$

$$\frac{1}{t} \cdot 1 - \exp[-C(d) \cdot t^k]$$  \hspace{1cm} (1.31)$$

where $C(d) = \prod_{i=1}^{k} \psi_i(d)$.

Note that the approximation used for equations (1.29) and (1.31) is $1 - \exp(-x) \approx \frac{1}{x} x$ for $x$ sufficiently small.

Both the multistage and multi-hit quantal response models are special cases of multi-event models. The multi-hit model arises if all $k$ events required to induce a response are the same. The multistage corresponds to the situation in which the events must occur in a specific order.

Compartmental analysis was suggested by Matis and Wehrly (1979) as another approach to the development of stochastic models for the carcinogenic process. Whitmore and Matis (1981) have presented a model of this type which incorporates causal biological theory into the chance mechanisms of the model. Additional examples of this method are the models proposed by Hartley et al. (1981) and Scott (1981). Using slightly different assumptions about the underlying stochastic process, these authors derived a model whose cumulative hazard is of the general form
\[ \Lambda(t;d) = \begin{cases} 
 g(d) [\mathcal{H}(t) - \mathcal{H}(\gamma(d))] & t > \gamma(d) \\
 0 & t < \gamma(d) 
\end{cases} \hspace{1cm} (1.32) \]

where \( g \) is a positive convex function of dose and \( \mathcal{H} \) is a positive non-decreasing function of time. The minimum cancer induction time, \( \gamma(d) \), is assumed to be zero in most applications. Because the hazard in this model factors as functions of dose and time, it is often referred to as the general product model.

Hartley and Sielken (1977) suggested that \( g \) and \( \mathcal{H} \) be modeled using low order polynomials with nonnegative coefficients. Daffer, Crump, and Masterman (1980), using the ideas in Crump (1978), estimated \( \mathcal{H} \) nonparametrically while modeling \( g \) with a polynomial having nonnegative coefficients. Crump et al. (1981) and Hartley and Sielken (1975a) modeled \( \mathcal{H}(t) \) with a Weibull functional form.

One further approach for modeling time to response is the regression model of Cox (1972). This model specifies a regression relationship for the hazard function at time \( t \) of the form

\[ \lambda(t;z) = \lambda_0(t) \exp(z'\beta), \hspace{1cm} (1.33) \]

where \( \lambda_0(t) \) is an arbitrary positive underlying hazard function, \( \beta' = (\beta_1, \beta_2, \ldots, \beta_s) \) is a vector of unknown regression parameters, and \( z' = (z_1, z_2, \ldots, z_s) \) is a vector of regressor variables or covariates whose components could possibly depend upon time. In these applications to time to response data from animal bioassays, only functions of dose are used as covariates. By allowing the covariate vector \( z \) to be time dependent, it is possible to allow for interactions between dose and
time. Kalbfleisch and Prentice (1980) have provided an excellent summary of the model and the extensive literature surrounding it. Prentice et al. (1982) and Peterson et al. (1982) used this approach for examining the dose response relationships found in animals exposed to gamma radiation. Cox model estimation procedures were the basis for the nonparametric modeling approach of Crump (1978) mentioned above. Further discussion of the Cox model is postponed until the presentation of non-parametric analyses of time to response data in Chapter 4.

1.4.2. Time Related Risk Estimates

Many different risk estimates can be considered with the inclusion of time to response information. The virtually safe dose is time specific, although the definition given in Section 1.2.3 does not show this. If \( F(t;d) \) represents the distribution for the time to response for an animal receiving dose \( d \), the VSD satisfies

\[
\pi = F(T;d) - F(T;0)
\]

(1.34)

for some fixed time point \( T \). Usual choices for \( T \) are the lifespan of the experimental animal or the end of the study. By allowing \( T \) to vary, the VSD can be defined at any time point of interest.

Several other quantities have been proposed for estimating risk in time to response models; these are presented below. The expected or mean time to response for a dose \( d \) is given by

\[
\]
\[ E[t;d] = \int_0^\infty u f(u;d) \, du, \quad (1.35) \]

where \( f(t;d) = \frac{\partial F(t;d)}{\partial t} \).

Hoel and Walburg (1972) suggested the use of the adjusted mean time to response as one possible risk measure. This quantity gives the mean time to response for an individual conditional on a response having occurred by time \( T \). This is given by

\[ \mu(T;d) = \frac{1}{F(T;d)} \int_0^T u f(u;d) \, du. \quad (1.36) \]

Sielken (1981) proposed two new definitions of acceptable risk, the mean free dose and the late risk dose, which are described below. The mean response free period in the first \( T \) months of exposure is given by

\[ T - \int_0^T (T-u) f(u;d) \, du. \quad (1.37) \]

The mean free dose is that dose which corresponds to a \( 100(\varepsilon) \) percent reduction in the mean response free period, where \( 0 < \varepsilon < 1 \).

The late risk dose is essentially the dose level which corresponds to an acceptable increase in risk after a relatively long period of exposure. Formally the late risk dose \( d^+ \) satisfies
\[ F(T; \delta) = F(\rho T; d^+) \]  

(1.38)

where \( \rho \) is a fraction near one.

Hoel (1982) studied the properties of these estimates and found that no single estimate can best describe the risk. The mean time to response, adjusted mean time to response, and the mean free dose give some indication as to whether one is dealing with an early or late time effect. This desirable property is weakened by the need to quantify the importance of differences in such effects. The late risk dose can be shown to correspond to specifying an allowable increase in the relative risk as in epidemiologic studies, but depends strongly on the actual spontaneous response rate.

For these reasons, Hoel recommended bivariate descriptions of risk, using in addition some measure of the likelihood of a response occurring within an animal's lifetime. Further examination of the properties of these risk estimates is needed. In particular, the advantages or disadvantages of using either the late risk dose or mean free dose measures have not been well established. For these reasons, only the excess risk and the virtually safe dose will be used in the analyses of this paper.

1.5. Review of "A Comparison of Statistical Methods for Low Dose Extrapolation Utilizing Time-To-Tumor Data."

In this section, a comparative study of different statistical extrapolation procedures which take into account both the presence of competing risks and time to response information is reviewed. Krewski
et al. (1983) summarized the collective analyses conducted by D.
Krewski, K. S. Crump, J. Farmer, D. W. Gaylor, R. Howe, C. Portier,
D. Salsburg, R. L. Sielken, and J. Van Ryzin of a large simulated data
base of time to response data. The data and the analyses from this
particular study represent a standard against which other analysis
techniques for time to response data can be judged.

Because it is not usually possible to quantitatively assess the
performance of the different extrapolation procedures for "real" data,
a simulation study was performed. The effects of competing risks, spo-
notaneous background responses, tumor latency, and experimental design can
also be observed for simulated data. Specific comparisons considered in
the design of the simulated assays are given in Table 1.2. Two repli-
cates of each of twenty-three possible 900 day experiments were gener-
ated. The simulated experiments generally involved five equally spaced
dose groups with 48 animals per dose. A more detailed description of the
design of the experiments is delayed until Chapter 3, where these data
are used for analysis purposes.

Three distinct time endpoints were of interest for this study. These
were the actual time to tumor, the time to death from tumor, and the time
to death with a tumor present. This time to tumor could be both observ-
able or unobservable. Although valid inferences concerning the time to
tumor distribution are possible only when all tumors are found in-
cidentally at necropsy or when the actual time to tumor is observ-
able, neither situation can be considered likely to occur in practice.
More common would be analyses of the death times for those dying with
tumor, for whom the cause of death might or might not be determined.
<table>
<thead>
<tr>
<th>ISSUES</th>
<th>COMPARISONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Response Curve</td>
<td>Linear vs. Sublinear at Low Doses</td>
</tr>
<tr>
<td>Hazard Function</td>
<td>Steep vs. Shallow</td>
</tr>
<tr>
<td>Tumor Lethality</td>
<td>Rapid vs. Moderate</td>
</tr>
<tr>
<td>Competing Risks</td>
<td>Dose Dependent vs. Moderate</td>
</tr>
<tr>
<td>Background Response</td>
<td>8 Percent vs. 1 Percent</td>
</tr>
<tr>
<td>Dose Response Curvature</td>
<td>Linear Trend: Low - High;</td>
</tr>
<tr>
<td></td>
<td>Nonlinear Trend: Low - Medium - High</td>
</tr>
<tr>
<td>Time to Tumor Model</td>
<td>Weibull: Log-linear vs. Product Hazards; Log</td>
</tr>
<tr>
<td></td>
<td>Linear: Weibull vs. Probit; Log Linear: Probit</td>
</tr>
<tr>
<td></td>
<td>vs. Logit</td>
</tr>
<tr>
<td>Background Component</td>
<td>Additive vs. Independent</td>
</tr>
<tr>
<td>Minimum Tumor Induction Time</td>
<td>Threshold vs. Nonthreshold</td>
</tr>
<tr>
<td>Number of Dose Groups</td>
<td>Three vs. Five</td>
</tr>
<tr>
<td>Allocation of Animals</td>
<td>Balanced vs. Unbalanced</td>
</tr>
<tr>
<td>Sacrifice Schedule</td>
<td>Interim vs. Terminal Only</td>
</tr>
</tbody>
</table>

*Adapted from Krewski et al. (1983)*
The analyses of these possibly distinct time points were expected to disagree because of differences in contributions to the likelihood equations used in model parameter estimation. Consequently the estimated VSDs were expected to be slightly different, although comparable. This was indeed true for the two extrapolation performance assessment measures considered. These measures represented, on a logarithmic scale, the relative errors of the VSD and the excess risk at the VSD.

In the first portion of the analysis, comparison was made between the time endpoints under consideration using the product hazard model of Crump et al. (1981). Analysis using unobserved time to tumor tended to give higher estimates of the VSD at the end of the study than if the response of interest was time to death from tumor. These two models produced higher estimates of the VSD than for analyses of an observable time to tumor or time to death with tumor present which did not differ significantly from each other. These comparisons were based upon the sign test applied across all forty-six data sets. Similar results were found with the excess risk measure and at earlier times of 500 and 700 days. Because of the similarity of the results obtained using the two performance criteria, no further comparisons were presented in the paper for these two criteria. Any further differences between the different times to response were not discussed and only analyses using observable times to tumor were presented.

Similar results were obtained from the three product hazard time to response models considered. Each of these models has a low order polynomial for the dose component, but a different functional form for the time component. The time components selected, and the authors with whom they are most commonly associated are a polynomial function (Hartley and
Sielken (1977)), a Weibull function (Crump et al. (1981)), and a non-parametric function (Daffer et al. (1980)). In general, estimates of the VSD from the Weibull and nonparametric time component models were close, and slightly higher than those from the Hartley-Sielken model. All three techniques tended to underpredict the excess risk; however, for each of the models, the risk at the predicted VSD for some data sets exceeded the desired risk by a factor of 100 or more. The point estimates of the VSD from the quantal response models were generally too large. Differences between these quantal response models were consistent with the differences reported in Section 1.3.

Of special interest for this thesis was the comparison of estimates at the end of study based upon the Crump et al. (1981) model and the multistage quantal response model. This comparison attempted to assess the extent to which the use of time to response data represents an improvement over the use of only quantal response data in the low dose extrapolation. In more than eighty percent of the cases, estimated values were within an order of magnitude of each other, regardless of the performance criterion used or whether one compared point estimates or confidence bounds. This suggested that the use of precise information on time to response may not result in estimates of risk in the low dose region that are substantially more precise than those based upon quantal data alone. Whether this phenomenon holds for the other time endpoints of interest was unclear, however.

The analysis summarized in this article is far more elaborate than what has been presented herein. Additional discussion of the results will be provided in the applications chapters of this thesis. It is nonetheless hoped that the review which has been presented has been
faithful to the spirit of the article and that the reader can see the significance of this truly monumental study.

1.6. Outline of Subsequent Chapters

Many possible methods have been proposed to model time to response data. The four strategies which were outlined in Section 1.4 arise from many different perspectives. In some instances, these perspectives reflected purely statistical considerations with little regard to the biology of carcinogenesis. In other instances, the different models of carcinogenesis give form and substance to the time to response model. In no instance can the best approach for modeling experimental dose and time response data be clearly stated. Yet, in many of these strategies, the dose-time response relationship could be represented by models with hazards which factored as functions of dose and time. It is therefore reasonable to further examine modeling strategies which are based upon factorable hazards in order to explain the data and provide useful risk assessments.

In the next chapter various models for time to response data are derived in which the hazard function factors as a function of dose and a function of time. These models do not assume, as have all previously considered product hazard models for risk assessment, that the function of dose is a polynomial. The models proposed include dose factors corresponding to simple pharmacokinetic models and to the quantal response models of Section 1.2. Parametric forms for the time factor are assumed for the estimation procedures derived.
The methods of Chapter 2 are applied in Chapter 3 to the simulated time to response data sets analyzed in Krewski et al. (1983), as well as to data obtained in the Chemical Industry Institute of Toxicology (CIIT) chronic toxicity study of formaldehyde (1982). The dose components used in these applications correspond to the probit, logit, and Weibull quantal response models. The CIIT data are analyzed using both administered and delivered dose measures. The fit of the quantal response model generalizations is assessed using efficient score statistics and a generalization of the logit and probit models, as given by Prentice (1976). Graphical techniques for assessing goodness of fit and the product hazards assumption are also presented. The results of modeling the simulated data sets are compared with those presented by Krewski et al. (1983). Noted in particular are differences in VSDs and parameter estimates due to different dose components, different time endpoints, and the use/non-use of time.

Product hazard models with nonparametric time are considered in Chapter 4. These models are a generalization of the regression model of Cox (1972). Different estimation procedures for the Cox model are discussed in this more general setting, as well as certain time endpoint limitations. Asymptotic properties of the parameter estimates are also derived. The data sets from Krewski et al. (1983) are analyzed in Chapter 5 using this nonparametric time approach. Comparisons similar to those in Chapter 3 are made for differences within these nonparametric analyses, as well as between parametric and nonparametric approaches.

Chapter 6 contains a series of results regarding the properties of the VSD in a quantal response setting and the relationship of these results to the VSD for the more general time to response setting. The
thesis is concluded with an overall summary of results and an indication of future research areas.
CHAPTER II
PRODUCT HAZARD MODELS FOR TIME TO RESPONSE
TOXICITY DATA USING PARAMETRIC TIME

2.1. Introduction

In Chapter 1, four general classes of models for time to response data were summarized. These classes were log-linear models, multi-event models, compartmental models, and Cox regression models. The last three model classes have, either by approximation or exact formulation, a hazard function with a product form. In this chapter, product hazard models for time to response data are examined as a general subclass of survival analysis models.

A product hazard model need not provide an adequate fit to either general survival or bioassay data. For example, Taulbee (1979) reported that a proportional hazards model did not fit the data for comparison of treatment regimens from a large study of coronary artery disease patients. Brown and Hoel (1983) showed that for serially sacrificed animals in the ED01 study of 2-AAF, a product hazard model did not fit the data from all dose groups. This model form did, however, provide an adequate data representation if the group receiving the highest dose was excluded. Thus, before accepting a product hazard form for modeling time to response data; the investigators should determine, if possible, whether such a form is reasonable.
Nonetheless a product hazard model is one of the simplest methods for incorporating covariate information into modeling failure rates. In particular, this model form has a history of usage for describing cancer data. Armitage and Doll (1954) were among the first to use a product hazard model in the analysis of human lung cancer. The models for risk assessment using animal bioassay data given by Hartley and Sielken (1975a, 1975b, 1977), Crump (1978), Daffer et al. (1980), and Crump et al. (1981) are of this form as well.

Following a summary of notation for general survival data, the likelihood for time to response toxicity data is presented for a product hazard model. Techniques are derived in the product hazard setting for incorporating standard quantal response models and non-linear kinetics into time to response models. Justification for these generalizations is also provided.

Four possible time end points for bioassay data are discussed and corresponding contributions to the likelihood of the data are presented. These end points are an observable time to tumor, an unobservable time to tumor, time to death from tumor, and time to death with tumor present. Methods are presented for estimation of model parameters for these response times, when a parametric underlying hazard is specified. Asymptotic distributions for the parameters in these models and their low dose risk estimates are derived. In addition, some possible strategies for assessing goodness of fit are presented.

2.2. Product Hazard Likelihood Construction

In survival analysis, the primary interest is in the study of the lifetime distributions for particular populations. In addition to time,
age, and mortality, other factors may be associated with the failure
rates in the population under study. These factors are termed
covariates. For comparison of different survival distributions, it is
sometimes possible to use measurements of the covariates to account for
the effect of these factors. This is accomplished by incorporating
the covariate information explicitly in the parametric form of the
hazard function.

Let $z' = (z_1, z_2, \ldots, z_s)$ denote a vector of covariates and $\lambda(t; z)$
be the associated hazard function. This nonnegative function of time
and the covariates can, of course, depend upon parameters
$\beta' = (\beta_1, \beta_2, \ldots, \beta_k)$, so that

$$\lambda(t; z) = \lambda(t; z, \beta).$$  \hfill (2.1)

The cumulative hazard function is defined as

$$\Lambda(t; z) = \int_0^t \lambda(u; z) \, du. \hfill (2.2)$$

The survival, distribution, and density functions are then

$$S(t; z) = \exp[- \Lambda(t; z)],$$  \hfill (2.3)

$$F(t; z) = 1 - S(t; z),$$  \hfill (2.4)

and

$$f(t; z) = \lambda(t; z) S(t; z),$$  \hfill (2.5)

respectively.

Let $z_j$ denote the observed covariates for animal $(j)$, with $\lambda(t; z_j)$,
F(t; z_j) and S(t; z_j) representing its hazard, distribution, and survival functions, respectively. Consider a sample of N animals in a study. Let t_j represent the time at which animal (j) was last observed.

Let

\[ \delta_j = \begin{cases} 1 & \text{if (j) experienced event by } t_j \\ 0 & \text{if (j) did not experience event by } t_j \end{cases}, \quad (2.6) \]

and

\[ \varepsilon_j = \begin{cases} 1 & \text{if (j) experienced event at } t_j \\ 0 & \text{if (j) experienced event at or before } t_j \end{cases}, \quad (2.7) \]

then the likelihood of the data is given by

\[ L = \prod_{j=1}^{N} \{ f(t_j; z_j) \delta_j F(t_j; z_j) 1 - \varepsilon_j \} \delta_j S(t_j; z_j) 1 - \delta_j. \quad (2.8) \]

If the hazard function has a product form

\[ \lambda(t; z) = \lambda_0(t) g(z), \quad (2.9) \]

and the covariate vector z is time independent, then

\[ \Lambda(t; z) = \int_0^t \lambda_0(u) g(z) \, du \]

\[ = \Lambda_0(t) g(z), \quad (2.10) \]

and

\[ L = \prod_{j=1}^{N} \left\{ \left\{ \lambda_0(t_j) g(z_j) \right\}^{\delta_j} \right. \]

\[ \left. \{ 1 - \exp[- \Lambda_0(t_j) g(z_j)] \}^{(1 - \varepsilon_j) \delta_j} \right. \]

\[ \left. \{ \exp[- \Lambda_0(t_j) g(z_j)] \}^{(1 - \delta_j + \varepsilon_j) \delta_j} \right\}. \quad (2.12) \]
In a typical animal bioassay, there is usually only one covariate measured, namely the administered dose. Because this dose has a consistent weekly cycle over the course of the bioassay, it can generally be assumed to be time independent. The distribution for time to response data under a product hazard model is thus more often given by

\[ F(t; d) = 1 - \exp[-g(d) \cdot H(t)], \quad (2.13) \]

where \( g(d) \) and \( H(t) \) are nonnegative functions of dose and time respectively.

It is possible to express the above likelihoods in a more efficient manner for an animal bioassay by taking advantage of the structure of the assay. Suppose that the compound of interest is administered to \( D \) dose groups at doses \( d_1, \ldots, d_D \). Letting \( j \) index the animals within the \( i \)-th dose group, each animal has associated with it a dose \( d_i \) and an observation time \( t_{ij} \) that depends upon the response of interest. Let \( n_{ijk} \) denote the number of animals with observation time \( t_{ij} \) of type \( k \), where:

\[
k = \begin{cases} 
1, & \text{if response occurs exactly at } t_{ij}, \\
2, & \text{if response occurs prior to } t_{ij}, \\
3, & \text{if response has not occurred by } t_{ij}.
\end{cases} \quad (2.14)
\]

With this notation, the likelihood of the data (2.8) becomes

\[
L = \prod_{i=1}^{D} \prod_{j|i} f(t_{ij}; d_i)^{n_{ij1}} F(t_{ij}; d_i)^{n_{ij2}} S(t_{ij}; d_i)^{n_{ij3}}, \quad (2.15)
\]

where \( j|i \) denotes the set of animals in the \( i \)-th group.
Using the notation in equation (2.13), the likelihood under the product hazard model (2.10) becomes

\[
L = \prod_{i=1}^{D} \prod_{j|i} \left\{ g(d_i) h(t_{ij}) \right\}^{n_{ij1}} \\
\quad \times \left\{ 1 - \left[ \exp -g(d_i) H(t_{ij}) \right] \right\}^{n_{ij2}} \\
\quad \times \left\{ \exp \left[ -g(d_i) H(t_{ij}) \right] \right\}^{(n_{ij1} + n_{ij3})},
\]

(2.16)

where \( h(t) = \partial H(t) / \partial t \).

2.3. General Forms for the Dose Component in the Product Hazard Model

In the major applications of a product hazard model for risk assessment \( g(d) \) has been chosen to be a polynomial with nonnegative coefficients. This choice is based upon the Armitage-Doll multistage model. Since the product hazard model is very general, the use of polynomials for \( g(d) \) is not necessary and other functional forms can and should be considered. In particular, \( g(d) \) can be chosen to correspond to quantal response models other than the multistage. For example, a dose component given by \( g(d) = k \ d^6 \) corresponds to the Weibull quantal response model. Derivation of the dose component in the product hazard model corresponding to any given quantal response model is provided in section 2.3.2. In addition, \( g(d) \) can be chosen to model the relationship between administered and effective dose in these quantal response generalizations. This application will be considered further in section 2.3.3. A discussion of modeling spontaneously occurring responses for product hazard models is provided in section 2.3.4.
2.3.1. Arguments for General Functional Forms

While polynomials are frequent choices for data modeling, they need not represent the true relationship between variables. Although very complex relationships can be described with polynomials, their use is often a matter of mathematical convenience. If there is reason to believe that a non-polynomial relationship describes particular data as well as or better than a polynomial one, modeling strictly with polynomials cannot be justified. Instead it would be wise to fit several different models, both polynomial and non-polynomial. This is not to say that mathematical modeling with polynomial functions is necessarily incorrect, but rather that curve fitting with other functional forms could be considered.

One possible choice for $g(d)$ in the product hazard model is a functional form which corresponds to a quantal response model other than the multistage model. Since all quantal response models are usually indistinguishable in the observable response range, the generalizations of the different models to include non-fixed time points should provide similar fits to the observed dose-time response surface. As noted in Chapter 1, quantal response models may differ substantially in the tails of their distributions; these differences will also be observed with their product hazard model generalizations. Consequently, the estimates of the excess risk and virtually safe dose obtained with time to response modeling can be expected to disagree in a manner consistent with quantal response modeling differences.

These differences in the VSD are a major reason for the use of other functional forms for the dose component in the modeling of time to
response data. Further, an investigator may prefer to fit quantal response data using a model other than the multistage. When using a product hazard model to fit time to response data, this same investigator might prefer to have a dose component corresponding to a quantal response model other than the multistage. The form for incorporating any quantal response model into the dose component \( g(d) \) is given below.

2.3.2. Quantal Response Model Generalizations

For a fixed time point \( T \), the function \( P(d) \) is used to characterize the observed dose response relationship. As described in Chapter 1, this function \( P(d) \) could arise from either tolerance distribution or mechanistic assumptions. For both of these general quantal response formulations, the same functional form for the dose component in the product hazard model can be derived. This functional form thus provides a natural product hazard time to response model with a dose component corresponding to a quantal response model \( P(d) \).

If \( P(d) \) is a tolerance distribution model, \( P \) is a distribution function and the cumulative hazard for the tolerances provides an equivalent characterization of the dose response relationship. If \( \mu(d) \) represents this cumulative dose hazard at time \( T \), then

\[
\mu(d) = -\log[1-P(d)]
\]  

(2.17)

If at every other time point \( t \), the cumulative hazards for dose are the same with only a scaling due to time differences, then the cumulative dose hazard \( \Lambda(d,t) \), given time \( t \), may be represented by
\[ \Lambda(d,t) = \mu(d) H(t), \quad (2.18) \]

where \( H(t) \) is the time scaling function with \( H(T) = 1 \). Fixing the dose in equation \( (2.18) \), \( \Lambda(d,t) \) can be chosen to represent the cumulative hazard for the time to response distribution. This product hazard form for the time to response implies that the proper choice for \( g(d) \) is \(-\log[1-P(d)]\).

Using the results of Hartley et al. (1981), this form for \( g(d) \) can be derived in a mechanistic model setting, as follows. Suppose the administration of the carcinogen consists of discrete packages which may hit precisely one of the cells in the target tissue. A cell, if attacked by a package, has a probability \( p(d) \) depending upon the dose of reaching an initiation stage. All damage to the cell required to cause initiation occurs at time \( T \), with initiation being reached \( \theta \) constant time units later. As soon as at least one cell reaches the initiation stage, a tumor growth is initiated in the tissue with the tumor apparent \( t \) additional time units later. If the initiation process is completely independent from cell to cell and there are essentially infinitely many cells in the tissue, then the probability of a tissue not having the tumor prior to time \( T \) is given by

\[ 1 - F(T;d) = [1 - p(d)]^{H(T-t-\theta)-H(w(d))}, \quad (2.19) \]

where \( h(t) \) represents the frequency distribution of the number of attacks, \( w(d) \) is a possibly dose dependent latency period, and

\[ H(t) = \int_0^t h(u) \, du. \quad (2.20) \]
Setting
\[ g(d) = -\log[1 - p(d)] \] \hspace{1cm} (2.21)

and
\[ \Psi(d) = H(\omega(d)) \cdot g(d), \] \hspace{1cm} (2.22)

the distribution function \( F(T; d) \) for the time to response is
\[ F(T; d) = 1 - \exp[-g(d) \cdot H(T - t - \Theta) + \Psi(d)] . \] \hspace{1cm} (2.23)

In most settings \( \omega(d) \) and thus \( \Psi(d) \) are equal to zero.

With this formulation of the product hazard model by Hartley et al. (1981), it becomes clearer that the functional relationship which incorporates a mechanistic quantal response model \( P(d) \) is given by
\[ g(d) = -\log[1 - P(d)] . \] \hspace{1cm} (2.24)

Thus, whether a quantal response model is thought of as a tolerance distribution or a mechanistic model, the natural product hazard time to response model corresponding to it is given by
\[ F(t; d) = 1 - \exp\{\log[1 - P(d)] \cdot H(t)\} \]
\[ = 1 - [1 - P(d)] . \] \hspace{1cm} (2.25)

Recall that for a meaningful product hazard survival model, \( g(z) \) is positive for all \( z \). This is satisfied for the above specification of \( g(d) \); since for all positive \( d \), \( 0 < P(d) < 1 \). Hartley and Sielken (1977) make the additional assumption, based upon observed properties of the Armitage-Doll model, that the function \( g(d) \) is convex near the origin; that is,
\[ \frac{\partial^2 g(d)}{\partial d^2} > 0 \]  \hspace{1cm} (2.27)

2.3.3. Incorporation of Pharmacokinetic Models in the Product Hazard Model

Quantal response models, as well as time to response models, should reflect the knowledge available about the biological effects for the compound under study. Taking these effects into account is generally termed the administered/delivered dose problem; that is, the prediction of the amount of the carcinogenically active form of the chemical that appears in specific target tissues as the result of an exposure to the parent chemical. This particular relationship has rarely been quantified experimentally. However, techniques for incorporating hypothetical administered/delivered dose relationships into quantal response modeling have been suggested. These methods are easily extended to time to response models via the methodology of the previous section.

Gehring et al. (1978) proposed a simple pharmacokinetic model for the functional relationship between the exposure concentration of a chemical and the concentration of covalently bound material in the target tissue. This relationship between administered and effective dose was then used for low dose extrapolation for a bioassay of vinyl chloride.

This model, represented in Figure 2.1, assumes that the excretion and detoxification processes are linear and the activation process
FIGURE 2.1 A SIMPLE PHARMACOKINETIC MODEL FOR THE METABOLIC FATE OF SOME CARCINOGENS
follows Michaelis-Menten kinetics. The concentrations of chemical, reactive metabolite, and covalently bound material are governed by a series of differential equations. The steady state solutions to these equations imply that the relationship between effective dose $D_E$ and administered dose $D_A$ is given by

$$D_E = \frac{\alpha D_A}{\beta + D_A}, \quad (2.28)$$

for positive constants $\alpha$ and $\beta$.

Another simple model using this same figure has been given by Krewski et al. (1982). This model assumes that the excretion and activation processes are linear, but the detoxification process follows Michaelis-Menten kinetics. The steady state solutions to the differential equations specifying the model imply that the effective dose is a sublinear function of the administered dose, whereas in equation (2.28), it is a supralinear function of administered dose.

A more complicated model for the possible metabolic fate of a chemical was given by Gehring and Blau (1977). This model extended the simple model above to allow covalent binding to nongenetic macromolecules and included processes for replication and repair of genetically bound material. Unfortunately, the steady state solution of the differential equations describing this model requires the estimation of nine parameters. Anderson et al. (1980) considered properties of these models for low dose risk estimation with vinyl chloride. Hoel et al. (1983) examined the implications of the simple pharmacokinetic model (2.28) on carcinogenic risk estimation. They found that the risk at low doses was greatly overestimated if the relationship between delivered
and administered dose was assumed to be linear, when in fact the true relationship was sublinear.

Any pharmacokinetic model can, at least theoretically, be incorporated into the quantal response procedures very directly. Suppose the relationship between effective and administered dose is given by

\[ d_E = R(d_A) \]  \hspace{1cm} (2.29)

If \( P(d) \) is the assumed effective dose response model, then the resulting administered dose response model is given by \( P(R(d_A)) \).

The excess risk can be easily defined for this new model and if the relationship \( R \) is monotonic, the VSD can be defined as well. The major problem with this approach is the number of parameters needed to describe \( P \) and \( R \). Since the number of dose groups in an animal bioassay is generally small, only the simplest models can be considered. Even as simple a model as (2.28) requires the estimation of at least one additional parameter.

These estimation problems also exist for the corresponding product hazard model generalizations, since the number of parameters needed to describe the dose component of the hazard can not exceed the number of dose groups. Yet, the relationship between administered and delivered dose is now extended with the previously described methodology: Recall that the product hazard time to response model corresponding to a given quantal response model \( P(d) \) has the dose component given by

\[ g(d) = -\log[1 - P(d)] \]  \hspace{1cm} (2.30)

If \( R(d) \) represents the relationship between administered and effective dose and \( P(d) \) describes the effective dose response function, then

\[ g(R(d_A)) = -\log[1 - P(R(d_A))] \]  \hspace{1cm} (2.31)
represents the dose component for the administered dose-time response relationship.

The potential estimation problems described above for the quantal response and time to response models which directly incorporate the relationship between administered and effective dose illustrate a basic difficulty in trying to simultaneously obtain both this relationship and the relationship between effective dose and the response of interest. If the effective dose corresponding to a given administered dose cannot be measured directly, but could be estimated by ancillary experiments, this predicted relationship and its variability could be incorporated, using Bayesian techniques, into the estimation of the dose response parameters. Joint estimation of the parameters in these two different effective dose relationships might also be considered by combining the data from the bioassay and the ancillary experiments.

2.3.4. Incorporation of Background Responses

In the above discussion, no provisions have been made for responses which occur spontaneously. Recall that background responses in the quantal response models could be assumed to occur either independently of those induced as a result of exposure or additively in a mechanistic fashion. This formulation is easily extended for time to response data. Let $T_{I}$ and $T_{A}$ denote the respective induction times for an independently occurring response and an additively occurring response, with the latter being either spontaneous or induced. The time to response $T$ is then equal to the minimum of $T_{I}$ and $T_{A}$. Let $\lambda_I(t)$ and $S_I(t)$ represent the hazard and survival functions, respectively, for an independently
occurring response; and $\lambda_A(t;d)$ and $S_A(t;d)$ denote the same quantities under the additive dose formulation. Then the time to response $T$ has survival and hazard functions given by

$$S(t;d) = \Pr(\min(T_I, T_A) > t;d) \quad (2.32)$$

$$= \Pr(T_I > t;d) \Pr(T_A > t;d) \quad (2.33)$$

$$= S_I(t) S_A(t;d) \quad (2.34)$$

and

$$\lambda(t;d) = -\frac{\partial \log[S(t;d)]}{\partial t} \quad (2.35)$$

$$= -\frac{\partial \log[S_I(t) S_A(t;d)]}{\partial t} \quad (2.36)$$

$$= -\frac{\partial \log[S_I(t)]}{\partial t} - \frac{\partial \log[S_A(t;d)]}{\partial t} \quad (2.37)$$

$$= \lambda_I(t) + \lambda_A(t;d). \quad (2.38)$$

If spontaneously occurring tumors arise in an additive dose-wise fashion, it is reasonable to assume that the time contribution for induced and spontaneous tumors is the same. Thus the time component in the product hazard model should be identical for additive background responses and induced responses. The hazard contribution may then be represented by

$$\lambda_A(t;d + \delta) = g(d + \delta) h(t), \quad (2.39)$$
where $\delta$ is a positive constant and $h(t) = \partial H(t)/\partial t$. The time component $h(t)$ for induced responses may be used for independently occurring responses if the hazard contributions are proportional; that is,

$$\lambda_I(t) = \gamma^* h(t). \tag{2.40}$$

for $\gamma^*$ positive. If independently occurring responses arise from a very different biological process, then it may not be valid to assume that the hazards are proportional. In this case,

$$\lambda_I(t) = h^*(t) \tag{2.41}$$

with $h^*(t) \not\propto h(t)$, and a non-product functional form for the hazard results.

If the time component $h(t)$ is assumed to be the same for both spontaneous and induced responses, then the hazard function is given by

$$\lambda(t; d) = [\gamma^* + g(d + \delta)] h(t). \tag{2.42}$$

Letting $\gamma = 1 - \exp(-\gamma^*)$, it then follows that background behavior can be satisfactorily included by setting

$$\lambda(t; d) = g^*(d) h(t), \tag{2.43}$$

where

$$g^*(d) = -\log[1 - P^*(d)], \tag{2.44}$$
and \( P^*(d) \) is a quantal response model with mixed background components.

2.4. Estimation of Model Parameters

In the formulation of the likelihood under a product hazard model, there is a possible identifiability problem. By using different scalars \( c \), \( \Lambda(t;d) \) can be expressed as a product of a dose function and a time function in infinitely many ways,

\[
\Lambda(t;d) = [c \, g(d)] \, [H(t)/c]. \tag{2.45}
\]

In order to avoid this scaling problem, it is necessary to specify either a dose \( d \) or a time \( t \) at which either \( g(d) \) or \( H(t) \) is fixed. It is assumed for the remainder of the thesis that such a specification has been made.

The parameter vector \( \tilde{\beta} \) may be estimated using maximum likelihood techniques. Let \( \tilde{\beta}' = (\tilde{\Theta}', \tilde{\Psi}') \), where \( \tilde{\Theta}' = (\tilde{\Theta}_1, \ldots, \tilde{\Theta}_r) \) and \( \tilde{\Psi}' = (\tilde{\Psi}_1, \ldots, \tilde{\Psi}_s) \). The cumulative hazard will then be written as

\[
\Lambda(t;d;\tilde{\beta}) = g(d;\tilde{\Theta}) \, H(t;\tilde{\Psi}) \tag{2.46}
\]

Using the notation of Section 2.2, let \( d_i \) denote the \( i \)-th dose level, and \( t_{ij} \) the \( j \)-th observation time in the \( i \)-th dose group. This observation time depends upon the response of interest, and any possible censoring due to early deaths. Thus the response of interest will determine the exact contribution of each animal to the likelihood. Again let \( n_{ijk} \) denote the number of animals with observation time \( t_{ij} \), where
\[
k = \begin{cases} 
1, & \text{if response occurs exactly at } t_{ij}, \\
2, & \text{if response occurs prior to } t_{ij}, \\
3, & \text{if response has not occurred by } t_{ij}
\end{cases}
\] (2.47)

The log-likelihood of the data is then given by

\[
\log(L) = \sum_i \sum_{j|i} \ell_{ij}, 
\] (2.48)

where

\[
\ell_{ij} = n_{ij1} \log\left\{ g(d_i; \theta) h(t_{ij}; \psi) \right\} 
+ n_{ij2} \log\left\{ 1 - \exp\left\{ -g(d_i; \theta) H(t_{ij}; \psi) \right\} \right\} 
- (n_{ij1} + n_{ij3}) g(d_i; \theta) H(t_{ij}; \psi)
\] (2.49)

and \( h(t; \psi) = \partial H(t; \psi)/\partial t. \)

The response of greatest interest is the time to tumor. If this time is unobservable, then \( n_{ij1} \) will be identically zero for all \( i \) and \( j \). If however, the time to tumor is observable, then \( n_{ij2} = 0 \). In the first case, all of the \( t_{ij} \) will be times to unscheduled death or scheduled sacrifice. In the observable time to tumor case, \( t_{ij} \) will be either exact time to tumor or time to death without tumor.

If the response of interest is time to death with tumor present, then the observation times are clearly times to death and \( n_{ij2} \) will be zero for all \( i \) and \( j \). This will also be the case if the tumor can be determined to be the cause of death and the response of interest is time to death from tumor. In this situation, animals which are found to have the tumor at a scheduled sacrifice time do not yet have the response of
interest and are therefore of type \( k = 3 \). The likelihood equations below are derived without assuming that either \( n_{ij1} = 0 \) or \( n_{ij2} = 0 \) for all \( i \) and \( j \).

The partial derivatives of (2.41) with respect to the parameters in \( \Omega \) and \( \Psi \), give the likelihood equations, namely,

\[
\frac{\partial \log(L)}{\partial \theta_k} = \sum_i \sum_j \frac{\partial \ell_{ij}}{\partial \theta_k} = 0 \quad (2.50)
\]

for \( k = 1, \ldots, r \); and

\[
\frac{\partial \log(L)}{\partial \psi_m} = \sum_i \sum_j \frac{\partial \ell_{ij}}{\partial \psi_m} = 0 \quad (2.51)
\]

for \( m = 1, \ldots, s \).

Let

\[
A_{ij} = \frac{n_{ij2}}{1 - \exp[-g(d_i; \theta)H(t_{ij}; \psi)] - (n_{ij1} + n_{ij2} + n_{ij3})} \quad (2.52)
\]

Now

\[
\frac{\partial \ell_{ij}}{\partial \theta_k} = \left[ \frac{n_{ij1} + A_{ij} H(t_{ij}; \psi)}{g(d_i; \theta)} \right] \frac{\partial g(d_i; \theta)}{\partial \theta_k} \quad (2.53)
\]

and

\[
\frac{\partial \ell_{ij}}{\partial \psi_m} = n_{ij1} \frac{\partial \log[H(t_{ij}; \psi)]}{\partial \psi_m} + A_{ij} \frac{g(d_i; \theta)}{g(d_i; \theta)} \frac{\partial H(t_{ij}; \psi)}{\partial \psi_m} \quad (2.54)
\]

In general, there are no explicit solutions to the likelihood equations. Maximum likelihood estimates of \( \theta \) and \( \psi \), denoted \( \hat{\theta} \) and \( \hat{\psi} \),
respectively, must be obtained using some iterative procedure. In the accompanying analyses, the FORTRAN subroutine package MAXLIK developed by Kaplan and Elston (1978) has been used to perform a direct search of the likelihood surface. This is achieved by performing a modified grid search that fits paraboloids to points on the likelihood surface.

An estimate of the variability of \( \hat{\beta}' = (\hat{\Theta}', \hat{\Psi}') \) is available from large sample theory. Since the expected value of the matrix of second partials as a function of the doses \( d_i \) and the times \( t_{ij} \) is intractable, the variance-covariance matrix is approximated by the inverse of the observed Fisher information matrix. The contributions to the second order partial derivatives needed for calculating this matrix are presented below.

Let

\[
B_{ij} = \frac{n_{ij} \exp[-g(d_i; \Theta) H(t_{ij}; \Psi)]}{\{1 - \exp[-g(d_i; \Theta) H(t_{ij}; \Psi)]\}^2}
\]

(2.55)

Then

\[
\frac{\partial^2 g_{ij}}{\partial \Theta_k \partial \Theta_{k'}} = \left[ \frac{n_{ij} + A_{ij} H(t_{ij}; \Psi)}{g(d_i; \Theta)} \right] \frac{\partial^2 g(d_i; \Theta)}{\partial \Theta_k \partial \Theta_{k'}}
\]

\[
- \left[ \frac{n_{ij}}{g^2(d_i; \Theta)} \right] \frac{\partial g(d_i; \Theta)}{\partial \Theta_k} \frac{\partial g(d_i; \Theta)}{\partial \Theta_{k'}}
\]

(2.56)

for \( k = 1, \ldots, r \) and \( k' = 1, \ldots, r \);

\[
\frac{\partial^2 l_{ij}}{\partial \Theta_k \partial \Psi_m} = \left[ A_{ij} - B_{ij} g(d_i; \Theta) H(t_{ij}; \Psi) \right] \frac{\partial g(d_i; \Theta)}{\partial \Theta_k} \frac{\partial H(t_{ij}; \Psi)}{\partial \Psi_m}
\]

(2.57)
for \( k = 1, \ldots, r \) and \( m = 1, \ldots, s \); and
\[
\frac{\delta^2}{\psi_m \psi_{m'}} \sum_{ij1} \frac{h(t_{ij}; \psi) \delta^2 h(t_{ij}; \psi) - \delta h(t_{ij}; \psi) \delta h(t_{ij}; \psi)}{h^2(t_{ij}; \psi)} + A_{ij} g(d; \Theta) \frac{\partial^2 H(t_{ij}; \psi)}{\partial \psi_m \partial \psi_{m'}} \\
- B_{ij} g^2(d; \Theta) \frac{\partial H(t_{ij}; \psi)}{\partial \psi_m} \frac{\partial H(t_{ij}; \psi)}{\partial \psi_{m'}}
\]
for \( m = 1, \ldots, s \) and \( m' = 1, \ldots, s \).

Let
\[
\hat{\Pi}(t; d) = F(t; d; \hat{\Theta}, \hat{\Psi}) - F(t; 0; \hat{\Theta}, \hat{\Psi}).
\]

Then \( \hat{\Pi}(t; d) \) is a consistent estimator of \( \Pi(t; d) \). Let \( \hat{\Sigma} \) denote the estimated variance-covariance matrix for \( \hat{\beta} \),
\[
a' = \left( \frac{\delta \hat{\Pi}(t; d)}{\delta \theta_1} \ldots \frac{\delta \hat{\Pi}(t; d)}{\delta \theta_r} \right) \quad \text{and}
\]
\[
b' = \left( \frac{\delta \hat{\Pi}(t; d)}{\delta \psi_1} \ldots \frac{\delta \hat{\Pi}(t; d)}{\delta \psi_m} \right).
\]

Using a linearized Taylor series approach the estimated large sample variance of \( \hat{\Pi}(t; d) \) for a specified dose and time is given by
\[
\sigma^2[\hat{\Pi}(t; d)] = (a \ b)' \hat{\Sigma}^{-1} (a \ b).
\]

In the product hazard model setting, the excess risk is given by
\[
\Pi(t; d) = \exp[-g(0) H(t)] - \exp[-g(d) H(t)];
\]
so that
\[
\Pi(t; d) \exp[g(0) H(t)] = 1 - \exp[-\{g(d) - g(0)\} H(t)]
\]
Since $g(d)$ is a positive increasing function and $H(t)$ is positive, the right hand side of (2.64) is always less than one. Depending upon the values of $\Pi(t; d)$, $g(0)$, and $H(t)$, the left hand side of (2.64) may be greater than one. Thus is is not always possible to obtain an estimate of the virtually safe dose (VSD) for any time $t$. If the VSD $d^*$ does exist, it satisfies
\[
\pi = \hat{\Pi}(t; d^*)
\]  
(2.65)
for small increases in risk $\pi$ and fixed time $t$. Again using a Taylor series approximation, the estimated large sample variance of $\hat{d}^*$ is
\[
\sigma^2(\hat{d}^*) = \left( \frac{\partial \hat{\Pi}(t; \hat{d}^*)}{\partial d} \right)^2 \frac{\sigma^2[\hat{\Pi}(t; \hat{d}^*)]}{\sigma^2(\hat{d}^*)} \]  
(2.66)

2.5. Goodness of Fit Procedures

As pointed out in Chapter 1, it is difficult to distinguish between the fits of the quantal response models for bioassay data. This is also true for the time to response models considered above. One method of testing sometimes used to distinguish between models may be termed embedding (e.g., Cox and Hinkley (1979)). For this method, a general parametric model family, which contains the desired models as special cases of this family, is selected. Usual asymptotic likelihood procedures are then used to assess the fit within the general model family. This approach will be discussed below for specific quantal response model generalizations. A graphical technique for goodness of fit will also be presented.
2.5.1. A Generalization of the Probit, Logit, and Weibull Models

Prentice (1976) suggested that many of the tolerance distribution models for quantal response data could be embedded in a location-scale family model given by

\[ P(d) = \int_{-\infty}^{\alpha + \beta \log d} f(x) \, dx, \]  

(2.67)

where

\[ f(x) = \frac{\exp(m_1 x)}{[1 + \exp(x)]^{(m_1 + m_2)} \beta(m_1, m_2)}, \]  

(2.68)

with \( m_1 \) and \( m_2 \) are positive and \( \beta(m_1, m_2) \) is the beta function.

The logit, probit, and Weibull models correspond to \( (m_1 = 1, m_2 = 1) \), \( (m_1 \to \infty, m_2 \to \infty) \), and \( (m_1 = 1, m_2 \to \infty) \) respectively. Properties of this model in a more general setting were discussed in Prentice (1975), who gave the reparameterization of the \( (m_1, m_2) \) space needed to avoid degeneracy of the limiting models. Even with these new parameters, the probit and Weibull models lie on the boundary of the parameter space. This boundary problem prohibits the proper use of likelihood ratio statistics. Feder (1968) considered properties of the log likelihood ratio statistic near the boundary, and these results could perhaps be extended to these cases.

With the reparameterized values for \( m_1 \) and \( m_2 \), the derivatives of the likelihood are regular as \( m_1 \to \infty \) and \( m_2 \to \infty \). Thus it is possible to consider efficient score statistics for assessing goodness of fit. This approach was used by Prentice (1976) for assessing the fit of these quantal response models. This same approach may be considered when \( g(d) = -\log[1 - P(d)] \) is used as the dose component in a product hazard
time to response model. This same approach may be used to assess the fit of the time component, either separately or in combination with tests for the dose component form.

Under the product hazard model, it is also possible to assess the fit of the dose component using a discrete dose function with a separate parameter for each dose group. The maximized likelihoods for this discrete model and the continuous model being tested can then be compared, adjusting for the number of parameters being estimated. Whether a formal likelihood ratio test is totally appropriate in this situation is, however, unclear.

2.5.2. Graphical Techniques

Another method for goodness of fit is the use of graphical representations of the data. If all response times are known exactly, i.e., no type \( k=2 \) observations, then graphs of Kaplan-Meier (1958) type estimators of the distribution function provide a visual approach for assessing goodness of fit. Nonparametric techniques for estimating the survival function, and hence the distribution function, are described explicitly in Chapter 4.

When no response time are known exactly, i.e., no type \( k=1 \) observations, it is also possible to estimate the survival function nonparametrically. Details of this approach are provided in Chapter 4. It should be noted that step function estimates in this case are extremely difficult computationally, and the most easily derived estimate of the survival is a piecewise exponential function.
If the exact time of the response of interest is known for some animals, but unknown for others in the same bioassay, piecewise exponential estimates of the distribution function may be obtained by generalizing the techniques of Chapter 4. Details of the derivation are left for future research.

Graphs also can be used to visually assess the appropriateness of the product hazard form. Suppose separate estimates, either parametric or nonparametric, of the cumulative hazard and distribution functions for time to response are available. If the hazard function is of a product form, then, when plotted, these dose-specific time functions should not intersect, and in fact the estimated cumulative hazard functions should be parallel. If these curves do intersect, there may be evidence of nonproportionality in the hazard, and a formal test for dose and time interaction should be considered.
CHAPTER III

ANALYSIS OF TIME TO RESPONSE TOXICITY DATA

USING PRODUCT HAZARD MODELS WITH PARAMETRIC TIME

3.1. Introduction

In this chapter, the methods of the previous chapter are applied to several time to response data sets. The first data set discussed is a toxicity and oncogenicity study of formaldehyde in rodents. These data are modeled with generalizations of the logit, probit, and Weibull quantal response models. Because additional biological information is available for formaldehyde, these data are also modeled using an alternative delivered dose measure.

The simulated data base of Krewski et al. (1983), which was summarized in Section 1.5, contains the remaining data sets. This data base was the basis for comparisons of numerous time to response modeling strategies. The results of these reanalyses using quantal response generalizations in a product hazard model are compared with the original conclusions. These data sets are also analyzed in Chapter 5 using the nonparametric methods to be described in Chapter 4.

Two response times are considered for analyzing these data, namely, the time to death with tumor and an unobservable time to tumor. In both cases, the times recorded are times to death; and any animal which dies without the tumor contributes a survival function value to the likeli-
hood. The difference lies in the contribution of animals found to have the tumor at death. For a time to death with tumor analysis, such an animal contributes a density function value to the likelihood; for an unobservable time to tumor analysis, the tumor is known to have occurred at some point prior to death and the likelihood contribution is a distribution function value.

While other response times, such as the observable time to tumor and the time to death from tumor, may be of greater interest, data of this type are not generally available. For this chapter, the time component selected is of a Weibull form, i.e., $H(t) = t^\lambda$. This choice was made because of the simplicity of the form and the following historical and theoretical reasons.

The Weibull form has been used for the analysis of time to response toxicity data by Hartley and Sielken (1975a) and Crump et al. (1981). For many of the general modeling strategies described in Section 1.4, the Weibull distribution was indicated as adequate for describing the time aspect of time to response data. For example, if the individual event times in a multi-event model have an exponential hazard, then the overall hazard function has a Weibull time form.

The Weibull distribution for times to tumor used in the log-linear model of Chand and Hoel (1974) had been suggested for human cancers by Cook et al. (1969) and Lee and O'Neill (1971). These earlier works showed that the incidence rate of certain tumors could be adequately represented by a product of a function of dose and a Weibull function of time. Day (1967), Peto et al. (1972), and Peto and Lee (1973) have provided further investigation of the Weibull distribution for time to tumor. Pike (1966) showed that certain theories of carcinogenesis would predict the Weibull distribution as the time to tumor distribution.
In all examples in this and later chapters, at most an independent background component is used. This choice was made for several reasons, which should not be viewed as a total rejection of additive background components. First, the inclusion of at most an independent background does not always imply low dose linearity. Second, the estimates of additive background parameters sometimes are so large as to have no practical meaning. Third, programming for models with an independent background is somewhat easier.

3.2. CIIT Formaldehyde Data

In June 1978, the Chemical Industry Institute of Toxicology (CIIT) in Research Triangle Park, N.C. began a long term inhalation study of the effects of formaldehyde on rats and mice. In this study, groups of approximately 120 male and 120 female Fischer-344 rats and C6B3F1 mice were exposed to 0, 2.0, 5.6, and 14.3 parts per million (ppm) of formaldehyde vapor for six hours per day, five days per week, for 24 months. This exposure period was followed by up to six months of non-exposure, with interim sacrifices conducted at 6, 12, 18, 24, 27, and 30 months. This data set represents one of the few chronic toxicity studies with detailed time information.

The major finding of this study was that squamous cell carcinomas were induced in the nasal cavities of 103 rats and 2 male mice exposed to 14.3 ppm, and 2 rats exposed to 5.6 ppm of formaldehyde gas. Also noted was an exposure related increase in the frequency, severity, and distribution of squamous metaplasia of the respiratory epithelium lining the anterior portion of the noses in rats from all exposure groups.
In contrast to the rat, noticeable irritant related effects were found in mice only at the highest exposure level. Swenberg et al. (1980) and Kerns et al. (1983) provide more detailed information for the interim and final results from this important study. Study

In this section, the twenty-four month data for rats exposed to formaldehyde (CIIT, (1982)) are analyzed using the methods of Chapter 2. These data are first analyzed using administered dose, and later using a delivered dose measure. The biological endpoint of interest is the presence of squamous cell carcinoma in the nasal cavity. Animals found to have this cancer in the non-exposure period are assumed to be lost to follow-up at twenty-four months.

3.2.1. Parametric Analyses Using Administered Dose Measures

Figure 3.1 contains the Kaplan-Meier estimates of the time to death with tumor distribution for the formaldehyde data, with a separate estimate computed for each dose group. These curves represent the hypothetical distribution function of times to death with tumor, which would result if no censoring had occurred. These data are analyzed using dose components corresponding to logit, probit, and Weibull quantal response models and Weibull time components. The functional forms for the distribution functions, for the specific product hazard models employed, are the

probit dose component:

\[ F(t; d) = 1 - \left( 1 - \frac{1}{\gamma} \right) \left( 1 - \Phi(\alpha + \beta \log d) \right)^t, \quad (3.1) \]
logit dose component:

\[ F(t;d) = 1 - \left( \frac{1 - \gamma}{1 + e^{\alpha d^\beta}} \right)^t \]  
(3.2)

and Weibull dose component:

\[ F(t;d) = 1 - \left[ (1 - \gamma)(e^{-e^{\alpha d^\beta}}) \right]^t \]  
(3.3)

Maximum likelihood estimates of the model parameters for time to death with tumor and unobservable time to tumor analyses are given in Tables 3.1 and 3.2, respectively. Goodness of fit for these models within the proportional hazards family was assessed using the general model of Prentice (1976). Tables 3.1 and 3.2 also contain the maximized log-likelihood values, goodness of fit score statistics, and associated p values.

Since there were only three groups receiving a positive dose, the Prentice model generalization, which contains four parameters, could not be used in its most general form. To allow testing of both logit and Weibull dose components, the parameter \( m_1 \) in the Prentice model was fixed at one. The resulting quantal response model is then given by

\[ P(d) = \int_{-\infty}^{\alpha + \beta \log d} f(x) \, dx \]  
(3.4)

where

\[ f(x) = \frac{\exp(x)}{m + 1} \left[ 1 + \exp(x) \right] \]  
(3.5)

and is more commonly known as the generalized logit.

Table 3.3 contains the maximum likelihood estimates of the VSD at twenty-four months for a risk of 1/1,000,000. Estimates are provided
<table>
<thead>
<tr>
<th>Parameter Estimates</th>
<th>Dose Components</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Probit</td>
</tr>
<tr>
<td>β</td>
<td>3.049</td>
</tr>
<tr>
<td>τ</td>
<td>7.720</td>
</tr>
<tr>
<td>m</td>
<td>NA\textsuperscript{a}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Maximized Log Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-4.482</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>$\sqrt{\text{Score Stat}}$</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NA</td>
<td>0.999</td>
</tr>
</tbody>
</table>

\textsuperscript{a}NA: Not applicable.

\textsuperscript{b}NC: Not calculated.
Table 3.2

FORMALDEHYDE - UNOBSERVABLE TIME TO TUMOR ANALYSIS
PARAMETER ESTIMATES AND GOODNESS OF FIT STATISTICS

<table>
<thead>
<tr>
<th>Parameter Estimates</th>
<th>Dose Components</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
<td>Logit</td>
<td>Weibull</td>
<td>Generalized-Logit</td>
</tr>
<tr>
<td>β</td>
<td>2.808</td>
<td>5.372</td>
<td>4.792</td>
<td>7.551</td>
</tr>
<tr>
<td>τ</td>
<td>2.040</td>
<td>2.040</td>
<td>2.040</td>
<td>2.040</td>
</tr>
<tr>
<td>m</td>
<td>NA(^a)</td>
<td>1.000</td>
<td>(\infty)</td>
<td>0.254</td>
</tr>
</tbody>
</table>

Maximized Log Likelihood

<table>
<thead>
<tr>
<th></th>
<th>-148.986</th>
<th>-148.994</th>
<th>-149.000</th>
<th>-148.986</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\sqrt{\text{Score Stat}})</td>
<td>NA</td>
<td>-0.001</td>
<td>0.001</td>
<td>NC(^b)</td>
</tr>
<tr>
<td>p value</td>
<td>NA</td>
<td>0.999</td>
<td>0.999</td>
<td>NC</td>
</tr>
</tbody>
</table>

\(^a\)NA: Not applicable.
\(^b\)NC: Not calculated.
<table>
<thead>
<tr>
<th>Time Method</th>
<th>Dose Components</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Probit</td>
<td>Logit</td>
</tr>
<tr>
<td>Quantal Response</td>
<td>2.07</td>
<td>0.86</td>
<td>0.75</td>
</tr>
<tr>
<td>Time to Death with Tumor</td>
<td>2.41</td>
<td>1.03</td>
<td>0.80</td>
</tr>
<tr>
<td>Unobservable Time to Tumor</td>
<td>2.32</td>
<td>0.98</td>
<td>0.80</td>
</tr>
</tbody>
</table>
for quantal response VSD with tumor incidence rates equal to the number of animals with nasal squamous cell carcinoma per animals whose nasal cavity had been examined at the end of exposure. For the quantal response and two time to response analyses, probit dose components provide the largest estimates of the VSD, and Weibull components provide the smallest. Across the three approaches considered for including or excluding time, estimates of the VSD obtained from a time to death with tumor analysis were less than those from an unobservable time to tumor analysis, but larger than those with a quantal response analysis. Nonetheless, the differences in the VSDs across time components were much smaller than the differences across dose components.

Visual assessments of the proportional hazards assumption and goodness of fit of the fitted models are difficult to make for these data, since no responses were reported at the 0 and 2.0 ppm dose groups, and the two responses occurring at 5.6 ppm were at the end of 24 months. Figures 3.2 and 3.3 display the estimated distribution functions from the time to death with tumor and unobservable time to tumor analyses with a logit dose component at each of the administered dose levels. The relative spacing of the curves across doses is basically the same, and is a consequence of the similarity of the estimates of the parameter \( \beta \) between corresponding time to death with tumor and unobservable time to tumor models. The steepness of the curves across time is due to the Weibull time exponent \( \tau \), which was around 2.0 for the unobservable time to tumor analyses but near 7.7 for time to death with tumor analyses. These figures illustrate the difference, which can potentially exist due to these different time to response endpoints. Since the recorded times are exactly the same for these analyses, any differences which exist are due to the likelihood contribution for an animal which had the tumor.
FIGURE 3.2  ESTIMATED TIME TO DEATH WITH TUMOR DISTRIBUTION FOR FORMALDEHYDE FROM LOGIT DOSE - WEIBULL TIME MODEL

FIGURE 3.3  ESTIMATED TIME TO TUMOR DISTRIBUTION FOR FORMALDEHYDE FROM LOGIT DOSE - WEIBULL TIME MODEL
For a time to death with tumor analysis, this contribution is a density function value; whereas for unobservable time to tumor analysis, the contribution is the value of the corresponding distribution function.

3.2.2. Parametric Analyses Using Delivered Dose Measures

Casanova-Schmitz et al. (1984) have obtained data on the concentration of formaldehyde that is covalently bound to the respiratory mucosal DNA of Fischer-344 rats following two six-hour inhalation exposures to gaseous formaldehyde. These data provide a direct measure of the short term delivered dose in target tissue as a function of the ambient-air formaldehyde concentration. These data also demonstrate that the delivered versus administered dose relationship is significantly nonlinear. Specifically, much less covalent binding was observed for administered doses at or below 2.0 ppm than would be predicted by linear extrapolation from the amount of covalent binding observed at concentrations at or above 6.0 ppm.

Starr and Buck (1985) have reanalyzed the incidence of nasal squamous cell carcinoma in the chronic bioassay with probit, logit, Weibull, and multistage quantal response models using short-term estimates of the concentration of covalently bound formaldehyde as the measure of exposure. The resulting estimates of the excess risk and their upper 95% confidence bounds were compared with those obtained using mean ambient air concentration at 0.1, 0.5, and 1.0 ppm exposure. These analyses showed that, depending upon the quantal response model employed, the estimated excess risk and upper confidence bounds were from less than one to eight orders of magnitude greater using administered dose.
In order to make a direct comparison of risk estimates based on delivered and administered doses for ambient air concentrations below 2.0 ppm, a linear relation passing through the origin and the concentration of covalently bound formaldehyde observed at 2 ppm was assumed. This assumption probably overestimates the amount of covalent binding that occurs at these concentrations. Specifically, while Casanova-Schmitz et al. (1984) found no statistically significant amount of binding at an administered dose of 0.3 ppm, the amount predicted, 0.0033 nmole/mg DNA, by this linear relationship was 50% larger than observed.

In this analysis and the time to response analyses below, the Casanova-Schmitz et al. (1984) observations at 2, 6, and 15 ppm were used to obtain estimates of the delivered dose corresponding to the mean exposure levels in the chronic bioassay. The observation at 2 ppm was used directly. Estimated concentrations of covalently bound formaldehyde corresponding to the 5.6 and 14.3 ppm exposure levels were obtained by linear interpolation between zero and the Casanova-Schmitz et al. (1984) observations at 6 and 15 ppm respectively. These estimated delivered dose values are presented in Table 3.4, which is adapted from Starr and Buck (1985). One critical assumption is required in order to set up a one-to-one correspondence between the estimates of covalent binding employed herein and the corresponding mean concentrations of formaldehyde to which animals were exposed during the bioassay. This assumption is that the kinetics of formaldehyde distribution to and disposition within target tissues are essentially steady-state after two six-hour exposures.

The covalent binding data are used for time to response analysis with dose components corresponding to the same three quantal response
<table>
<thead>
<tr>
<th>Airborne Formaldehyde Concentration (ppm)</th>
<th>Concentration of Covalently Bound ([^{14}\text{C}]\text{Formaldehyde}) (nmole/mg DNA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>0.002 + .003\textsuperscript{a}</td>
</tr>
<tr>
<td>2.0</td>
<td>0.022 + .006</td>
</tr>
<tr>
<td>5.6</td>
<td>0.217\textsuperscript{b}</td>
</tr>
<tr>
<td>6.0</td>
<td>0.233 + .023</td>
</tr>
<tr>
<td>10.0</td>
<td>0.406 + .099</td>
</tr>
<tr>
<td>14.3</td>
<td>0.602\textsuperscript{c}</td>
</tr>
<tr>
<td>15.0</td>
<td>0.631 + .064</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Mean + standard error, as determined by Casanova-Schmitz et al. (1984).

\textsuperscript{b}Estimated by linear interpolation between zero and amount of binding measured at 6 ppm.

\textsuperscript{c}Estimated by linear interpolation between zero and amount of binding measured at 15 ppm.
models of the previous section. Again a Weibull form for the time component is considered, and the time to death with tumor and unobservable time to tumor are analyzed. Note that a subtle logical fallacy exists in trying to use the same dose component to describe what are in effect two qualitatively different dose-time response surfaces. If the relationship between administered and delivered dose is nonlinear, then the same model cannot simultaneously provide logically valid descriptions of both surfaces.

Maximum likelihood estimates of risk at the end of 24 months with an unobservable time to tumor analysis for ambient air concentrations of 0.1, 0.5, and 1.0 ppm are summarized in Table 3.5. Corresponding upper 95% confidence bounds for these estimates, obtained using the approximate normality of the estimated model parameters, are presented in Table 3.6. The same risk estimates and bounds for a time to death with tumor analysis are summarized in Tables 3.7 and 3.8.

The probit dose component model consistently provided the lowest risk estimates and upper bounds, regardless of the time endpoint considered. Indeed, except for computations at 1.0 ppm for administered doses, the risk estimates and bounds for this dose component were too small to be differentiated from zero with any real precision. For both time to death with tumor and unobservable time to tumor analyses, risks and bounds obtained with a logit dose component were consistently one or two orders of magnitude smaller than those using a Weibull dose component.

For both time endpoint analyses, every model, and at every concentration in the range of interest for which a non-zero risk could be calculated, the risks and upper bounds based on administered dose were greater than the corresponding values based on delivered dose. This
result is displayed in Tables 3.9 and 3.10, which present the ratios of these quantities. These ratios provide a measure of sensitivity of the risks estimates and upper bounds to the change from administered to delivered dose. For both time analyses, the small reduction in risk estimates and upper bounds occurred at 0.1 ppm concentration in the logit dose component models, with the greatest reduction at 1.0 ppm for the same models. Interestingly, the ratios for the logit and Weibull dose component models increased systematically with increasing ambient air formaldehyde concentration, indicating that these models were relatively more responsive to the change from administered to delivered dose at higher concentrations than they were at lower concentrations.

The one to two order of magnitude difference in risk estimates and upper bounds for the logit and Weibull dose component time to response models is comparable to the differences found by Starr and Buck (1985) for the quantal response model analyses of this same data. In general, the ratios were larger with the time to response analyses; although the time to response estimates of risk and the upper confidence bounds were somewhat smaller than the corresponding quantal response analyses.

The quantal response versus time to response differences could perhaps be due to differences in the data employed in the analyses or the times at which tumors were reported. For the quantal response analyses, animals necropsied at 6, 12, and 18 month sacrifices were excluded; all animals whose nasal cavities were examined at or before the cessation of exposure at 24 months are included in the time to response analyses. Another difference in the analyses concerns the time at which tumors were reported; the two tumors observed in the rats exposed to 5.6 ppm of formaldehyde were found only at the end of twenty-four months, whereas
### TABLE 3.5

**MAXIMUM LIKELIHOOD ESTIMATES OF RISK BASED ON ADMINISTERED DOSE (A) AND DELIVERED DOSE (D) AT SELECTED AMBIENT AIR FORMALDEHYDE CONCENTRATIONS FOR UNOBSERVABLE TIME TO TUMOR ANALYSIS**

<table>
<thead>
<tr>
<th>Concentration, ppm</th>
<th>Dose Measure</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>A</td>
<td>&lt; 1.00(-23)(^a)</td>
<td>4.72(-12)</td>
<td>4.82(-11)</td>
</tr>
<tr>
<td>0.1</td>
<td>D</td>
<td>&lt; 1.00(-23)</td>
<td>1.63(-14)</td>
<td>8.74(-13)</td>
</tr>
<tr>
<td>0.5</td>
<td>A</td>
<td>&lt; 1.00(-23)</td>
<td>2.69(-8)</td>
<td>1.08(-7)</td>
</tr>
<tr>
<td>0.5</td>
<td>D</td>
<td>&lt; 1.00(-23)</td>
<td>7.24(-11)</td>
<td>1.15(-9)</td>
</tr>
<tr>
<td>1.0</td>
<td>A</td>
<td>5.88(-13)</td>
<td>1.11(-6)</td>
<td>2.99(-6)</td>
</tr>
<tr>
<td>1.0</td>
<td>D</td>
<td>&lt; 1.00(-23)</td>
<td>2.70(-9)</td>
<td>2.54(-8)</td>
</tr>
</tbody>
</table>

\(^a\)Values in parentheses are powers of 10.

### TABLE 3.6

**UPPER 95% CONFIDENCE BOUNDS ON RISK BASED ON ADMINISTERED DOSE (A) AND DELIVERED DOSE (D) AT SELECTED AMBIENT AIR FORMALDEHYDE CONCENTRATIONS FOR UNOBSERVABLE TIME TO TUMOR ANALYSIS**

<table>
<thead>
<tr>
<th>Concentration, ppm</th>
<th>Dose Measure</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>A</td>
<td>&lt; 1.00(-23)(^a)</td>
<td>3.45(-11)</td>
<td>3.45(-10)</td>
</tr>
<tr>
<td>0.1</td>
<td>D</td>
<td>&lt; 1.00(-23)</td>
<td>1.38(-13)</td>
<td>7.21(-12)</td>
</tr>
<tr>
<td>0.5</td>
<td>A</td>
<td>&lt; 1.00(-23)</td>
<td>1.41(-7)</td>
<td>5.55(-7)</td>
</tr>
<tr>
<td>0.5</td>
<td>D</td>
<td>&lt; 1.00(-23)</td>
<td>4.72(-10)</td>
<td>7.35(-9)</td>
</tr>
<tr>
<td>1.0</td>
<td>A</td>
<td>6.16(-12)</td>
<td>4.86(-6)</td>
<td>1.28(-5)</td>
</tr>
<tr>
<td>1.0</td>
<td>D</td>
<td>&lt; 1.00(-23)</td>
<td>1.54(-8)</td>
<td>1.42(-7)</td>
</tr>
</tbody>
</table>

\(^a\)Values in parentheses are powers of 10.
### TABLE 3.7

**MAXIMUM LIKELIHOOD ESTIMATES OF RISK BASED ON ADMINISTERED DOSE (A) AND DELIVERED DOSE (D) AT SELECTED AMBIENT AIR FORMALDEHYDE CONCENTRATIONS FOR TIME TO DEATH WITH TUMOR ANALYSIS**

<table>
<thead>
<tr>
<th>Concentration, ppm</th>
<th>Dose Measure</th>
<th>Dose Components</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>A</td>
<td></td>
<td>1.78(-12)</td>
<td>4.62(-11)</td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>D</td>
<td>&lt; 1.00(-23)</td>
<td>5.64(-14)</td>
<td>9.73(-13)</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>A</td>
<td>&lt; 1.00(-23)</td>
<td>1.65(-8)</td>
<td>1.16(-7)</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>D</td>
<td>&lt; 1.00(-23)</td>
<td>1.59(-10)</td>
<td>1.15(-7)</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>A</td>
<td>5.43(-14)</td>
<td>1.65(-7)</td>
<td>3.36(-6)</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>D</td>
<td>&lt; 1.00(-23)</td>
<td>4.88(-9)</td>
<td>2.43(-8)</td>
<td></td>
</tr>
</tbody>
</table>

*aValues in parentheses are powers of 10.

### TABLE 3.8

**UPPER 95% CONFIDENCE BOUNDS ON RISK BASED ON ADMINISTERED DOSE (A) AND DELIVERED DOSE (D) AT SELECTED AMBIENT AIR FORMALDEHYDE CONCENTRATIONS FOR TIME TO DEATH WITH TUMOR ANALYSIS**

<table>
<thead>
<tr>
<th>Concentration, ppm</th>
<th>Dose Measure</th>
<th>Dose Components</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>A</td>
<td>&lt; 1.00(-23)*a</td>
<td>1.31(-11)</td>
<td>3.29(-10)</td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>D</td>
<td>&lt; 1.00(-23)</td>
<td>4.74(-13)</td>
<td>8.03(-12)</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>A</td>
<td>&lt; 1.00(-23)</td>
<td>8.68(-8)</td>
<td>5.94(-7)</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>D</td>
<td>&lt; 1.00(-23)</td>
<td>1.04(-9)</td>
<td>7.36(-9)</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>A</td>
<td>6.05(-13)</td>
<td>3.68(-6)</td>
<td>1.44(-5)</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>D</td>
<td>&lt; 1.00(-23)</td>
<td>2.77(-8)</td>
<td>1.36(-7)</td>
<td></td>
</tr>
</tbody>
</table>

*aValues in parentheses are powers of 10.*
### TABLE 3.9

RATIOS OF RISK ESTIMATES BASED ON ADMINISTERED DOSE TO RISK ESTIMATES BASED ON DELIVERED DOSE AT SELECTED AMBIENT AIR FORMALDEHYDE CONCENTRATIONS FOR UNOBSERVABLE TIME TO TUMOR ANALYSIS

<table>
<thead>
<tr>
<th>Concentration, ppm</th>
<th>Risk Measure</th>
<th>Dose Components</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Probit</td>
</tr>
<tr>
<td>0.1</td>
<td>Upper, 95%</td>
<td>NC</td>
</tr>
<tr>
<td>0.1</td>
<td>MLE</td>
<td>NC</td>
</tr>
<tr>
<td>0.5</td>
<td>Upper 95%</td>
<td>NC</td>
</tr>
<tr>
<td>0.5</td>
<td>MLE</td>
<td>NC</td>
</tr>
<tr>
<td>1.0</td>
<td>Upper 95%</td>
<td>NC</td>
</tr>
<tr>
<td>1.0</td>
<td>MLE</td>
<td>NC</td>
</tr>
</tbody>
</table>

\( ^a \)NC: Not calculated.

\( ^b \)MLE: Maximum likelihood estimates.

### TABLE 3.10

RATIOS OF RISK ESTIMATES BASED ON ADMINISTERED DOSE TO RISK ESTIMATES BASED ON DELIVERED DOSE AT SELECTED AMBIENT AIR FORMALDEHYDE CONCENTRATIONS FOR TIME TO DEATH WITH TUMOR ANALYSIS

<table>
<thead>
<tr>
<th>Concentration, ppm</th>
<th>Risk Measure</th>
<th>Dose Components</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Probit</td>
</tr>
<tr>
<td>0.1</td>
<td>Upper, 95%</td>
<td>NC( ^a )</td>
</tr>
<tr>
<td>0.1</td>
<td>MLE</td>
<td>NC</td>
</tr>
<tr>
<td>0.5</td>
<td>Upper 95%</td>
<td>NC</td>
</tr>
<tr>
<td>0.5</td>
<td>MLE</td>
<td>NC</td>
</tr>
<tr>
<td>1.0</td>
<td>Upper 95%</td>
<td>NC</td>
</tr>
<tr>
<td>1.0</td>
<td>MLE</td>
<td>NC</td>
</tr>
</tbody>
</table>

\( ^a \)NC: Not calculated.

\( ^b \)MLE: Maximum likelihood estimates.
the 14.3 ppm exposure group had tumors reported throughout the period from 11 to 24 months.

3.3. Krewski et al. (1983) Simulated Data Base

The 46 sets of computer generated bioassay data considered by Krewski et al. (1983) in "A Comparison of Statistical Methods for Low Dose Extrapolation Utilizing Time To Tumor Data", are also used as examples of the methodology of the previous chapter. The conclusions drawn from the following reanalyses are then compared with the results given by these authors.

3.3.1. Construction of the Data Base

Recall that these data represented two replicates of each of 23 carefully selected experimental conditions. These conditions, summarized in Chapter 1, provide a preliminary study of a variety of plausible biological effects, including linearity and sublinearity of the dose response relationship in the low dose region and different rates of tumor occurrence with time.

The typical experiment in the study had the following characteristics:

1) length of experiment of 900 days,

2) five equally spaced dose groups with 48 animals per dose,
3) moderate competing risks (50% at 500 days, 90% at 900 days),

4) no minimum tumor induction time,

5) an 8% background tumor rate at 900 days, and

6) an independent background.

Exceptions to the last five conditions, and different time to tumor models led to the various underlying data sets from which the simulation samples were derived.

Before proceeding with the analyses, first consider the design of this simulated data base. The generation of any time to tumor data involves making assumptions about the underlying mathematical model used to describe the carcinogenic process. For these data, the general product, log-linear, and proportional hazards models were used to varying degrees for determining the time to tumor distribution. These models may be linear or sublinear at low doses and can exhibit low, moderate, or high curvature at higher doses. Similar assumptions are also needed to accommodate mortality due to competing risks. The subsequent time to death after tumor development and the time to death from competing risks were both assumed to follow Weibull distributions for these data sets. Whether these specific assumptions are warranted of course depends upon the poorly-quantified biological mechanisms governing tumorigenesis.
3.3.2. Analyses of the Data

Tables A.1 through A.23, found in the Appendix, contain the point estimates for the VSD at 900 days for an increased risk of 1/1,000,000. The same three choices for the dose component, namely, probit, logit, and Weibull, were employed for these analyses. Again two different times to response are considered for each of these models, namely, the time to death with tumor and an unobservable time to tumor. Both time endpoints are analyzed parametrically with a Weibull time function and nonparametrically using the methods to be described in Chapter 4. The true value of the VSD for an observable time to tumor as determined for each of the experiments is presented, as well as the predicted end-of-study quantal response VSD. Attempts to estimate an effective number of animals for use in the quantal response models were generally unsuccessful, since the resulting dose response patterns did not permit estimation of all model parameters. For this reason, quantal response analyses are based upon the total number of animals in the experiments.

Table 3.11 is a duplicate of values contained in Table A.1 of the Appendix for the first replicate of experiment one. Several points can be made about this table and similar comparisons can be made for each of the other tables in the appendix. First, there is substantial agreement in the estimates provided by time to response and quantal response models, although the quantal response VSDs were somewhat smaller. Second, across all five time analyses considered, a probit component provided the largest VSDs while the Weibull dose component provided the smallest. Third, across all three dose components there was substantial agreement between the time to death with tumor and the unobservable time to tumor analyses, for both parametric and nonparametric time components.
TABLE 3.11

ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS
BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 1

TRUE VSD = 1.614(-3)a

Replicate 1

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
<td>Logit</td>
<td>Weibull</td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>3.03(-1)</td>
<td>1.54(-1)</td>
<td>1.44(-1)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>3.42(-1)</td>
<td>1.65(-1)</td>
<td>1.13(-1)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>3.31(-1)</td>
<td>1.62(-1)</td>
<td>1.39(-1)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>3.41(-1)</td>
<td>1.63(-1)</td>
<td>1.20(-1)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>3.45(-1)</td>
<td>1.65(-1)</td>
<td>1.23(-1)</td>
</tr>
</tbody>
</table>

a Values in parentheses are powers of 10.
Fourth, there was also considerable agreement between the use of parametric and nonparametric time components, across dose components and for both time to death with tumor and unobservable time to tumor analyses.

The behavior of each of the dose component models using a Weibull time component models is summarized across all 46 data sets in Figures 3.5 and 3.6 for the time to death with tumor and unobservable time to tumor analyses, respectively. The x axis represents the ratio of the estimated model VSD and the true VSD for an observable time to tumor on a log scale, and the y axis represents the frequency of the data sets observed.

This ratio measure will be used throughout the discussion of this simulated data base to assess the difference between the estimated model VSD and the true VSD obtained from the underlying time to tumor distribution. A value of two for this ratio indicates that the estimated model VSD is 100 times larger than the true VSD; similarly an estimated VSD which is one tenth of the true VSD would have a value of -1 for this ratio.

These logarithmic relative errors in the estimated VSD are on a scale where magnitudes can be compared. Therefore, any significance tests used in this dissertation for differences in distributions of these ratios are based upon the Wilcoxon paired signed-rank statistic. This test for equality of medians was selected rather than the sign test employed by Krewski et al. (1983) in their analyses because it has greater power.

Figures 3.5 and 3.6 demonstrate that for both the time to death with tumor and the unobservable time to tumor analyses, these product hazard models tend to overpredict the VSD regardless of the dose component employed. The Weibull dose component tends to give the least
Figure 3.5 Frequency distribution of the values of 
$\log_{10}[\text{VSDFOMED/VSDFTRUE}]$ from time to death with tumor analyses using probit, logit, and weibull dose and weibull time components ($T=900$ days)
FIGURE 3.6 FREQUENCY DISTRIBUTION OF THE VALUES OF LOG$_{10}$[VSDMODEL/VSDTRUE] FROM UNOBSERVABLE TIME TO TUMOR ANALYSES USING PROBIT, LOGIT, AND WEIBULL DOSE AND WEIBULL TIME COMPONENTS (T=900 DAYS)
amount of overestimation with the greatest amount of overestimation obtained for a probit dose component.

The virtually safe dose estimates are not expected to precisely match the true VSDs for several reasons. First, the time endpoint used in both of these analyses is the time of death. These death times are the farthest from the underlying time to tumor distribution from which the true VSDs were calculated. Second, the true VSD values, used as the standard by Krewski et al. (1983) and in these analyses, are calculated using the underlying time to tumor model only, and as such ignore the known competing risk processes. Now, the probability of observing a tumor in the presence of competing risks is necessarily less than in the absence of competing risks. This follows since to observe a tumor in an animal at time \( t \), it first must have survived the competing risks and have concurrently developed the tumor by time \( t \). Thus the VSDs for actually observing a tumor would be greater than the true VSDs reported. Despite these points, it is highly undesirable to have the large amount of overestimation summarized in these figures.

3.3.3. Comparison Across Time Endpoints

Krewski et al. (1983) looked for systematic differences using the sign test among the four possible response time endpoints with the product hazard model of Crump et al. (1981), which has a polynomial dose component and a Weibull time component. In their analyses, unobservable time to tumor analyses tended to yield higher estimates of VSD than did analyses using time to death from tumor, which in turn yielded higher
estimates than either time to death with tumor or observable time to
tumor analyses. These last two approaches did not differ appreciably.

The reanalyses using other dose component forms agreed only par-
tially with this finding. P values for the equality of medians of the
distributions of log relative error in VSD distributions from the time
to death with tumor and the unobservable time to tumor analyses were
less than 0.05 using a probit dose component, greater than 0.05 for a
logit, and less than 0.01 for a Weibull component. Thus, in contrast
to the Krewski et al. (1983) result, a time to death with tumor analysis
does not always give a consistently greater estimate of the VSD than
does the corresponding unobservable time to tumor analysis.

One possible explanation of this disagreement rests with the form
of the time to tumor distribution used to generate the data. In 18 of the
23 simulated experiments, the underlying time to tumor distribution was
specified by a product hazard form using a polynomial for the dose com-
ponent. Thus the point estimate for the VSD from models with a poly-
nomial dose component might be expected to be closer to the true VSD
than for other dose component models. This point may not be as serious
as one might expect for these reanalyses, since the time endpoints anal-
yzed are farthest from the underlying time to tumor distribution. Yet,
for the Krewski et al. (1983) polynomial dose component analyses, the
point estimates for these same response times did not provide as much
overestimation.
3.3.4. Comparison Among Dose Components

Another interesting point about model differences can be made. For these 46 data sets, the ordering of VSDs which was given for quantal response models in Chapter 1 was also observed; that is, regardless of the response time endpoint analyzed, the estimated VSDs were ordered as follows:

Probit > Logit > Weibull.

This initially surprising result is easily resolved by considering the functional relationship that the VSD must satisfy for a specified time point. Further details of this point are discussed in Chapter 6.

3.3.5. Comparison of Time to Response and Quantal Response Models

Despite the tendency to overestimate the VSD for each of these models, regardless of the response time analyzed, there does not appear to be serious disagreement with the results of the quantal response analyses. Figure 3.7 provides a summary of the behavior of the quantal response VSDs as compared with the true VSDs. These estimates also tend to overpredict the true VSD. For one replicate of two different experiments, the estimated model parameters were such that the corresponding estimate of the VSD was not significantly different from zero. Quantal response models did not provide an adequate fit to the observed dose response relationship for these two data sets, however. Goodness of fit with quantal response models was also a problem for several other data
FIGURE 3.7  FREQUENCY DISTRIBUTION OF THE VALUES OF \( \log_{10}(VSD_{\text{model}}/VSD_{\text{true}}) \) FROM PROBIT, LOGIT, AND WEIBULL QUANTAL RESPONSE MODELS (T=900 DAYS)
sets. Estimated VSDs from some of these data sets tended to be too large, but other poor fitting data sets resulted in underestimation of the true VSD.

The differences between time to response VSDs and quantal response VSDs are given more directly in Figures 3.8 and 3.9 for the two response time endpoints analyzed. These figures represent the ratio of the time to response VSD to the quantal response VSD on a logarithmic scale. This is of course just the difference in the log relative errors

\[ \log_{10}\left( \frac{\hat{VSD}_{\text{Time}}}{VSD_{\text{Quantal}}} \right) = \log_{10}\left( \frac{\hat{VSD}_{\text{Time}}}{VSD_{\text{True}}} \right) - \log_{10}\left( \frac{\hat{VSD}_{\text{Quantal}}}{VSD_{\text{True}}} \right). \] (3.6)

The two problem data sets for which the predicted quantal response VSD was zero accounted for two of the observations in the group in these figures for which this log-ratio value was greater than three. One additional data set was also always in the 3-plus group for all model and all time combinations considered. This particular data set produced quantal response estimates of the VSD which greatly underpredicted the true VSD, and whose time to response VSD overpredicted by a similar order of magnitude.

Krewski et al. (1983) concluded for an observable time to tumor analysis, that no apparent difference exists between time to response and quantal response estimates of the VSD. They found that for a multi-stage dose component model, these estimates were within an order of magnitude for 40 of 46 data sets. Figures 3.8 and 3.9 would lead one to a similar conclusion for three different dose components and two different time to response analyses. The above reanalyses of this data base found that for probit, logit, and Weibull dose components in a time to death with tumor analysis, the estimated VSDs were within an order of magni-
FIGURE 3.8 FREQUENCY DISTRIBUTION OF DIFFERENCES IN VALUES OF $\log_{10}(\frac{\text{VSD}_{\text{MODEL}}}{\text{VSD}_{\text{TRUE}}})$ FROM TIME TO DEATH WITH TUMOR ANALYSES USING WEIBULL TIME COMPONENTS AND QUANTAL RESPONSE MODELS FOR PROBIT, LOGIT, AND WEIBULL DISE COMPONENTS (T=900 DAYS)
FIGURE 3.9 FREQUENCY DISTRIBUTION OF DIFFERENCES IN VALUES OF LOG₁₀[VSDMODEL/VSDTRUE] FROM UNOBSERVABLE TIME TO TUMOR ANALYSES USING WEIBULL TIME COMPONENTS AND QUANTAL RESPONSE MODELS FOR PROBIT, LOGIT, AND WEIBULL DOSE COMPONENTS (T=900 DAYS)
tude for 40, 38, and 38 of the 46 data sets, respectively; the proportions for the unobservable time to tumor analysis were even larger at 42, 41, and 43 of the 46, respectively.

Despite the substantial agreement suggested by the above figures and proportions, formal significance tests that the distributions of log relative errors in quantal response and time to response VSDs are the same, reject at the 0.01 level for probit and logit dose component, but accept at the 0.05 level for a Weibull dose component. These results were the same for both the time to death with tumor and the unobservable time to tumor analyses. Since there were always three data sets for which the difference in log relative errors was greater than 3.0, it is desirable to remove these possible outliers and retest the equality of the distributions. The conclusions are the same, however, except for the Weibull dose component in the unobservable time to tumor analysis, where the p value for no difference in medians is now less than 0.01. Whether these statistically significant differences have any real meaning when one talks in terms of orders of magnitude is questionable.

Further study of those data sets for which these estimates tended to most disagree was next considered. Krewski et al. (1983) found that the least disagreement occurred in cases where mortality was not highly dose dependent. Further examination of the underlying characteristics for these discrepant experiments was generally unrevealing. For the one experiment that was linear at low doses, had low curvature at high doses, and moderate tumor lethality, both replicates tended to have values of the ratio greater than one. Such an experiment would not generally be considered unusual, however.

Further examination of the estimated quantal and time to response VSDs showed that for the time to death with tumor analyses, the time to
response VSDs were closer to the true VSD for probit, logit, and Weibull dose components in 17, 20, and 32 of the 46 data sets, respectively. Corresponding frequencies for the unobservable time to tumor analyses are 13, 19, and 28 of the 46 data sets for these same dose components. Thus in the majority of cases when the dose component used corresponds to either a probit or logit quantal response model, the time to response VSDs are farther from the true VSD than the quantal response VSD. However, for a Weibull dose component, the converse is true, although the time to response and quantal response VSD may not be significantly different.

3.3.6. Variation Between Replicates

The above results suggest that there may be statistically significant differences in the estimates of the VSD obtained from time to response and quantal response analyses. Whether these differences are of any real importance is subject to question, especially in light of the general agreement of the estimates. One final point should be raised about the differences in the experiments.

The frequency distributions discussed in sections 3.3.2 through 3.3.5 include variation due to differences between experimental conditions, as well as variability between replicates generated under identical experimental conditions. Figures 3.10 and 3.11 attempt to isolate the magnitude of the latter error by taking the difference in the value of the log-ratio in replicate one and that in replicate two, for time to death with tumor and unobservable time to tumor analyses, respectively. Although the variation in replicates is generally somewhat
Figure 3.10 Frequency distribution of differences between replicates in values of $\log_{10}(VSD_{MODEL}/VSD_{TRUE})$ from time to death with tumor analyses using probit, logit, and Weibull dose and Weibull time components (T=900 days)
FIGURE 3.11 FREQUENCY DISTRIBUTION OF DIFFERENCES BETWEEN REPLICATES IN VALUES OF $\log_{10}\left(\frac{VSD_{MODEL}}{VSD_{TRUE}}\right)$ FROM UNOBSERVABLE TIME TO TUMOR ANALYSES USING PROBIT, LOGIT, AND WEIBULL DOSE AND WEIBULL TIME COMPONENTS (T=900 DAYS)
less than the total variation depicted in the previous histograms, the
difference was found to be well in excess of three for some experiments.

Thus the question of whether the use of time contributes substan-
tially to quantitative risk estimation does not appear to be settled by
these analyses. The figures above suggest that little difference exists
between time to response and quantal response VSDs, and, for some dose
components, the quantal response VSDs are closer to the true VSD than
the corresponding time to response VSD. Substantial variation among
the replicates of the experiments is present, however, and would tend to
weaken these conclusions. Further discussion of these points is delayed
until the discussion of nonparametric time analyses in Chapter 5 and the
summary in Chapter 7.
CHAPTER IV
PRODUCT HAZARD MODELS FOR TIME TO RESPONSE
TOXICITY DATA USING NONPARAMETRIC TIME

4.1. Introduction

In Chapter 2, the formulation of the likelihood of the data from an animal bioassay with recorded times to response was given. This was of course merely a special case of a more general survival experiment with numerous covariates being measured. As a review of the notation and likelihood construction, let $z_j$ denote the observed covariates for animal $(j)$; with $\lambda(t;z_j)$, $F(t;z_j)$, and $S(t;z_j)$ representing its hazard, distribution, and survival functions, respectively. Consider a sample of $N$ animals in a study. Let $t_j$ represent the time at which animal $(j)$ was last observed. Let

$$\delta_j = \begin{cases} 1 & \text{if (j) experienced event by time } t_j \\ 0 & \text{if (j) did not experience event by } t_j \end{cases}$$

(4.1)

and

$$\varepsilon_j = \begin{cases} 1 & \text{if (j) experienced event at } t_j \\ 0 & \text{if (j) experienced event at or before } t_j \end{cases}$$

(4.2)

then

$$L = \prod_{j=1}^{N} \left\{ f(t_j; z_j) \frac{\varepsilon_j}{F(t_j; z_j)} \right\}^{\delta_j} \left\{ \frac{1-\varepsilon_j}{1-F(t_j; z_j)} \right\}^{1-\delta_j} S(t_j; z_j)^{(1-\delta_j)}.$$  

(4.3)
If the exact time of event is known for all animals, then $\varepsilon_j = 1$ and the likelihood reduces to

$$ L = \prod_{j=1}^{N} f(t_j; z_j) ^ {\delta_j} S(t_j; z_j) ^ {1-\delta_j} $$

$$ = \prod_{j=1}^{N} \lambda(t_j; z_j) ^ {\delta_j} S(t_j; z_j). $$

(4.4)

(4.5)

If the exact time of event is not known for any animal, then $\varepsilon_j = 0$ and the likelihood becomes

$$ L = \prod_{j=1}^{N} F(t_j; z_j) ^ {\delta_j} S(t_j; z_j) ^ {1-\delta_j}. $$

(4.6)

Suppose the hazard function has the following product form:

$$ \lambda(t; z) = \lambda_0(t) g(z; \beta) $$

(4.7)

Maximum likelihood estimation of the parameters in the product hazard model (4.7) is considered in this chapter for the case when the underlying hazard $\lambda_0(t)$ is essentially unspecified. The estimation of $\beta$, in the presence of the nuisance parameter $\lambda_0(t)$, is more complicated than when the time component is specified. When the time of event is not completely known, parameter estimation is more complicated and requires much greater use of iterative calculations. Therefore, the simpler estimation, when the time to event is known exactly, is first considered.

The estimation techniques described in this chapter are derived under the assumption that the censoring times are independent of the times to events. When the censoring may in fact be due to the covariate information, these formulations may not be correct, for example, see Kalbfleisch and Prentice (1980). If censoring is not independent, Kalbfleisch et al. (1983) recommend the use of cause specific hazard functions or other methods for modeling competing risks.
4.2. Estimation Techniques When Exact Times are Known

Numerous approaches have been put forth for the maximum likelihood estimation of parameters $\hat{\beta}$ and $\lambda_0(t)$ for the Cox (1972) proportional hazards model. These techniques are easily modified to handle the more general product hazard model. Three specific methods for the estimation in the general case are described below. When no tied times to event occur, these methods will provide identical results for the parameter vector $\hat{\beta}$.

4.2.1. Approximation Method

Underlying this approach is the desire to simplify the likelihood of the data by expressing $\lambda_0(t)$ using only a few parameters. One particular way is to assume $\lambda_0(t)$ is constant over a number of time intervals. Thus divide the range of $t$ into $M$ fixed consecutive intervals $I_k = (t_{k-1}, t_k]$ for $k = 1, \ldots, M$, and suppose

$$\lambda_0(t) = \lambda_k$$

(4.8)

for $t_{k-1} < t \leq t_k$; then the hazard rate is

$$\lambda(t; z) = \lambda_k g(z; \hat{\beta})$$

(4.9)

for $t_{k-1} < t \leq t_k$. Let $N_k$ denote the set of all animals in the study at any time during $I_k$, $I_{kj}$ denote the part of $I_k$ for which animal $(j)$ was in the study, and $h_{kj}$ be the length of $I_{kj}$. 
For the period of exposed risk in \( I_k \), the cumulative hazard function for animal \((j)\) is

\[
\Lambda(t; z_{\sim j}) = \lambda_k h_{kj} g(z_{\sim j}; \beta).
\]

(4.10)

Let

\[
\delta_{kj} = \begin{cases} 
1 \text{ if } (j) \text{ has event in } I_k \\
0 \text{ otherwise.}
\end{cases}
\]

(4.11)

The overall likelihood function is then

\[
L(\lambda_1, \ldots, \lambda_M; \beta) = \prod_{k=1}^{M} L_k(\beta),
\]

(4.12)

where

\[
L_k(\beta) = \prod_{j \in N_k} \left[ \lambda_k g(z_{\sim j}; \beta) \right] \delta_{kj} \exp[- \lambda_k h_{kj} g(z_{\sim j}; \beta)].
\]

(4.13)

If the values of the parameters \( \beta \) are fixed, then

\[
\hat{\lambda}_k = \frac{\sum_{j \in N_k} \delta_{kj}}{\sum_{j \in N_k} h_{kj} g(z_{\sim j}; \beta)}
\]

(4.14)

is the maximum likelihood estimator of \( \lambda_k \). Substituting (4.14) into (4.13) yields the maximized value of the likelihood, given \( \beta \), as

\[
\hat{L}(\beta) = \prod_{k=1}^{M} \hat{L}_k(\beta)
\]

(4.15)

where

\[
\hat{L}_k(\beta) = \left[ \frac{\sum_{j \in N_k} \delta_{kj}}{\sum_{j \in N_k} h_{kj} g(z_{\sim j}; \beta)} \right] \prod_{j \in N_k^d} g(z_{\sim j}; \beta)
\]

(4.16)
and $N_k^D$ is the set of those animals which have event times in $I_k$.

Because the choice of intervals $I_k$ is somewhat arbitrary, closer approximations to $\lambda_0(t)$ are obtained by using smaller and smaller intervals. If we assume that no two events occur at the same time and if $t(1), \ldots, t(k)$ represent the distinct times of events, then in the limit, the intervals are formed by the $t(i)$ and

$$\hat{\lambda}_i \approx \frac{1}{[t(i) - t(i-1)]} \sum_{j \in R(t(i))} g(z_j; \beta) ,$$  \hspace{1cm} (4.17)

where $t(i)$ is the $i$-th ordered time of event, $z(i)$ is the covariate value observed for the animal with event time $t(i)$, and $R(t(i))$ is the risk set consisting of those animals that have not experienced the event of interest just before $t(i)$. The maximum likelihood estimator of $\beta$ then maximizes

$$\widehat{L}(\beta) \propto \prod_{i=1}^{k} \left( \sum_{j \in R(t(i))} \frac{g(z_j; \beta)}{g(z(i); \beta)} \right) .$$  \hspace{1cm} (4.18)

Adjustments for the presence of ties in the event times are quite straightforward. Let $(i|1), (i|2), \ldots, (i|m_i)$ represent the $m_i$ animals whose observed times to event are at time $t(i)$. Then the limiting values are

$$\hat{\lambda}_i \approx \frac{m_i}{[t(i) - t(i-1)]} \sum_{j \in R(t(i))} g(z_j; \beta) ,$$  \hspace{1cm} (4.19)
and

\[
\hat{L}(\beta) \propto \prod_{i=1}^{m_i} \frac{\prod_{j=1}^{k} g(z_{(i,j)}; \beta)}{\sum_{j \in R(t)} g(z_j; \beta)}^{m_i}.
\]  

(4.20)

This formulation of the likelihood was given by Holford (1976), with the above derivation given by Elandt-Johnson and Johnson (1980). Breslow (1974) derived the same approximated likelihood, using the times between two successive deaths as the intervals rather than the fixed intervals of the above derivation and assuming censored observations occur at the left hand endpoints of the intervals. The details of Breslow's derivation are similar and are not presented. The same result is also obtained if censored observations in the intervals between failures are ignored.

4.2.2. Partial Likelihood Method

The likelihood in equation (4.18) was obtained by Cox (1972) for

\[ g(z; \beta) = \exp(z' \beta) \]

using a conditional probability argument similar to that below. This method is termed "partial likelihood" since it utilizes information only on those who were present in the study just prior to each event of interest, and it does not utilize times of withdrawal between events.

Again let \( t^{(1)} < t^{(2)} < \ldots < t^{(k)} \) be the ordered times to response; assume for now that there are no ties. Let \( A_i \) represent the event that item (i) had the response of interest at time \( t^{(i)} \) and let \( B_i \) be the event that describes the observed process up to time \( t^{(i)} \) including all response and censoring information as well as the information that a response was recorded at \( t^{(i)} \). If \( A_0 \) and \( B_0 \) represent the history of the process to
time \( t = 0 \) and \( B_{k+1} \) the history to time \( t = \infty \), then the time interval \([0, \infty)\) and the event space can be easily broken into intervals as follows:

\[
\begin{array}{cccc}
\text{Time} & 0 & t_{(1)} & t_{(2)} & \ldots & t_{(k)} & \infty \\
\text{Event Information} & A_1 & A_2 & & & A_k & \\
\text{Process Information} & B_1 \setminus B_0 & B_2 \setminus B_1 & & & B_{k+1} \setminus B_k & \\
\end{array}
\]

With this diagram in mind, it is not difficult to see that the full likelihood of the data is given by

\[
L = \prod_{i=1}^{k} \Pr(A_i \mid B_i) \prod_{i=1}^{k+1} \Pr(B_i \mid B_{i-1}, A_{i-1}) .
\]

If \( z(i) \) and \( r(i) \) once again denote the covariate vector and risk set corresponding to \( t(i) \) respectively, then

\[
\Pr(A_i \mid B_i) = \frac{\lambda_0(t(i)) g(z(i); \beta)}{\sum_{j \in R(t(i))} \lambda_0(t(i)) g(z(j); \beta)}
\]

\[
= \frac{g(z(i); \beta)}{\sum_{j \in R(t(i))} g(z(j); \beta)} .
\]

Thus, \( \Pr(A_i \mid B_i) \) is independent of \( \lambda_0(t) \). Cox's partial likelihood (4.24) is obtained by substituting equation (4.23) into the first factor of the full likelihood (4.21).
\[ L(\beta) = \prod_{i=1}^{k} \frac{g(z(i); \beta)}{\sum_{j \in R(t(i))} g(z(j); \beta)} \]  

(4.24)

This is of course the same as equation (4.18) derived using the approximation method in section 4.2.1.

Cox (1975) provided a heuristic argument for the asymptotic normality of the parameter estimates obtained by the partial likelihood approach for \( g(z; \beta) = \exp(z' \beta) \). Tsiatis (1981) and Bailey (1983) gave detailed treatments of the consistency and asymptotic normality of the estimates of beta and of the survival function for Cox's model. Tsiatis's results were derived under random censoring and random sampling of covariates. Bailey's results used fixed arbitrary censoring times and covariates. These two methods do not heavily depend upon the particular form for \( g(z; \beta) \), and thus can be easily extended to the present case.

If ties are present in the data, Cox (1972) suggested the following: let \( (i|1), (i|2), \ldots, (i|m_i) \) represent the \( m_i \) individuals whose observed event times are \( t(i) \) and \( R(t(i), m_i) \) denote the set of all distinct sets of \( m_i \) individuals drawn from \( R(t(i)) \). Then instead of (4.23), the typical contribution to the partial likelihood is now

\[ \Pr(A_i|B_i) = \frac{\prod_{j=1}^{m_i} \frac{g(z(i,j); \beta)}{\sum_{j \in R(t(i), m_i)} \prod_{j \in \ell} g(z(j); \beta)}}{\prod_{j=1}^{m_i} g(z(i,j); \beta)} \]  

(4.25)

This quantity is based upon a formal generalization of the product hazard model to discrete time using a logistic model. Peto (1972) noted
that if time is continuous and ties merely represent tied groupings of data then equation (4.25) is not the correct likelihood contribution. The correct contribution is even more difficult computationally and the denominator involves the evaluation of \( m_i \) factorial orderings of \( m_i \) tied deaths at \( t(i) \). Peto therefore suggested the following rough approximation.

If \( N_i \) is the number of animals in the risk set \( R(t(i)) \), then the average hazard contribution for any animal in the risk set is given by

\[
\frac{\sum_{\ell \in R(t(i))} g(z_{\ell}; \beta)}{N_i} \tag{4.26}
\]

Thus allowing for all possible ways of selecting the \( m_i \) ties from the risk set, Peto's approximation yields:

\[
L(\beta) = \prod_{i=1}^{k} \frac{\prod_{j=1}^{m_i} g(z_{(i|j)}; \beta)}{\left[ \frac{\sum_{\ell \in R(t(i))} g(z_{\ell}; \beta)}{N_i} \right]^{m_i}} \tag{4.27}
\]

\[
\alpha \prod_{i=1}^{\alpha} \frac{\prod_{j=1}^{m_i} g(z_{(i|j)}; \beta)}{\left[ \frac{\sum_{\ell \in R(t(i))} g(z_{\ell}; \beta)}{N_i} \right]^{m_i}} \tag{4.28}
\]

Note that equation (4.28) is equivalent to the multiple events likelihood (4.20) obtained from the approximation method in section 4.2.1.
4.2.3. Marginal Likelihood Approach

Kalbfleisch and Prentice (1973) suggested another conditional probability approach to estimation based upon the ranks of the observed times to event. If the underlying hazard is completely unknown, then the inference about \( \lambda_0(t) \) is unchanged regardless of the magnitude of the order statistics \( t(1), \ldots, t(k) \). Thus the ranks contain all the vital information about \( \beta \) and the marginal distribution of the ranks should be considered.

The marginal likelihood is proportional to the probability that the rank vector \( \tilde{r}(t) \) is that observed, which in the presence of no censoring or tied event times, is

\[
\Pr(\tilde{r}(t)) = \Pr\{ \text{ranks} = (1), \ldots, (k) \} = \int_0^\infty \cdots \int_0^\infty \prod_{i=1}^k f(t(i), z(i)) \, dt(k) \cdots dt(1),
\]

where \( f(t; z) = \lambda_0(t) \, g(z) \exp[- \Lambda_0(t) \, g(z)] \).

This probability is next shown to be equal to the likelihood obtained when using either the approximate or partial likelihood methods above. Set

\[
u_j(t) = \frac{\exp[- \Lambda_0(t) \sum_{i=j}^k g(z_i; \beta)]}{\exp[- \Lambda_0(t) \sum_{i=j}^k g(z_i; \beta)]}
\]

Then

\[
\frac{\partial u_j(t)}{\partial t} = -u_j(t) \lambda_0(t) \sum_{i=j}^k g(z_i; \beta),
\]

(4.32)
\[ u_j(t(j-1)) = 1, \quad (4.33) \]

and
\[ u_j(\infty) = 0. \quad (4.34) \]

Now
\[
\det \left( \frac{\partial u_i(t(i))}{\partial t} \right) = (-1)^k \prod_{i=1}^{k} \left\{ \exp\{-\Lambda_0(t(i))\} \lambda_0(t(i)) \sum_{\ell=i}^{k} g(z_{\ell}; \beta) \right\} \]
\[
= (-1)^k \prod_{i=1}^{k} \left\{ \exp\{-\Lambda_0(t(i))\} g(z_{i}; \beta) \lambda_0(t(i)) \sum_{\ell=i}^{k} g(z_{\ell}; \beta) \right\} \]
\[
= (-1)^k \prod_{i=1}^{k} f(t(i); z(i)) \prod_{i=1}^{k} \frac{\sum_{\ell=i}^{k} g(z_{\ell}; \beta)}{g(z(i); \beta)} \quad (4.37) \]

Therefore, substituting (4.37) into (4.30), it follows by the usual change of variables formulae that
\[
Pr(r(t)) = \prod_{i=1}^{k} \frac{g(z_{i}; \beta)}{\sum_{\ell=i}^{\infty} g(z_{\ell}; \beta)} \int \ldots \int du_k \ldots du_1 \]
\[
= \prod_{i=1}^{k} \frac{g(z_{i}; \beta)}{\sum_{\ell \in R(t(i))} g(z_{\ell}; \beta)} \quad (4.38) \]

which is the same as approximate or partial likelihood result for no ties.

Q.E.D.

The situation to handle ties and censoring for this approach is more complicated and was given for Cox's model by Kalbflesich and Prentice (1980):

\[
L(\beta) = \prod_{i=1}^{m_i} \frac{g(z(i); \beta)}{\sum_{j=1}^{m_i} \Pi_{r \in \mathcal{R}(t(i))} \frac{1}{\Pi_{r \in \mathcal{R}(t(i))}} g(z_{\ell}; \beta)} \quad (4.40) \]
where \( i_1, \ldots, i_{m_i} \) are the individuals who have the response of interest at \( t_{(i)} \), \( Q_i \) is the set of permutations of the symbols \( \{i_1, \ldots, i_{m_i}\} \), \( P = (p_1, \ldots, p_{m_i}) \) is an element of \( Q_i \), and \( R(t_{(i)}; p_r) \) denotes the set difference of \( R(t_{(i)}) \) and \( \{p_1, \ldots, p_{r-1}\} \). This is extremely awkward computationally, even for a single covariate, and if the number of tied event times is not too large, the approximate method is used instead.

4.2.4. Hazard and Survival Function Estimation

Regardless of the technique used to estimate \( \beta \), the most commonly used estimates of the underlying hazard are given by the approximate likelihood method. If estimates of the hazard are available, then a piecewise linear cumulative hazard estimate is obtained by integration. The survival function can then be estimated by exponentiating the negative of this estimated cumulative hazard. For a given dose, this results in a piecewise exponential survival function.

Kalbfleisch and Prentice (1980) derived a different maximum likelihood estimate of the survival function, whose construction parallels that of the Kaplan-Meier estimator. This derivation follows.

Let \( S_0(t) \) be an arbitrary survival function, so that

\[
S(t; z) = S_0(t)^g(z; \beta) .
\]

(4.41)
Let $S(t+0; z)$ represent the survival function at a time point slightly later than time $t$. Then the contribution to the likelihood of the data for an animal with event at $t_{(i)}$ is

$$A_i = S(t_{(i)}; z_{(i)}) - S(t_{(i)} + 0; z_{(i)}) \quad \text{(4.42)}$$

and for an animal observed at $t_{\ell}$ without the event

$$B_{\ell} = S(t_{\ell} + 0; z_{\ell}) \quad \text{(4.43)}$$

Let $D_i$ be the set of animals with event time $t_{(i)}$ and $C_i$ be the animals observed in the interval $[t_{(i)}, t_{(i+1)}]$ who do not have the event. The likelihood function can then be written as

$$L = \prod_{i=0}^{k} \left\{ \prod_{j \in D_i} A_j \prod_{\ell \in C_i} B_{\ell} \right\} \quad \text{(4.44)}$$

This likelihood is maximized by choosing $S_0(t) = S_0(t_{(i)} + 0)$ for $t_{(i)} < t \leq t_{(i+1)}$ to be a step function with steps only at the $t_{(i)}$. Let the hazard function at $t_{(i)}$ corresponding to $S_0$ be $1 - \alpha_{(i)}$. Then using equation 4.41,

$$S_0(t_{(i)}) = \prod_{j=1}^{i-1} \alpha_j \quad \text{(4.45)}$$

and the above likelihood (4.44) is equal to

$$L(\beta, \alpha) = \prod_{i=1}^{k} \left\{ \prod_{j \in D_i} (1 - \alpha_j) \prod_{\ell \in R(t_{(i)}) \setminus D_i} \frac{g(z_{\ell}; \beta)}{g(z_{\ell}; \beta_{(i)})} \right\}, \quad \text{(4.46)}$$

where $R(t_{(i)}) \setminus D_i$ is the risk set excluding those animals in $D_i$. 
After some algebraic manipulation, the likelihood equations imply that the maximum likelihood estimates of $a_i$ satisfy

$$\frac{\sum_{j \in D_i} g(z_j; \hat{\beta})}{\sum_{n \in D_i} 1 - a_i} = \sum_{i \in R(t_{(i)})} g(z_i; \hat{\beta}),$$

where $\hat{\beta}$ is the maximum likelihood estimation of $\beta$ obtained by one of the above methods. It then follows that

$$\hat{S}(t; z) = \prod_{i \mid t_{(i)} \leq t} a_i^\gamma g(z_i; \hat{\beta}).$$

4.2.5. Discrete Time Model Estimation

When the number of tied event times is large, Prentice and Kalbfleisch (1979) noted that the approximate likelihood method yields poor estimates of the parameter vector $\beta$. These authors recommended that a discrete time model be used in this situation. Two different approaches for generalizing the Cox proportional hazards model to include discrete times have been given. The Cox (1972) discrete model was presented in the partial likelihood method section 4.2.2, as a way of handling ties. When the grouping intervals are small, this model yields parameter estimates which are very close to the continuous time estimates. Kalbfleisch and Prentice (1973) showed that, by grouping the times in the continuous model, another discrete model was produced which had the advantage that the same parameter vector $\beta$ was estimated.

The discrete proportional hazards model of Kalbfleisch and Prentice (1973) is obtained by assuming that the event times fall into disjoint
intervals \([t(0) = 0, t(1), t(2), \ldots, t(k), t(k+1) = \infty]\). If the underlying survival is continuous, then letting

\[
\lambda_i = 1 - \exp\left[-\int_{t(i-1)}^{t(i)} \lambda_0(u) \, du\right],
\]

\[(4.49)\]

the hazard contribution in the \(i\)-th interval is given by

\[
\lambda(t, z) = 1 - (1 - \lambda_i)^{\frac{g(z; \beta)}{z}}.
\]

\[(4.50)\]

If \(D_i\) denotes the set of animals that have the response of interest in the \(i\)-th interval, the likelihood of the data is

\[
L(\lambda, \ldots, \lambda_k, \beta) = \prod_{i=1}^{k} \left\{ \prod_{j \in D_i} \left[ 1 - (1 - \lambda_i)^{\frac{g(z_j; \beta)}{z}} \right] \prod_{\xi \in R(t(i)) \setminus D_i} (1 - \lambda_i)^{\frac{g(z_{\xi}; \beta)}{z}} \right\}
\]

\[(4.51)\]

which is the same as \((4.47)\) above with \(\lambda_i = 1 - \alpha_i\).

4.3. Estimation Techniques When Exact Times are Unknown

This situation arises when the exact time to the response of interest is not known. An example is the estimation of the time to tumor distribution when tumors are observable only at the death of the animal. Kodell et al. (1982), Dinse (1982), Lagakos (1982), Dinse and Lagakos (1982), and Turnbull and Mitchell (1984) have all considered the case when it is possible to determine the cause of death of the animal. Kodell et al. (1982) provide joint nonparametric estimators for disease resistance and survival functions. Turnbull and Mitchell (1984) obtained the nonparametric maximum likelihood estimates for the time to tumor and
time to death due to tumor distributions. Using the same model as Turnbull and Mitchell, Dinse and Lagakos (1982) provided a simple approximation to these same quantities. Lagakos (1982) discussed some difficulties involved in estimating the time to tumor distribution, when the cause of death is not or can not be determined.

In this section, an approximate likelihood method for estimating the time to tumor distribution, when the tumor is unobservable and the cause of death may not be known, is considered. This approach is similar to that given in section 4.2.1 for observable times to event. Again divide the range of $t$ into $M$ fixed consecutive intervals $I_k = (t_{k-1}, t_k]$ for $k = 1, \ldots, M$, and suppose

$$\lambda_0(t) = \lambda_k$$  \hspace{1cm} (4.52)

for $t_{k-1} < t \leq t_k$; so that the hazard rate is

$$\lambda(t; z) = \lambda_k g(z; \beta)$$  \hspace{1cm} (4.53)

for $t_{k-1} < t \leq t_k$. Let $N_k$ denote the set of all animals in the study at any time during $I_k$, $I_{kj}$ denote the part of $I_k$ for which animal $(j)$ was in the study, and $h_{kj}$ be the length of $I_{kj}$.

For the period of exposed risk in $I_k$, the cumulative hazard function for animal $(j)$ is

$$\Lambda(t; z_j) = \Lambda_k h_{kj} g(z_j; \beta).$$  \hspace{1cm} (4.54)

Let

$$\delta_{kj} = \begin{cases} 
1 & \text{if response for (j) is reported in } I_k \\
0 & \text{otherwise.}
\end{cases}$$  \hspace{1cm} (4.55)
The overall likelihood function is then

$$L(\lambda_1, \ldots, \lambda_M; \beta) = \prod_{k=1}^{M} L_k(\beta)$$

(4.56)

where

$$L_k(\beta) = \prod_{j \in N_k} \left[ \frac{\exp[-\lambda_k h_{kj} g(z_j; \beta)]}{\exp[-\lambda_k h_{kj} g(z_j; \beta)]} \delta_{kj} \right] \text{ for } \beta = \hat{\beta}$$

(4.57)

If the values of the parameters $\beta$ are fixed, then the maximum likelihood estimator of $\lambda_k$ satisfies the equation,

$$\sum_{j \in N_k} \frac{\delta_{kj} h_{kj} g(z_j; \beta)}{1 - \exp[-\lambda_k h_{kj} g(z_j; \beta)]} = \sum_{j \in N_k} \theta_{kj} g(z_j; \beta)$$

(4.58)

which is obtained by equating the derivative of equation (4.57) to zero.

In general, equation (4.58), which depends only on the interval $I_k$, will not have an explicit solution. Consequently the underlying parameters $\lambda_k$ can not always be eliminated from the overall estimation process. If no animals have the same observation time for the response of interest, i.e., no ties, it is possible to provide the following solution. Let

$$
\psi_{km} = h_{km} g(z_m; \beta)
$$

(4.59)

and

$$A_k = \sum_{j \in N_k} h_{kj} g(z_j; \beta)$$

(4.60)

If the intervals $I_k$ can be chosen so that

$$\delta_{kj} = \begin{cases} 
1 & \text{for } j = m \\
0 & \text{for all other } j \in I_k 
\end{cases}$$

(4.61)
then

\[ \hat{\lambda}_k = -\log[1 - \psi_{km}/A_k]/\psi_{km} \]  \hspace{1cm} (4.62)

and

\[ \psi_{km} \log[\Lambda_k(\beta)] = \psi_{km} \log[\psi_{km}] + (A_k - \psi_{km}) \log[A_k - \psi_{km}] \]
\[ - A_k \log[A_k] . \]  \hspace{1cm} (4.63)

Thus by appropriate choice of the intervals \( I_k \), it is possible to eliminate certain of the underlying parameters from the model.

If there are times at which events are reported for more than one animal, the situation is again complicated. An approximation which is good either as an initial estimate or final estimate of \( \lambda_k \) is to replace the contribution of each animal by an average contribution of those with the same reported time to response. Specifically, suppose animals \( (k11), (k12), \cdots, (km_k) \) are reported to have responded in the interval \( I_k \) and

\[ B_k = \sum_{j=1}^{m_k} h_{kj} \log(z_{km_k}; \beta) . \]  \hspace{1cm} (4.64)

Then

\[ \hat{\lambda}_k = -m_k \log[1 - B_k/m_k]/B_k \]  \hspace{1cm} (4.65)

This approximation is exact in the event when the covariate information is identical for the \( m_k \) animals.

The most information about \( \lambda_k \) is obtained with intervals as small as possible. If no events of interest are reported in a specific interval \( (t_{k-1}, t_k) \), then \( \hat{\lambda}_k = 0 \) and the interval contributes nothing to the log-likelihood. Therefore, appropriate choices for the times
\( t_k \) are the times at which a response of interest, such as death with tumor, is reported.

The estimation of the parameter vector \( \hat{\beta} \) above also yields an estimate of the underlying hazard. This hazard estimate can then be used to construct a piecewise exponential estimate of the survival function. Unlike the situation when the exact times of response are known, a maximum likelihood estimate of the underlying survival function similar to the Kaplan-Meier estimate is not easily derivable, as the following example shows:

Let \( t_1 < t_2 < t_3 < t_4 \) denote the observation times for four animals, such that only 1 and 4 have the response of interest by times \( t_1 \) and \( t_4 \). Let \( g_1, \ldots, g_4 \) represent the estimated value of the function \( g(z; \hat{\beta}) \) for each of these animals. If \( S_i \) is the underlying survival function at \( t_i \), then the likelihood of these data is given by

\[
L = (1-S_1)^{g_1} S_2^{g_2} S_3^{g_3} (1-S_4)^{g_4}
\]

where \( S_1 > S_2 > S_3 > S_4 \). It is not difficult to see that \( \hat{S}_4 = 0 \) since the last term is then the maximum value of 1. Explicit solutions for the remaining \( \hat{S}_i \) are not always obtainable, but depend upon the values of \( g_1, g_2, \) and \( g_3 \). In particular \( \hat{S}_2 \) and \( \hat{S}_3 \) may not be equal, as would be the case for the Kaplan-Meier type estimator.

This example is not unrepresentative of the survival function estimation difficulties when response times are not known exactly. In order to obtain an estimator of this type, it would be necessary to estimate a parameter for each time point in the study. Thus this particular approach for estimating the underlying survival is computationally unrealistic.
4.4. Likelihood Construction For Bioassay Data

When only one discrete covariate is measured, as is the case for the usual animal bioassay, the more general likelihood equations of the previous sections can be simplified. Reduced forms for the approximation methods of sections 4.2.1 and 4.3 are next presented. These simplifications are primarily given as aids to anyone calculating the likelihood value and its derivatives, and are not intended to be a thorough treatment of these parameter estimation methods.

4.4.1. Approximation Method With Exact Response Times Known

Let \( d_1, \ldots, d_D \) represent the \( D \) dose groups and \( t_{(1)}, \ldots, t_{(T)} \) be the times at which a response was observed. Let

\[ m_j = \text{number of animals with } d=d_j \text{ responding}, \]

\[ r_i = \text{number of animals responding at } t=t_{(i)}, \]

and

\[ p_{ij} = \text{number of animals with } d=d_j \text{ in the risk set at } t=t_{(i)}. \]

Let \( \beta' = (\beta_1, \ldots, \beta_s) \); \( g_j = g(d_j; \beta) \); and for \( k, k' = 1, \ldots, s \), let

\[ (g_j)_k = \frac{\partial g(d_j; \beta)}{\partial \beta_k} \quad (4.67) \]

and

\[ (g_j)_{kk'} = \frac{\partial^2 g(d_j; \beta)}{\partial \beta_k \partial \beta_{k'}} \quad (4.68) \]
With this notation, the log-likelihood of the data, \( \mathcal{L} \), is given by:

\[
\mathcal{L} = \mathcal{L}_1 - \mathcal{L}_2;
\]

where

\[
\mathcal{L}_1 = \sum_{j=1}^{D} m_j \log[g_j],
\]

and

\[
\mathcal{L}_2 = \sum_{i=1}^{T} r_i \log\left[ \sum_{j=1}^{D} p_{ij} g_j \right].
\]

The likelihood equations are then given by:

\[
\frac{\partial \mathcal{L}}{\partial \beta_k} = \frac{\partial \mathcal{L}_1}{\partial \beta_k} - \frac{\partial \mathcal{L}_2}{\partial \beta_k} = 0
\]

where

\[
\frac{\partial \mathcal{L}_1}{\partial \beta_k} = \sum_{j=1}^{D} m_j \frac{(g_j)_k}{g_j}
\]

and

\[
\frac{\partial \mathcal{L}_2}{\partial \beta_k} = \sum_{i=1}^{T} r_i \frac{\sum_{j=1}^{D} p_{ij} (g_j)_k}{\sum_{j=1}^{D} p_{ij} g_j}
\]

for \( k = 1, \ldots, s \).

Even for this single covariate case, explicit solutions of the likelihood equations are not generally obtainable. However the asymptotic normality of the maximum likelihood estimator \( \beta \) can be established using the results of Tsiatis (1981) or Bailey (1983). Since the expectations of the matrix of second partials are not easily computed, the inverse of the observed matrix of negative second partials can be used to approximate the variance-covariance matrix for \( \beta \).
With the same notation as above,

\[ \frac{\partial^2 \ell}{\partial \beta_k \partial \beta_{k'}} = \frac{\partial^2 \ell_1}{\partial \beta_k \partial \beta_{k'}} - \frac{\partial^2 \ell_2}{\partial \beta_k \partial \beta_{k'}} \]

(4.75)

with

\[ \frac{\partial^2 \ell_1}{\partial \beta_k \partial \beta_{k'}} = D \sum_{j=1}^{\Sigma} m_j \frac{g_{j} (g_{j})_{kk'} - (g_{j})_{k} (g_{j})_{k'}}{g_j^2} \]

(4.76)

and

\[ \frac{\partial^2 \ell_2}{\partial \beta_k \partial \beta_{k'}} = \sum_{i=1}^{T} \left( D \sum_{j=1}^{\Sigma} p_{ij} (g_j)_{k} - D \right) \sum_{j=1}^{\Sigma} p_{ij} (g_j)_{k'} \]

(4.77)

where

\[ A_{ikk'} = D \sum_{j=1}^{\Sigma} p_{ij} g_j \sum_{j=1}^{\Sigma} p_{ij} (g_j)_{kk'} \]

\[ - D \sum_{j=1}^{\Sigma} p_{ij} (g_j)_{k} \sum_{j=1}^{\Sigma} p_{ij} (g_j)_{k'} \]

(4.78)

for \( k, k' = 1, \ldots, s \).

If \( g(d; \beta) = -\log[1 - P(d; \beta)] \) is the dose component in the model corresponding to a quantal response model \( P(d; \beta) \), then

\[ \frac{\partial g(d; \beta)}{\partial \beta_k} = \frac{\partial P(d; \beta)}{\partial \beta_k} \frac{\partial P(d; \beta)}{1 - P(d; \beta)} \]

(4.79)

and

\[ \frac{\partial^2 g(d; \beta)}{\partial \beta_k \partial \beta_{k'}} = \frac{\partial^2 P(d; \beta)}{\partial \beta_k \partial \beta_{k'}} + \frac{\partial P(d; \beta)}{\partial \beta_k} \frac{\partial P(d; \beta)}{\partial \beta_{k'}} \frac{1}{[1 - P(d; \beta)]^2} \]

(4.80)

for \( k, k' = 1, \ldots, s \).
4.4.2. Approximation Method With Exact Response Times Unknown

Again let \(d_1, \ldots, d_D\) represent the \(D\) dose levels, and \(t(1), \ldots, t(T)\) be the times at which the response of interest was recorded. The true responses are assumed to have occurred at times prior to the \(t(i)\). Let

\[ g_j = g(d_j; \beta), \]

\[ n_{ij} = \text{number of animals with dose } d = d_j \text{ reported with response in } \text{i-th interval}, \]

\[ m_{ij} = \text{total time contribution to } i\text{-th interval from animals with } d = d_j \text{ reported with response}, \]

\[ r_{ij} = \text{total contribution to } i\text{-th interval from animals with } d = d_j, \]

and

\[ \hat{\lambda}_i = \text{estimate of hazard function for } i\text{-th interval.} \]

Then, if \(\ell = \log(L)\) is the log-likelihood,

\[ \ell = \sum_{i=0}^{T} \sum_{j=1}^{D} \left\{ n_{ij} \log[\exp(\hat{\lambda}_i m_{ij} g_j/n_{ij}) - 1] - \hat{\lambda}_i r_{ij} g_j \right\}. \tag{4.81} \]

Let

\[ A_{ij} = \frac{m_{ij}}{1 - \exp(-\hat{\lambda}_i m_{ij} g_j/n_{ij})} - r_{ij} \tag{4.82} \]

and

\[ B_{ij} = \frac{m_{ij}^2 \hat{\lambda}_i \exp(-\hat{\lambda}_i m_{ij} g_j/n_{ij})}{n_{ij} [1 - \exp(-\hat{\lambda}_i m_{ij} g_j/n_{ij})]^2}, \tag{4.83} \]
then

\[ \frac{\partial \xi}{\partial \beta_k} = \sum_{i=0}^{T} \lambda_i \left[ \sum_{j=1}^{D} A_{ij} \frac{\partial g_j}{\partial \beta_k} \right] \]

and

\[ \frac{\partial^2 \xi}{\partial \beta_k \partial \beta_{k'}} = \sum_{i=0}^{T} \lambda_i \left[ \sum_{j=1}^{D} A_{ij} \frac{\partial^2 g_i}{\partial \beta_k \partial \beta_{k'}} \right] - B_{ij} \frac{\partial g_i}{\partial \beta_k} \frac{\partial g_i}{\partial \beta_{k'}} \]

for \( k, k' = 1, \ldots, s \).
CHAPTER V

ANALYSIS OF TIME TO RESPONSE TOXICITY DATA
USING PRODUCT HAZARD MODELS WITH NONPARAMETRIC TIME

5.1. Introduction

The Krewski et al. (1983) simulated data base was analyzed in Chapter 3 using a product hazard model with a variety of dose components and a Weibull parametric time component. In this chapter, these same data sets are further analyzed using the methods of Chapter 4 with a nonparametric time component. Dose components for the product hazard model corresponding to the probit, logit, and Weibull quantal response models are again employed, and both time to death with tumor and unobservable time to tumor analyses are considered. As was the case in Chapter 3, the log relative error in virtually safe dose, log10(VSDModel/VSDTrue), is used in this chapter for comparing the estimated VSD with the true observable time to tumor VSD.

When the exact times of the response of interest are known, as is the case for a time to death with tumor analysis, the estimation techniques of Section 4.2 are applicable. For the analyses presented here, the approximation method is used to estimate the model parameters and two different methods are used for estimating the underlying survival function. When the exact times of the response of interest are unknown, as is the case for an unobservable time to tumor analysis, the estima-
tion technique of Section 4.3 is applicable. For this time analysis, only one method of estimating the underlying survival function is employed.

5.2. Differences Due to Survival Function Estimators

For the approximation methods, the underlying hazard function is taken to be piecewise constant, and thus the estimated cumulative hazard is piecewise linear. A natural estimator of the underlying survival function is the exponential of the negative of this cumulative hazard. Another technique, which leads to a step function estimate of the underlying survival function similar to the Kaplan-Meier estimate, has been proposed by Kalbfleisch and Prentice (1973). When the response times are known exactly, this approach is very easy to use. When the response times are not known, a step function estimator of survival is computationally infeasible, since a separate parameter is required for each time at which a death occurs.

While these methods produce similar estimates of the underlying survival, they are definitely different in appearance and there are probably systematic differences in the estimates of the virtually safe doses obtained from the two methods. The piecewise exponential form may be more meaningful for risk estimation, however, since it does not assume that changes in the time to response occur only at discrete time points. These differences and similarities are next examined in greater detail.

Since a step function estimator of the underlying survival function
is computationally intractable for an unobservable time to tumor analysis, the primary evidence for differences in the two methods of estimating the survival function is obtained for a time to death with tumor analysis. Estimates of the cumulative hazard and underlying survival function for the first replicate of the first experiment are given in Figures 5.1 and 5.2 for a Weibull dose component model. The patterns observed for this data set are fairly representative of those noticed for many other data sets as well, although the pattern was reversed for other data sets. Thus it does not appear that the use of any particular method of estimation will always over- or underpredict the underlying survival.

With respect to VSD estimates, there was substantial disagreement for all three dose components considered. For the probit dose component models, the estimated VSD was always larger with a step function estimate of survival than with a piecewise exponential estimate. For the logit dose component models, exactly the reverse was true. For Weibull dose component models, larger VSDs were obtained for 32 of 46 data sets using a step function estimator. As would be expected, the Wilcoxon paired signed-rank tests for equality of the medians of the distributions of log-relative errors in VSD rejected equality at the 0.01 level for all three dose components.

5.3. Comparison of Parametric and Nonparametric Time Components

Tables A.1 through A.23 in the Appendix were discussed in Chapter 3 with a Weibull function for the time component. In this chapter, a discussion of the remaining rows of these tables, corresponding to nonpara-
FIGURE 5.1  ESTIMATED CUMULATIVE HAZARD FUNCTION FOR TIME TO DEATH WITH TUMOR USING WEIBULL DOSE AND TIME COMPONENTS FOR REPLICATE 1 OF EXPERIMENT 1

FIGURE 5.2  ESTIMATED SURVIVAL FUNCTIONS FOR TIME TO DEATH WITH TUMOR USING WEIBULL DOSE AND TIME COMPONENTS FOR REPLICATE 1 OF EXPERIMENT 1
metric time analyses, is provided. For the time to death with tumor analyses, estimates of the VSD presented use the step function estimate of the underlying survival. For the unobservable time to tumor analyses, estimates employing the piecewise exponential form of the survival are displayed.

Figures 5.3 and 5.4 provide a summary of the behavior of these nonparametric estimates for the time to death with tumor and the unobservable time to tumor analyses, respectively. Examination of these Figures, Figures 3.5 and 3.6 in Chapter 3, and Tables A.1 to A.23 reveal few instances where the parametric and nonparametric analyses differed by more than one order of magnitude. This result is true for other time points and risk levels as well. For the time to death with tumor, p values for equality of the distribution of the log-ratios were greater than 0.05 for all three dose components considered. Thus, the null hypothesis that the medians of the distributions of the log-relative errors in VSD are different for parametric and nonparametric time analyses cannot be rejected. For the unobservable time to tumor analyses, p values for this test were less than 0.05 for both the probit and Weibull dose components models. Thus, there is an apparent difference in the distributions of the log-ratio values for the probit and Weibull dose component models. This difference is probably due to the general decrease in estimated VSD from using parametric to using nonparametric time components for this time to response analysis. Specifically, for 30 and 32 of the 46 data sets corresponding to the probit and Weibull dose components, respectively, the parametric time VSD was greater than the nonparametric time VSD. For the logit dose component, only 20 of 46 data sets had a larger parametric time estimate; hence, the formal sig-
FIGURE 5.3 FREQUENCY DISTRIBUTION OF THE VALUES OF \[ \log_{10}(\text{VSD}_{\text{MODEL}}/\text{VSD}_{\text{TRUE}}) \] FROM TIME TO DEATH WITH TUMOR ANALYSES USING PROBIT, LOGIT, AND WEIBULL DOSE AND NONPARAMETRIC TIME COMPONENTS (T=900 DAYS)
Figure 5.4: Frequency distribution of the values of $\log_{10}\left[\frac{VSD_{MODEL}}{VSD_{TRUE}}\right]$ from unobservable time to tumor analyses using probit, logit, and weibull dose and nonparametric time components (T=900 days)
nificance test for shift might not be expected to reject equality of the distributions.

Estimates of the model parameters for the two analyses are also quite comparable, as should be expected. Because it is necessary to specify either a dose or a time at which the dose or time component in the hazard is fixed, some scaling adjustment is needed to make these comparisons. The correspondence in parameter values can be made as follows. For the parametric time analyses, the time component in the hazard at 900 days, H(900), was set equal to one. Because the underlying hazard is eliminated from the nonparametric analyses, the option of specifying a time at which H(t) is fixed is not available. Thus, for these analyses the dose component g(d) was set to one for a dose value of 1.0.

Let \( g_P(d) \) and \( H_P(t) \) represent the dose and time components in the cumulative hazard for a parametric time model, and \( g_N(d) \) and \( H_N(t) \) denote the same for a nonparametric model. Suppose the cumulative hazards are the same; that is

\[
 g_P(d) H_P(t) = g_N(d) H_N(t). \tag{5.1}
\]

Since \( H_N(900) \) and \( g_N(1) \) both equal to one,

\[
 g_P(d) = g_N(d) H_N(900). \tag{5.2}
\]

and

\[
 H_P(t) = g_P(1) H_P(t). \tag{5.3}
\]

The last two equations can then be used to equate corresponding dose and time parameters. For example, suppose a Weibull dose component is used for the parametric and nonparametric time to response models; then
\[ g(d) = \gamma + \exp \left[ \alpha + \beta \log(d) \right] \]  
\[ g_N(d) = 1 - \exp(\alpha_N) + \exp \left[ \alpha_N + \beta_N \log(d) \right]. \]

Thus,
\[ \gamma = \log(900) \left[ \exp(\alpha_N) - 1 \right], \]
\[ \alpha_N = \alpha + \log[\log(900)], \]
and
\[ \beta_N = \beta. \]

Similar relationships are available for the estimated variance-covariance matrices and for other dose components. These approximations provide an excellent method of checking parameter estimates and for obtaining initial estimates for maximization programs as well.

5.4. Comparison of Dose Components and Time Endpoints

As with the parametric analyses, the product hazard models employed tended to overpredict the VSD irrespective of the dose component considered. The Weibull and probit dose components again tend to provide the least and greatest amount of overestimation, respectively. The relative ordering of the estimates themselves agrees with that found for quantal response and the parametric time analyses, namely that estimates from the probit dose component models are larger than logit estimates which are in turn larger than the Weibull.

Estimates of the VSD obtained from nonparametric time to death with tumor and unobservable time to tumor analyses are not always the same.
For the logit dose component models, there was no systematic difference in the log-relative errors of estimated VSDs; this was also the case for the parametric time analyses. However, the findings for probit and Weibull dose components are exactly the reverse of those found using parametric time components. Specifically, there does not appear to be any systematic differences for the Weibull components ($p > 0.05$), but such differences do exist for probit dose components ($p < 0.01$).

Further examination of Tables A.1 through A.23 reveals that for 35, 29, and 28 of the 46 data sets, corresponding to probit, logit, and Weibull dose components, respectively, the time to death with tumor VSDs were less than the unobservable time to tumor VSDs. In light of the different parametric and nonparametric results for this comparison, it does not appear that the Krewski et al. (1983) finding of a difference in these two time endpoints for a multistage dose component holds for all possible dose component models.

5.5. Comparison of Time to Response and Quantal Response Models

Figures 5.3 and 5.4 suggest somewhat more difference in the estimated time to response and the quantal response VSDs than was apparent with the parametric time analyses. Figures 5.5 and 5.6 are analogous to Figures 3.8 and 3.9 for the parametric time forms, and summarize the data set by data set difference between the use and non-use of time.

For the nonparametric time to death with tumor analyses, the proportion of the corresponding VSDs that were within an order of magnitude of each other was 40/46 for a probit dose component, 39/46 for a logit component, and 37/46 for a Weibull. 40, 37, and 36 of the 46 estimated VSDs
FIGURE 5.5 FREQUENCY DISTRIBUTION OF DIFFERENCES IN VALUES OF $\log_{10}[VSD_{\text{MODEL}}/VSD_{\text{TRUE}}]$ FROM TIME TO DEATH WITH TUMOR ANALYSES USING NONPARAMETRIC TIME COMPONENTS AND QUANTAL RESPONSE MODELS FOR PROBIT, LOGIT, AND WEIBULL DOSE COMPONENTS ($T=900$ DAYS)
FIGURE 5.6 FREQUENCY DISTRIBUTION OF DIFFERENCES IN VALUES OF LOG₁₀(VSDMODEL/VSDTRUE) FROM UOBSERVABLE TIME TO TUMOR ANALYSES USING NONPARAMETRIC TIME COMPONENTS AND QUANTAL RESPONSE MODELS FOR PROBIT, LOGIT, AND WEIBULL DOSE COMPONENTS (T=900 DAYS)
from the observable time to tumor analyses with probit, logit, and
Weibull dose components, respectively, were within an order of magnitude
of the corresponding quantal response VSDs. No characteristics of the
data sets which produced VSD estimates that differed by more than an
order of magnitude seem unusual, however.

As with the parametric time analyses, there were statistically
significant differences in the distributions of log-relative errors in
VSD using all 46 data sets for time to response and quantal response
models for both probit and logit dose component models. Again, no
apparent differences were found for the Weibull dose components. The
same three problem data sets have log-ratio values greater than three
for nonparametric time components. Excluding these potential outliers,
differences are still apparent for probit dose components, no longer
apparent for logit components, and now apparent for Weibull. These
results do not greatly differ from the visual impression which Figures
5.5 and 5.6 provide. For the probit and logit dose components, the time
to response VSDs are usually greater than the quantal response VSDs.
Excluding the observations in the far right bar would not change this
impression for the probit, but might for the logit. For the Weibull
dose component, the time to response VSDs are generally smaller than
the quantal response VSDs and excluding the observations in the 3-plus
group definitely enhances the difference between the two methods.

Once again, the probit and logit quantal response models provide
estimates of the virtually safe dose which are closer to the true VSD
than the corresponding time to response models. For the probit model,
30 of 46 data sets had an estimated quantal response VSD which was more
precise than the estimated unobservable time to tumor VSD. The logit
quantal response VSDs were more precise 24 and 25 of 46 times for unobservable time to tumor and time to death with tumor, respectively. For both time endpoints analyzed, the estimated time to response VSD was closer in 33 of 46 cases than was the quantal response VSD. Therefore whether the use of time contributes substantially to quantitative risk estimation seems to depend primarily on the dose component employed in the product hazard model, and not upon the method for incorporating time into the hazard nor the response time analyzed.
CHAPTER VI

PROPERTIES OF THE VIRTUALLY SAFE DOSE

The virtually safe dose was used throughout Chapters 3 and 5 to quantify the risk associated with exposure to a potential carcinogen. Similarities and differences in estimated time to response and quantal response VSDs were noted in those chapters. Theoretical reasons for these differences and similarities are provided in Section 6.1. In Chapters 1 and 2, the large sample properties of this risk measure were provided. Some small sample properties of this parameter are presented in Section 6.2. Section 6.3. discusses the different methods which have been proposed for setting confidence bounds on the quantal response and time to response VSD.

6.1. Comparison of Time to Response and Quantal Response Virtually Safe Doses

Methods for incorporating quantal response models into time to response models were described in Chapter 2. This section explores the relationship between the VSD from a quantal response analysis and the VSD from the product hazard time to response analysis corresponding to this quantal response model.
Let $P(d)$ be a quantal response model and $H(t)$ be the time component in its corresponding product hazard time to response model. Suppose that background responses have been included in the time model, as given in Section 2.3.4, so that

$$g(d) = -\log[1 - P^*(d)],$$  \hspace{1cm} (6.1)

where

$$P^*(d) = \gamma + (1-\gamma) P(d+\delta)$$  \hspace{1cm} (6.2)

is the same quantal response model with mixed background components.

For this situation, the time to response VSD satisfies:

$$\pi = F(t;d) - F(t;0)$$

$$= [1 - P^*(0)]^H(t) - [1 - P^*(d)]^H(t).$$  \hspace{1cm} (6.3)

(6.4)

Recall from Section 2.4 that it is always possible to choose the model parameters so that for the time point $T$, $H(T)$ equals some fixed given value. If this value is selected to be one, then at time $T$, the time to response VSD satisfies

$$\pi = P^*(d) - P^*(0).$$  \hspace{1cm} (6.5)

which is the same equation satisfied by the quantal response VSD.

Thus any differences which exist between the time to response and quantal response VSD at time $T$ are due purely to differences in the estimated parameters which specify the dose response relationship.

The relationship between these two VSDs at other time points is best studied using Taylor series expansions. Now

$$[1 - P^*(0)]^H(t) - [1 - P^*(d)]^H(t)$$

$$= (1-\gamma)^H(t) \{[1 - P(0)]^H(t) - [1 - P(d+\delta)]^H(t)\},$$  \hspace{1cm} (6.6)
\[ [1 - P(\delta)]^H(t) - [1 - P(d+\delta)]^H(t) \]
\[ = \sum_{i=1}^{\infty} \binom{H(t)}{i} (-1)^i [P(d+\delta) - P(\delta)] \quad (6.7) \]

Considering only the first term in this expansion, the time to response VSD is an approximate solution to the following equation.

\[ \pi = H(t) (1-\gamma)^H(t) [P(d+\delta) - P(\delta)] \quad (6.8) \]

This is again the form of the equation satisfied by the quantal response VSD.

For time prior to T, H(t) is less than one and the binomial coefficients in the series expansion (6.7) alternate in sign and decrease in absolute value. If \( \delta \) is zero, the sequence, \( a_k = P(d + \delta)^k - P(\delta)^k \), is always decreasing since P(d) is less than one. In this case the terms in the above expansion converge rapidly to zero. If \( \delta \) is positive, the \( a_k \) sequence need not be strictly decreasing. Standard number theory results show there is, however, a value K such that for all \( k \) greater than K, the sequence \( a_k \) is decreasing. Depending upon the value of H(t) and this integer K, the remaining terms in the expansion may not be negligible and substantial amount of dose and time information may be lost if the approximation (6.8) is used.

For time later than T, H(t) is greater than one and the series expansion (6.7) cannot be expected to converge as rapidly as it might if H(t) were smaller than one. Thus the quantal response and time to response model VSDs might be expected to differ most in this situation. For example, suppose H(t) equals two and both background parameters are
zero; then the first order expansion requires that terms of order $p^2(d)$, be ignored. Since $P(\hat{VSD}) = \pi$, this term may not be negligible if the risk level $\pi$ is fairly large.

Thus, the easiest comparison of the time to response and quantal response VSDs at a particular time point can be made when the model parameters are chosen so that the time component is one. Note that for the parametric analyses of the Krewski et al. (1983) simulated data summarized in Chapter 3, the value of the time component at 900 days was fixed to be one. However, for the nonparametric analyses of Chapter 4, the underlying cumulative hazard was allowed to vary. Estimates of the cumulative hazard at 900 days were generally less than one in these analyses, although for some data sets the estimates were as large as 2.5.

6.2. Distribution of Quantal Response Virtually Safe Doses

When the time component in the product hazard model is equal to one, the time to response VSD satisfies the same equation (6.5) as does the quantal response VSD. Therefore it is anticipated that the properties of the time to response VSD should be similar to those of the quantal response VSD. Certain of these properties are examined below.

6.2.1. Small Sample Properties of the VSD

Krewski and Van Ryzin (1981) showed that under suitable mild regularity conditions for a quantal response model, the model parameters are asymptotically normally distributed. Consequently the estimated
excess risk, $\hat{VSD}$, $1/\hat{VSD}$, and $\log(\hat{VSD})$ are also asymptotically normal. Because of the non-negativity constraints on the parameters in the multistage model, these results do not always hold. The large sample distribution for the parameters in this model has been derived by Crump et al. (1977). Portier and Hoel (1983) determined that for the multistage model, large sample theory does not provide a good approximation of the distribution observed for small bioassays obtained by Monte Carlo simulation. The constrained nature of the model parameters in this model leads to a bimodal distribution for small samples, with the two modes corresponding to the presence or absence of non-zero estimates of the linear coefficient in the model.

Evidence is next presented that, even for moderate sample sizes, the $\hat{VSD}$, $\log(\hat{VSD})$, and $1/\hat{VSD}$ are not normally distributed for the three log tolerance distributions discussed throughout. Since these models satisfy the regularity conditions of Krewski and Van Ryzin (1981), the use of confidence bounds based upon normality of these quantities should be questioned.

Figures 6.1 and 6.2 give the density derived by Monte Carlo simulation for the parameters $\alpha$ and $\beta$ in the probit quantal response model fit to the CIIT formaldehyde data, as well as the large sample normal approximation to this density. There does not appear to be any significant departure from normality of these primary parameters. Figures 6.3, 6.4, and 6.5 give the associated densities for the VSD, $\log(\text{VSD})$, and $1/\text{VSD}$ for a risk of $1/100,000$. These densities are skewed and formal significance tests reject normality at the .05 level. Similar results have been found for this data set for other models and other risk levels as well. The following additional example suggests that this non-normality is not merely an artifact of this data set.
FIGURE 6.1 ASYMPTOTIC AND SIMULATED DENSITIES OF PARAMETER ALPHA FROM PROBIT MODEL USING FORMALDEHYDE DATA

FIGURE 6.2 ASYMPTOTIC AND SIMULATED DENSITIES OF PARAMETER BETA FROM PROBIT MODEL USING FORMALDEHYDE DATA
FIGURE 6.3 ASYMPTOTIC AND SIMULATED DENSITIES OF VSD FROM PROBIT MODEL USING FORMALDEHYDE DATA

FIGURE 6.4 ASYMPTOTIC AND SIMULATED DENSITIES OF LOG(VSD) FROM PROBIT MODEL USING FORMALDEHYDE DATA

FIGURE 6.5 ASYMPTOTIC AND SIMULATED DENSITIES OF 1/VSD FROM PROBIT MODEL USING FORMALDEHYDE DATA
The dose response function predicted by a logit model with an independent background for the bioassay of dieldrin considered by the Food Safety Council (1980) is given in Figure 6.6. This data set is most different from the formaldehyde data set in that a significant number of control animals had the biological endpoint of interest (liver tumor). Figures 6.7, 6.8, and 6.9 give the simulated densities of the parameters $\alpha$, $\beta$, and $\gamma$, respectively, for the parameters in the logit quantal response model with independent background. The densities of VSD, $\log(\text{VSD})$, and $1/\text{VSD}$ for a risk of $1/1,000,000$ are given in Figures 6.10, 6.11, and 6.12. These figures also suggest non-normality, but the skewness tends to be in the opposite direction. For example, the distribution for the VSD for formaldehyde is skewed to the right, whereas for dieldrin it is skewed to the left.
FIGURE 6.6  PREDICTED LOGIT QUANTAL RESPONSE MODEL FOR DIELDRIN DATA
FIGURE 6.7 ASYMPTOTIC AND SIMULATED DENSITIES OF PARAMETER ALPHA FROM LOGIT MODEL USING DIELDRIN DATA

FIGURE 6.8 ASYMPTOTIC AND SIMULATED DENSITIES OF PARAMETER BETA FROM LOGIT MODEL USING DIELDRIN DATA

FIGURE 6.9 ASYMPTOTIC AND SIMULATED DENSITIES OF PARAMETER GAMMA FROM LOGIT MODEL USING DIELDRIN DATA
FIGURE 6.10  ASYMPTOTIC AND SIMULATED DENSITIES OF VSD FROM LOGIT MODEL USING DIELDRIN DATA

FIGURE 6.11  ASYMPTOTIC AND SIMULATED DENSITIES OF LOG(VSD) FROM LOGIT MODEL USING DIELDRIN DATA

FIGURE 6.12  ASYMPTOTIC AND SIMULATED DENSITIES OF 1/VSD FROM LOGIT MODEL USING DIELDRIN DATA
6.2.2. Bimodality of log(VSD) Distribution

One additional point can be raised with regard to the distribution of the VSD. For certain cases of the model parameters in the log tolerance distribution models, it is shown below that if the model parameter estimates are normally distributed, then the estimated log(VSD) has a bimodal distribution. This construction involves the ratio of two normal variables.

Fieller (1932) showed that if \( X \) and \( Y \) are bivariate normal with means \( \mu_x \) and \( \mu_y \) and variance-covariance matrix

\[
\Sigma = \begin{pmatrix} \sigma_x^2 & \rho \sigma_x \sigma_y \\ \rho \sigma_x \sigma_y & \sigma_y^2 \end{pmatrix}
\]  

(6.9)

and \( Z = X/Y \), then the density of \( Z \) is given by

\[
f_Z(z) = a \frac{\exp\left(-d/2a^2\right)}{\pi b^2} \left\{1 + \frac{r}{\phi(r)} \int_0^r \phi(u) \, du \right\};  
\]  

(6.10)

where

\[
\phi(x) = \exp(-x^2/2)/\sqrt{2\pi},
\]  

(6.11)

\[
a = \sigma_x \sigma_y \sqrt{1 - \rho^2},
\]  

(6.12)

\[
b = \sqrt{\frac{\sigma_x^2 - 2\rho \sigma_x \sigma_y z + \sigma_y^2 z^2}{\sigma_x^2 - 2\rho \sigma_x \sigma_y z + \sigma_y^2 z^2}},
\]  

(6.13)

\[
c = z \left( \rho \sigma_x \sigma_y \mu_y - \mu_x \sigma_y^2 \right) + \rho \mu_x \sigma_x \sigma_y - \sigma_x^2 \mu_y,
\]  

(6.14)

\[
d = \mu_x^2 \sigma_y^2 - 2\rho \mu_x \sigma_x \mu_y \sigma_y + \sigma_x^2 \mu_y^2,
\]  

(6.15)

and

\[
r = c / ab.
\]  

(6.16)

Marsaglia (1965) showed that if \( U \) and \( V \) are independent standard normal variables and \( a \) and \( b \) are nonnegative constants, then the variable \( W = (a + U)/(b + V) \) has a density given by
\[ f_w(w) = \frac{\exp[-(a^2+b^2)/2]}{\sqrt{1+w^2}} \left\{ 1 + \frac{q}{\phi(q)} \int_0^q \phi(u) \, du \right\}, \quad (6.17) \]

where

\[ q = \frac{b + aw}{\sqrt{1+w^2}}. \quad (6.18) \]

This variable may be bimodal or unimodal depending upon whether the parameters \( a \) and \( b \) fall into the appropriate region of the \((a,b)\) space as given in Figure 6.13. The line dividing the regions is asymptotic to \( a = \pm2.257 \).
FIGURE 6.13 REGIONS DETERMINING BIMODALITY OF \((a+u)/(b+v)\) FOR INDEPENDENT STANDARD NORMAL VARIABLES U AND V
If \((a, b)\) lies in region I or III then the variable \(W\) is bimodal; otherwise \(W\) is unimodal. Marsaglia (1965) presents this figure for \(a\) and \(b\) positive. If \(f_{a, b}(w)\) represents the density of \(w\) for a given value of \(a\) and \(b\), then

\[
f_{a, b}(w) = f_{-a, b}(-w) = f_{a, -b}(-w) = f_{-a, -b}(w); \quad (6.19)
\]

thus the existence of two modes does not depend on the sign of \(a\) and \(b\).

This bimodality result can easily be extended to the ratio of two non-standard normal variables as follows: If \(X\) and \(Y\) are bivariate normal,

\[
V = (Y - \mu_Y)/\sigma_Y, \quad (6.20)
\]

and

\[
U = \frac{(X - \mu_X) - \rho \sigma_X V}{\sigma_X \sqrt{1 - \rho^2}}; \quad (6.21)
\]

then \(U\) and \(V\) are independent standard normal variables. Reversing these equations, if we let \(Z = X/Y\),

\[
a = \frac{\mu_X \sigma_Y - \rho \sigma_X \mu_Y}{\sigma_X \sigma_Y \sqrt{1 - \rho^2}}, \quad (6.22)
\]

and

\[
b = \mu_Y/\sigma_Y; \quad (6.23)
\]

then

\[
-\rho + \frac{\sigma_Y}{\sigma_X} Z = \sqrt{1 - \rho^2} (a + U)/(b + V). \quad (6.24)
\]

The bimodality of \(Z\) thus depends upon which region contains this particular point \((a, b)\).

Now consider a bioassay where the probability of response \(P(d)\) is given by a log tolerance distribution model without any background parameters; that is,
\[ P(d) = F(\alpha + \beta \log d), \]  

(6.25) where \( F \) is a standardized distribution function. Under suitable mild regularity conditions, the maximum likelihood estimates \( \hat{\alpha} \) and \( \hat{\beta} \) are asymptotically normal, specifically,

\[
\sqrt{n} \begin{pmatrix} \hat{\alpha} - \alpha \\ \hat{\beta} - \beta \end{pmatrix} \to N(0, \Sigma)
\]

(6.26) where the form of \( \Sigma \) is given in Section 1.2. If \( \hat{\Sigma} \) is a consistent estimator of \( \Sigma \), then

\[
\begin{pmatrix} \hat{\alpha} \\ \hat{\beta} \end{pmatrix} \overset{d}{\to} N \left( \begin{pmatrix} \alpha \\ \beta \end{pmatrix}, \hat{\Sigma}/n \right).
\]

(6.27) For a small added risk \( \pi \), the estimated VSD, VSD, satisfies

\[
\pi = F(\hat{\alpha} + \hat{\beta} \log(VSD)); \text{ thus}
\]

\[
\log(VSD) = \frac{F^{-1}(\pi) - \hat{\alpha}}{\hat{\beta}}
\]

(6.28) may be expressed as a ratio of two approximately normal random variables \( X = F^{-1}(\pi) - \hat{\alpha} \) and \( Y = \hat{\beta} \). If the approximation of equation (6.27) is assumed to be exact, then \( Z = \log(VSD) \) may possibly be a bimodal variable. Let \( \hat{\rho}_{\alpha \beta} \), \( \hat{\sigma}_\alpha \), and \( \hat{\sigma}_\beta \) be the estimated correlation and standard deviations of \( \alpha \) and \( \beta \); then

\[
a = \frac{\hat{\sigma}_\beta (F^{-1}(\pi) - \hat{\alpha}) + \hat{\rho}_{\alpha \beta} \hat{\sigma}_\alpha \hat{\beta}}{\hat{\sigma}_\alpha \hat{\sigma}_\beta \sqrt{1 - \hat{\rho}_{\alpha \beta}^2}}
\]

(6.29) and

\[
b = \frac{\hat{\beta}}{\hat{\sigma}_\beta}
\]

Since \( \hat{\beta} \) is required to be positive for a log tolerance model, b is always positive, and if there is a significant dose response
relationship, $b$ will be at least 3.0. The value of $a$ depends upon the shape of the function $F$ in its lower tail, the risk level, the estimated values of the parameters, and the estimated variance covariance matrix for the model. The location of the second mode, which depends explicitly upon the location of $(a,b)$, is therefore also highly data dependent. Whether this mode is of any consequence for the setting of confidence bounds on the VSD using lognormality of VSD, is not easily determined and should be studied further.

One remaining aspect of the distribution theory of the quantal response VSD should be mentioned. Fieller (1932) showed that if $\frac{\mu_Y}{\sigma_Y}$ is large, then the random variable $T$ given by

$$T = \frac{Z \mu_Y - \mu_X}{\sqrt{\sigma_X^2 - 2\rho\sigma_X\sigma_Y Z + \sigma_Y^2 Z^2}}$$

is approximately normally distributed. For this approximation, $3$ or $4$ is sufficiently large. Thus if $\hat{\beta}$ is significantly non-zero, then $Z = \log(\text{VSD})$ can be transformed to an approximate normal variable.

6.3. Confidence Bounds for the Virtually Safe Dose

Perhaps of as much interest as differences in the point estimates of the time to response VSD would be any differences in its corresponding lower confidence bounds, since these quantities are also frequently considered for regulatory decisions. Unfortunately there is no single accepted method for setting confidence bounds, either in a quantal response or time to response framework.
6.3.1. Confidence Bound Methods

For the probit, logit, Weibull, and gamma multi-hit quantal response models; Krewski and Van Ryzin (1981) described the construction of confidence bounds for the VSD using approximate normality of $\hat{\text{VSD}}$, $\hat{\log(\text{VSD})}$, and $1/\text{VSD}$. The results of section 6.2.2 raise doubts about this approach. Crump et al. (1977) proposed a bound for the multistage model VSD which is based upon a likelihood ratio statistic. Specifically, an upper bound for the linear coefficient is selected using a likelihood ratio test; the corresponding VSD is then taken as the lower bound. Crump et al. (1977) also suggested the use of bounds derived via simulation. Buck and Starr (1984) compared these different methods for a large group of simple experiments and found substantial disagreement among the different approaches.

Hartley and Sielken (1977) set the lower bounds on the VSD for their time to response model using a resampling scheme as follows: For an experiment, sample the data with replacement $G-1$ times to form $G$ data sets of the same general structure. Estimate the VSD for each of the data sets. Construct a lower confidence bound on the $\hat{\log(\text{VSD})}$ using the estimated standard error of the $\log(\hat{\text{VSD}})$ and percentage points of the $t_{G-1}$ distribution. Exponentiate this bound to obtain the bound on the VSD.

Crump et al. (1981), in analogy with the technique of Crump et al. (1977), set the bound on the polynomial in dose, Weibull in time product hazard time to response VSD via an upper bound on the linear coefficient in dose. Dafer et al. (1980) have derived estimates of the lower confidence bound for their nonparametric product hazard model.
in a similar manner.

Krewski et al. (1983) reported differences in the confidence bounds on the time to response VSD derived using the methods of Hartley and Sielken (1977) and Crump et al. (1981). No explicit construction of bounds using large sample normality of VSD or any monotonic transformation of the VSD in the time response setting has been given. It is anticipated that differences in confidence bound estimates for the multistage quantal response model demonstrated by Buck and Starr (1984) would also be observed for the more general product hazard time to response models. Further research is still needed comparing confidence bound methods and setting confidence bounds for the VSD.

6.3.2. Transformation to Achieve Normality

The results of section 6.2.2. raise serious questions about the use of normality of the VSD or transformations of it for setting lower confidence bounds on the VSD. Since the distributions of log(VSD) and 1/VSD tend to be skewed in opposite directions for these and other data sets similarly analysed, it may happen that some other transformation of VSD could provide a more normal distribution to be used for confidence bound construction.

Let \( \hat{\Theta} \) be an estimate of a parameter \( \Theta \) such that \( \sqrt{n} (\hat{\Theta} - \Theta) \) is approximately normal with mean 0 and variance \( \sigma^2_{\Theta} \). An approximate lower 100(1-\( \alpha \))% confidence limit on \( \Theta \) is given by

\[
\hat{\Theta}_L = \hat{\Theta} - z_{1-\alpha} \hat{\sigma}_{\Theta} / \sqrt{n},
\]

where \( z_p \) is the \( p \)-th percentage point of the normal distribution and \( \hat{\sigma}^2_{\Theta} \) is a consistent estimator of \( \sigma^2_{\Theta} \).
Suppose the parameter $\Psi = f(\Theta)$ is a monotonic transformation of $\Theta$. Then, if $\Psi = f(\hat{\Theta}), \sqrt{n} (\hat{\Psi} - \Psi)$ is approximately normal with mean 0 and variance $(\partial \Psi / \partial \Theta)^2 \sigma_\Theta^2$. An approximate lower 100(1-\alpha)\% confidence limit on $\Theta$ may be obtained by first constructing approximately upper limits on $\Psi$, if $f$ is strictly decreasing, or lower limits on $\Psi$, if $f$ is strictly increasing. The bound $\Psi_B$ on $\Psi$ is given by

$$\Psi_B = \hat{\Psi} - z_{1-\alpha} f'(\hat{\Theta}) \sigma_\Theta / \sqrt{n}, \quad (6.33)$$

so that the approximate lower 100(1-\alpha)\% confidence limit for $\Theta$ is

$$\Theta_L = f^{-1}(\Psi_B). \quad (6.34)$$

If the parameter $\Theta$ is always positive, as is the case for VSD, it is desirable that the bound $\Theta_L$ be nonnegative. This may not always be the case for equation (6.32), but it is possible to construct approximate confidence limits with this property using an appropriate choice of transformations.

One large family of transformations with this desired property is given by

$$f(\Theta, r) = \begin{cases} 
\log(\Theta) & \text{if } r = 0 \\
(\Theta)^{-r} & \text{if } r > 0
\end{cases}. \quad (6.35)$$

Once a family of transformations has been determined, a criterion for the "most normal" member of that family must be established. Many possible tests are available for normality, including tests of skewness and kurtosis. Filliben (1975) proposed a test based upon the Pearson correlation of the order statistics with the population medians of the order statistics from a normal distribution. Since the population
medians and expected values of the order statistics are essentially the same for even small samples, a suitable maximization criterion might be the correlation with respect to the normal population means.

Preliminary results with this criterion within the transformation family (6.35) for the CIIT formaldehyde data suggest that the "best" transformation for normality is both model and risk level specific. Further study of this phenomenon is warranted.

One additional transformation to achieve normality for setting confidence limits on the VSD is that given by Fieller (1932). This non-monotonic transformation of the log(VSD), presented in equation (6.31), might also be useful to set confidence bounds. Results with the CIIT formaldehyde data indicate that this transformation may result in confidence bounds, which are closer to the bound obtained by simulation than the bounds obtained using either a logarithmic or inverse transformation.
CHAPTER VII
SUMMARY AND SUGGESTIONS FOR FUTURE RESEARCH

7.1. An Overview

Product hazard survival models are a general technique for including time into carcinogenic risk assessment. Many different functional forms are commonly used for modeling the dose response relationships observed in long-term animal bioassays. The product hazard models used to date for modeling the dose and time response relationships of the same data have chosen a polynomial with positive coefficients for the dose factor in the hazard. This choice corresponds to only one of the common quantal response models. An approach for including any quantal response model into the hazard was presented. This approach could also allow the pharmacokinetics of the administered and delivered response relationship to be included in a product hazard model. One advantage to using other quantal response models for the dose component is that generally the estimated model parameters are asymptotically normally distributed, which is not the case for a polynomial dose component.

Estimation techniques for both parametric and nonparametric time components in the hazard were described in Chapters 2 and 4, respectively. Parametric time estimation involved a full likelihood approach and did not require different methods for observable and unobservable time endpoints. Nonparametric estimation techniques for time to death or observable time to tumor data are easy generalizations of usual Cox
model methods. An approximate likelihood technique for estimating model parameters, when the time to tumor is unobservable and the cause of death cannot be determined, was derived.

Product hazard models with dose components corresponding to probit, logit, and Weibull quantal response models were applied to both experimental and simulated time to tumor data in Chapters 3 and 5. A long term study of inhalation exposure to formaldehyde in rats was analyzed using both administered dose and a measure of the dose delivered to the cancer target site. These data showed a one to two order magnitude reduction in risk estimates and their confidence bounds at low doses, when the delivered dose measure was employed.

A major focus of this research was on the potential difference in estimates of risk that might result with the inclusion of time. The large simulated data base of Krewski et al. (1983) was used to address this issue. The results of Chapters 3 and 5 suggest that differences in point estimates of risk for the quantal response and time to response models may not be substantial. Further, the use of time to response models did not always give predicted virtually safe doses that were closer to the true VSDs than those predicted by the simpler quantal response models. Any differences found between the time to response and quantal response models were dependent upon the particular model form considered. Whether these statistically significant differences have any practical meaning is unclear, and may, in fact, depend upon the test statistic being considered for the comparisons of the two methods. No comparisons of confidence limits for the risk estimates were provided, since there does not appear to be any advantage to any of the numerous method proposed for setting these bounds. Although approximate confid-
ence limit can be obtained using large sample normal theory, the results of Chapter 6 suggest that the usual risk estimates are not normally distributed even for fairly large data sets.

Several other points were studied using these simulated data sets. No major differences in estimated virtually safe doses were found between parametric and nonparametric time analyses. Substantial differences were found between different dose components used, with exactly the same ordering observed for estimated time to response VSDs as occurs for quantal response models. Depending upon the dose component and time estimation technique employed, different time endpoint analyses sometimes produced similar risk estimates and sometimes did not. The sizable variability in risk estimates between replicates in this simulated database raised some doubts about all of the above conclusions, and suggested that more replicates of experimental conditions are needed to adequately address these important risk assessment issues.

7.2. Nonproportional Hazard Survival Models

As noted at the start, proportional hazards modeling is only one method for dealing with general survival and time to response data. In addition, proportional hazards models need not provide an adequate fit for these types of data. However, the product hazard form is frequently applicable, especially when the covariate measured is essentially time invariant. Attempts at verifying and/or testing the proportionality assumption should be considered each time that a product hazard model is used.

Using the visual verification of proportional hazards described in
Chapter 2, no element of the Krewski et al. (1983) data base appeared to seriously violate the proportionality assumption. Although a product hazard model was used to generate the time to tumor distribution for 19 of the 23 experiments simulated, the presence of dose-dependent competing risk and time to death after tumor processes was expected to result in data which was not strictly proportional across dose groups. The time endpoints considered in the analyses do not look at cause of death or observable time to tumor, but use the least amount of information about the time processes involved.

Nonetheless, the four experiments, where log-linear models rather than product hazards were used for the time to tumor distribution, should be considered in greater detail. For two of these experiments, the time to tumor followed a Weibull log-linear model. For both replicates of one of these experiments, the predicted VSDs were always higher than the true VSD regardless of the time point analyzed; for both replicates of the other Weibull experiment, the predicted VSDs were generally lower. For the probit log-linear experiment, the predicted VSDs were generally lower than the true VSD for both replicates. However, product hazard models with a probit dose component always overestimated the VSD for one of the replicates of this experiment. For the logit log-linear experiment, all estimated VSDs for one replicate were overestimates, as well as for the probit dose component product hazard VSDs in the other replicate. The logit and Weibull dose component model VSDs in this second replicate were underestimates.

Since the results are mixed for these four experiments, no general statement can be made about the effect of modeling non-product hazard toxicity data with a product hazard model. Further examination
of this effect and exploration of non-product hazard modeling techniques is in order.

Another issue with non-product hazards deserves further consideration. As noted in Chapter 2, when spontaneously occurring and induced tumors arise from fundamentally different biological processes, a non-product hazard function should be employed. No consideration of this issue for time to response models has been reported to date.

7.3. Other Functional Forms for Time

For the Krewski et al. (1983) data sets, substantial agreement exists between corresponding estimates of the VSD for the parametric and nonparametric analyses of time to death with tumor. For the analyses of the unobservable time to tumor endpoint, the large majority of corresponding VSD estimates fell within an order of magnitude of each other. However, sufficient evidence to reject the null hypothesis of equal medians did exist for the probit and Weibull dose component analyses for this time endpoint.

Although not explicitly demonstrated, there was considerable agreement among corresponding model parameter estimates for these same data analyzed using parametric and nonparametric time. This close agreement of parameter estimates and VSDs suggests that the choice of a Weibull time component for the parametric analyses was not unreasonable. The Weibull form for the time component in the product hazard model is the simplest non-trivial form which could be considered. Despite the simplicity of the form and the historical reasons for using the Weibull to describe cancer data, other functional forms for the time parameter
should be investigated. In particular, the goodness of fit of the
Weibull form can be explicitly tested by embedding it in a more general
parametric model. One easy extension of the Weibull is a mixture of
Weibulls, such as

\[ H(t) = t^k \left(1 + \alpha t^\beta\right) \]  

(7.1)

One further point should be considered when discussing the Weibull
time component. For one of the experiments there was a minimum tumor
induction time of 500 days for an independently occurring spontaneous
tumor and 300 days for an additive dose-wise spontaneous or induced
tumor. In both replicates of this experiment, the true VSDs were over-
estimated by two or more orders of magnitude regardless of the dose
component, time endpoint, or analysis strategy used. Whether this one
experiment is typical of experiments for which there is a real minimum
induction time is unclear. Also unclear is whether the use of a differ-
ent functional form for the time component, for example, a Weibull com-
ponent with a lag parameter, might have led to more accurate results.

7.4. Problems with Regard to Time Lag Parameters

Another point which arose during the course of this research was
the inadequacy of maximum likelihood estimation to handle a lag
parameter in time. The time form used in the parametric analyses was
a special case of the more general Weibull form with a lag; that is,

\[ H(t,\Delta) = \begin{cases} 
(t - \Delta)^k, & \text{if } t > \Delta \\
0, & \text{otherwise}
\end{cases} \]  

(7.2)
If the lag parameter $\Delta$ is not a function of dose, then maximum likelihood estimates of $\Delta$ tended to be placed at a time just prior to the first positive event. These estimates are also very poorly specified, in that a large adjustment in this parameter made essentially no difference in the log-likelihood of the data. Further there is no reason to believe that this particular outcome of the experiment is the only one possible, and hence that the time to first positive response could not be much earlier or much later. These problems with constant lag parameters and their estimation deserve additional consideration.

A more important point is the biological interpretation of a non-dose-dependent lag parameter in the product hazard model. For times prior to $\Delta$, an animal is at no risk for tumor development regardless of its exposure, whereas for times just larger that $\Delta$ the animal is at risk. This literal interpretation of the above form is biologically unreasonable. Any time form with a constant lag parameter suffers from this same malady.

More credible time forms would have the parameter $\Delta$ be a function of the exposure. The best function to consider is subject to as much interpretation and disagreement as which functional form is best for modeling quantal response data. If biological evidence regarding the disposition and metabolism of the carcinogen over time is available, such evidence should be considered. One way of incorporating such information into the modeling would be through Bayesian priors for the parameter $\Delta$. This is another area for needed collaboration among statisticians and the remaining scientific community.
7.5. Pharmacokinetic Models for Time to Response Data

The use of more biologically plausible measures of delivered dose than just the administered dose was demonstrated in Chapter 2. Many authors have addressed the problems of relating administered and delivered dose, yet only recently have attempts been made to incorporate these relationships into risk assessment. Further study of these points is in order.

The use of simple pharmacokinetic models presented in Chapter 2 are one way of incorporating the relationship directly into the estimation of risks using bioassay data. Other methods using ancillary experimental data might involve joint estimation of parameters for both the bioassay and the ancillary experimental results or the use of Bayesian techniques.

7.6. Consideration of Other Time Endpoints and Risk Estimates

The Krewski et al. (1983) data provide information on four possible time endpoints. The conclusions drawn from reanalyses of two of these endpoints did not always agree with the original findings. Although the effort required to examine the remaining less commonly occurring endpoints would be substantial, further analyses should be considered. With these additional analyses, more complete answers could be given regarding the differences in estimates of the virtually safe dose resulting from the use of different dose components and time endpoints.

In Chapter 2, several different risk measures other than the VSD were presented. Preliminary work regarding the properties of these estimates has been done by others, but more is left to be done. The
problems of simulating a large number of time to response data sets in order to assess the properties of the VSD and other risk measures are now better understood. While an enormous amount of work would be involved, the results of these simulations could not only be used to examine the properties of the risk estimates, but also provide further guidance concerning the analysis of data with a variety of plausible biological effects.


TABLE A.1

ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS
BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 1

TRUE VSD = 1.614(-3)\(^a\)

Replicate 1

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
<td>Logit</td>
<td>Weibull</td>
<td></td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>3.03(-1)</td>
<td>1.54(-1)</td>
<td>1.44(-1)</td>
<td></td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>3.42(-1)</td>
<td>1.65(-1)</td>
<td>1.13(-1)</td>
<td></td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>3.31(-1)</td>
<td>1.62(-1)</td>
<td>1.39(-1)</td>
<td></td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>3.41(-1)</td>
<td>1.63(-1)</td>
<td>1.20(-1)</td>
<td></td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>3.45(-1)</td>
<td>1.65(-1)</td>
<td>1.23(-1)</td>
<td></td>
</tr>
</tbody>
</table>

Replicate 2

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
<td>Logit</td>
<td>Weibull</td>
<td></td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>4.86(-2)</td>
<td>7.54(-3)</td>
<td>5.62(-3)</td>
<td></td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>1.01(-1)</td>
<td>2.56(-2)</td>
<td>8.01(-3)</td>
<td></td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>5.46(-2)</td>
<td>8.47(-3)</td>
<td>5.68(-3)</td>
<td></td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>7.78(-2)</td>
<td>1.38(-2)</td>
<td>6.63(-3)</td>
<td></td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>8.11(-2)</td>
<td>1.50(-2)</td>
<td>7.38(-3)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Values in parentheses are powers of 10.


<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>6.25(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>5.51(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>6.21(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>5.03(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>5.26(-2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Replicate 2</th>
<th>Dose Component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>4.10(-1)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>3.81(-1)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>4.08(-1)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>3.19(-1)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>3.34(-1)</td>
</tr>
</tbody>
</table>

\* Values in parentheses are powers of 10.
\textbf{TABLE A.3}

\textbf{ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 3}

\textbf{TRUE VSD = 1.614(-3)a}

\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Replicate 1} & & & \\
\hline
\textbf{Time Strategy} & \textbf{Dose Component} & & \\
& \textbf{Probit} & \textbf{Logit} & \textbf{Weibull} \\
\hline
Quantal Response - Total No. of Animals & 2.35(-1) & 1.02(-1) & 9.37(-2) \\
Time to Death with Tumor - Weibull Time Component & 2.31(-1) & 8.31(-2) & 5.26(-2) \\
Unobservable Time to Tumor - Weibull Time Component & 2.58(-1) & 1.03(-1) & 7.58(-2) \\
Time to Death with Tumor - Nonparametric Time Component & 2.46(-1) & 9.73(-2) & 6.20(-2) \\
Unobservable Time to Tumor - Nonparametric Time Component & 2.46(-1) & 9.33(-2) & 5.93(-2) \\
\hline
\end{tabular}

\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Replicate 2} & & & \\
\hline
\textbf{Time Strategy} & \textbf{Dose Component} & & \\
& \textbf{Probit} & \textbf{Logit} & \textbf{Weibull} \\
\hline
Quantal Response - Total No. of Animals & 2.16(-1) & 8.97(-2) & 8.28(-2) \\
Time to Death with Tumor - Weibull Time Component & 4.00(-1) & 2.15(-1) & 1.43(-1) \\
Unobservable Time to Tumor - Weibull Time Component & 3.78(-1) & 1.92(-1) & 1.32(-1) \\
Time to Death with Tumor - Nonparametric Time Component & 3.94(-1) & 2.11(-1) & 1.59(-1) \\
Unobservable Time to Tumor - Nonparametric Time Component & 4.21(-1) & 2.32(-1) & 1.85(-1) \\
\hline
\end{tabular}

\textsuperscript{a} Values in parentheses are powers of 10.
TABLE A.4

ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS
BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 4

TRUE VSD = 1.614(-3)a

Replicate 1

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td></td>
<td>6.81(-2)</td>
<td>1.42(-2)</td>
<td>1.17(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td></td>
<td>6.69(-2)</td>
<td>8.99(-3)</td>
<td>2.72(-3)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td></td>
<td>8.09(-2)</td>
<td>1.41(-2)</td>
<td>7.94(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td></td>
<td>6.61(-2)</td>
<td>8.53(-3)</td>
<td>2.74(-3)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td></td>
<td>6.72(-2)</td>
<td>8.87(-3)</td>
<td>2.90(-3)</td>
</tr>
</tbody>
</table>

Replicate 2

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td></td>
<td>1.70(-1)</td>
<td>6.91(-2)</td>
<td>6.57(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td></td>
<td>2.21(-1)</td>
<td>7.72(-2)</td>
<td>4.48(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td></td>
<td>2.11(-1)</td>
<td>7.17(-2)</td>
<td>5.05(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td></td>
<td>2.32(-1)</td>
<td>8.63(-2)</td>
<td>5.35(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td></td>
<td>2.29(-1)</td>
<td>8.16(-2)</td>
<td>5.04(-2)</td>
</tr>
</tbody>
</table>

a Values in parentheses are powers of 10.
TABLE A.5

ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS
BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 5

TRUE VSD = 5.220(-6)\(^a\)

Replicate 1

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td></td>
<td>5.17(-5)</td>
<td>3.85(-8)</td>
<td>9.22(-9)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td></td>
<td>6.82(-4)</td>
<td>2.74(-6)</td>
<td>1.21(-7)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td></td>
<td>5.17(-5)</td>
<td>3.85(-8)</td>
<td>9.22(-9)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td></td>
<td>7.32(-4)</td>
<td>3.71(-6)</td>
<td>1.01(-7)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td></td>
<td>7.51(-4)</td>
<td>3.79(-6)</td>
<td>1.05(-7)</td>
</tr>
</tbody>
</table>

Replicate 2

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td></td>
<td>1.47(-1)</td>
<td>2.89(-2)</td>
<td>1.64(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td></td>
<td>1.98(-1)</td>
<td>6.75(-2)</td>
<td>1.57(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td></td>
<td>1.55(-1)</td>
<td>3.17(-2)</td>
<td>1.31(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td></td>
<td>1.65(-1)</td>
<td>3.77(-2)</td>
<td>1.03(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td></td>
<td>1.67(-1)</td>
<td>3.87(-2)</td>
<td>1.86(-3)</td>
</tr>
</tbody>
</table>

\(^a\) Values in parentheses are powers of 10.
**TABLE A.6**

ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS
BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 6

TRUE VSD = 5.220(-6)\(^a\)

<table>
<thead>
<tr>
<th>Replicate 1</th>
<th>Dose Component</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time Strategy</strong></td>
<td><strong>Probit</strong></td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>5.17(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>7.00(-3)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>5.17(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>7.07(-3)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>7.00(-3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Replicate 2</th>
<th>Dose Component</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time Strategy</strong></td>
<td><strong>Probit</strong></td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>1.54(-1)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>1.79(-1)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>1.59(-1)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>1.67(-1)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>1.66(-1)</td>
</tr>
</tbody>
</table>

\(^a\) Values in parentheses are powers of 10.
TABLE A.7

ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS
BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 7

TRUE VSD = 5.220(-6)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>1.08(-3)</td>
<td>3.05(-5)</td>
<td>2.38(-5)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>2.80(-3)</td>
<td>4.60(-5)</td>
<td>6.01(-6)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>4.08(-3)</td>
<td>9.22(-5)</td>
<td>1.71(-5)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>2.55(-1)</td>
<td>9.27(-2)</td>
<td>5.13(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>2.94(-1)</td>
<td>1.10(-1)</td>
<td>6.63(-2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>1.06(-2)</td>
<td>8.65(-4)</td>
<td>6.70(-4)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>9.44(-3)</td>
<td>4.01(-4)</td>
<td>1.48(-4)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>1.02(-2)</td>
<td>5.28(-4)</td>
<td>2.70(-4)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>1.20(-2)</td>
<td>7.07(-4)</td>
<td>1.91(-4)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>1.24(-2)</td>
<td>6.62(-4)</td>
<td>1.85(-4)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Values in parentheses are powers of 10.


<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>3.92(-1)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>2.03(-1)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>3.36(-1)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>2.24(-1)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>2.39(-1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>7.85(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>2.47(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>1.56(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>3.16(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>2.75(-2)</td>
</tr>
</tbody>
</table>

Values in parentheses are powers of 10.

**TABLE A.8**

**ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 8**

**TRUE VSD = 5.220(-6)**
TABLE A.9

ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS
BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 9

TRUE VSD = 1.614(-3)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>4.89(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>1.35(-1)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>6.87(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>1.17(-1)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>1.13(-1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>8.22(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>8.05(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>7.68(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>7.90(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>7.93(-2)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Values in parentheses are powers of 10.
TABLE A.10

ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS
BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 10

TRUE VSD = 4.851(-6)\(^a\)

Replicate 1

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
<td>Logit</td>
<td>Weibull</td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>8.82(-3)</td>
<td>1.09(-3)</td>
<td>9.70(-4)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>1.59(-2)</td>
<td>1.32(-3)</td>
<td>6.22(-4)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>1.56(-2)</td>
<td>1.46(-3)</td>
<td>8.83(-4)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>1.80(-2)</td>
<td>1.69(-3)</td>
<td>6.10(-4)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>1.88(-2)</td>
<td>1.85(-3)</td>
<td>6.99(-4)</td>
</tr>
</tbody>
</table>

Replicate 2

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
<td>Logit</td>
<td>Weibull</td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>4.34(-2)</td>
<td>8.54(-3)</td>
<td>7.72(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>7.06(-2)</td>
<td>1.19(-2)</td>
<td>6.13(-3)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>5.01(-2)</td>
<td>7.42(-3)</td>
<td>5.35(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>7.53(-2)</td>
<td>1.34(-2)</td>
<td>5.63(-3)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>7.75(-2)</td>
<td>1.43(-2)</td>
<td>6.14(-3)</td>
</tr>
</tbody>
</table>

\(^a\) Values in parentheses are powers of 10.
TABLE A.11

ESTIMATED VIRTUALLY SAFE DOES FOR RISK OF 1/1,000,000 AT 900 DAYS BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 11

TRUE VSD = 1.305(-6)\(^a\)

Replicate 1

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>1.72(-9)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>5.99(-8)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>5.44(-8)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>3.67(-7)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>5.20(-7)</td>
</tr>
</tbody>
</table>

Replicate 2

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>1.81(-6)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>2.68(-1)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>3.14(-1)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>2.53(-1)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>2.56(-1)</td>
</tr>
</tbody>
</table>

\(^a\) Values in parentheses are powers of 10.
TABLE A.12

ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS
BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 12

TRUE VSD = 1.305(-6)\textsuperscript{a}

Replicate 1

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>0.00</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>1.75(-5)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>1.35(-11)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>2.87(-5)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>3.36(-6)</td>
</tr>
</tbody>
</table>

Replicate 2

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>8.58(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>7.04(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>8.74(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>7.61(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>7.62(-2)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Values in parentheses are powers of 10.
TABLE A.13

ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 13

TRUE VSD = 3.380(-2)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Replicate 1</th>
<th>Time Strategy</th>
<th>Dose Component</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quantal Response - Total No. of Animals</td>
<td>3.98(-1)</td>
<td>2.74(-1)</td>
<td>2.69(-1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>4.33(-1)</td>
<td>2.62(-1)</td>
<td>2.23(-1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>4.38(-1)</td>
<td>2.74(-1)</td>
<td>2.48(-1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>4.27(-1)</td>
<td>2.60(-1)</td>
<td>2.24(-1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>4.31(-1)</td>
<td>2.61(-1)</td>
<td>2.25(-1)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Replicate 2</th>
<th>Time Strategy</th>
<th>Dose Component</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quantal Response - Total No. of Animals</td>
<td>1.56(-1)</td>
<td>4.96(-2)</td>
<td>4.49(-2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>2.59(-1)</td>
<td>1.04(-1)</td>
<td>7.81(-2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>2.46(-1)</td>
<td>9.61(-2)</td>
<td>7.66(-2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>2.59(-1)</td>
<td>1.07(-1)</td>
<td>7.45(-2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>2.66(-1)</td>
<td>1.08(-1)</td>
<td>7.54(-2)</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Values in parentheses are powers of 10.
TABLE A.14

ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 14

TRUE VSD = 5.439(-6)\textsuperscript{a}

Replicate 1

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>6.22(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>2.24(-3)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>6.02(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>2.07(-3)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>2.26(-3)</td>
</tr>
</tbody>
</table>

Replicate 2

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>8.65(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>7.56(-3)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>9.13(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>6.02(-3)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>6.06(-3)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Values in parentheses are powers of 10.
### Table A.15

**Estimated Virtually Safe Doses for Risk of 1/1,000,000 at 900 Days by Dose Component and Time Endpoint Analysis - Experiment 15**

TRUE VSD = 2.947(-3)\(^a\)

#### Replicate 1

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td></td>
<td>1.50(-2)</td>
<td>1.09(-3)</td>
<td>6.23(-4)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td></td>
<td>1.67(-2)</td>
<td>1.15(-3)</td>
<td>2.08(-4)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td></td>
<td>1.60(-2)</td>
<td>1.11(-3)</td>
<td>5.13(-4)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td></td>
<td>1.60(-2)</td>
<td>1.05(-3)</td>
<td>2.61(-4)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td></td>
<td>1.60(-2)</td>
<td>1.00(-3)</td>
<td>2.48(-4)</td>
</tr>
</tbody>
</table>

#### Replicate 2

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td></td>
<td>2.27(-2)</td>
<td>3.51(-3)</td>
<td>3.09(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td></td>
<td>7.46(-3)</td>
<td>2.04(-4)</td>
<td>6.32(-5)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td></td>
<td>1.87(-2)</td>
<td>2.26(-3)</td>
<td>1.90(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td></td>
<td>7.30(-3)</td>
<td>1.98(-4)</td>
<td>3.96(-5)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td></td>
<td>7.66(-3)</td>
<td>2.14(-4)</td>
<td>4.44(-5)</td>
</tr>
</tbody>
</table>

\(^a\) Values in parentheses are powers of 10.
TABLE A.16

ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS
BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS – EXPERIMENT 16

TRUE VSD = 2.058(-2)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Replicate 1</th>
<th>Dose Component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
</tr>
<tr>
<td>Quantal Response – Total No. of Animals</td>
<td>7.23(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor – Weibull Time Component</td>
<td>1.81(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor – Weibull Time Component</td>
<td>1.05(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor – Nonparametric Time Component</td>
<td>1.34(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor – Nonparametric Time Component</td>
<td>1.36(-2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Replicate 2</th>
<th>Dose Component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
</tr>
<tr>
<td>Quantal Response – Total No. of Animals</td>
<td>9.38(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor – Weibull Time Component</td>
<td>1.20(-1)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor – Weibull Time Component</td>
<td>9.75(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor – Nonparametric Time Component</td>
<td>1.02(-1)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor – Nonparametric Time Component</td>
<td>1.04(-1)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Values in parentheses are powers of 10.
TABLE A.17

ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS
BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 17

TRUE VSD = 2.310(-3)\(^a\)

**Replicate 1**

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>2.38(-2)</td>
<td>3.86(-3)</td>
<td>2.90(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>2.48(-1)</td>
<td>1.13(-1)</td>
<td>3.56(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>1.82(-1)</td>
<td>4.84(-2)</td>
<td>2.20(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>1.97(-1)</td>
<td>5.70(-2)</td>
<td>2.73(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>2.01(-1)</td>
<td>5.98(-2)</td>
<td>2.96(-2)</td>
</tr>
</tbody>
</table>

**Replicate 2**

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>3.61(-3)</td>
<td>1.00(-4)</td>
<td>5.33(-5)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>1.06(-2)</td>
<td>6.06(-4)</td>
<td>5.61(-5)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>5.72(-3)</td>
<td>1.83(-4)</td>
<td>6.10(-5)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>9.79(-3)</td>
<td>4.51(-4)</td>
<td>6.09(-5)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>1.08(-2)</td>
<td>5.29(-4)</td>
<td>7.15(-5)</td>
</tr>
</tbody>
</table>

\(^a\) Values in parentheses are powers of 10.
TABLE A.13

ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 18

TRUE VSD = 3.201(-6)a

Replicate 1

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td></td>
<td>6.72(-2)</td>
<td>1.21(-2)</td>
<td>9.00(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td></td>
<td>8.63(-2)</td>
<td>1.81(-2)</td>
<td>6.12(-3)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td></td>
<td>8.47(-2)</td>
<td>1.63(-2)</td>
<td>8.54(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td></td>
<td>7.94(-2)</td>
<td>1.42(-2)</td>
<td>6.49(-3)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td></td>
<td>7.80(-2)</td>
<td>1.35(-2)</td>
<td>6.03(-3)</td>
</tr>
</tbody>
</table>

Replicate 2

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td></td>
<td>3.64(-2)</td>
<td>3.50(-3)</td>
<td>2.12(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td></td>
<td>5.16(-2)</td>
<td>7.72(-3)</td>
<td>1.37(-3)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td></td>
<td>4.57(-2)</td>
<td>4.75(-3)</td>
<td>2.03(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td></td>
<td>5.03(-2)</td>
<td>5.76(-3)</td>
<td>1.95(-3)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td></td>
<td>4.89(-2)</td>
<td>5.40(-3)</td>
<td>1.79(-3)</td>
</tr>
</tbody>
</table>

a Values in parentheses are powers of 10.
### TABLE A.19

ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS
BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 19

TRUE VSD = 1.305(-5)\(^a\)

#### Replicate 1

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td></td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td></td>
<td>2.09(-1)</td>
<td>6.93(-2)</td>
<td>3.18(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td></td>
<td>2.31(-1)</td>
<td>8.48(-2)</td>
<td>5.88(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td></td>
<td>2.11(-1)</td>
<td>7.03(-2)</td>
<td>4.74(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td></td>
<td>2.14(-1)</td>
<td>7.06(-2)</td>
<td>4.87(-2)</td>
</tr>
</tbody>
</table>

#### Replicate 2

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td></td>
<td>1.82(-2)</td>
<td>2.75(-3)</td>
<td>2.32(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td></td>
<td>1.58(-2)</td>
<td>1.08(-3)</td>
<td>3.11(-4)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td></td>
<td>1.75(-2)</td>
<td>1.54(-3)</td>
<td>7.61(-4)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td></td>
<td>1.83(-2)</td>
<td>1.54(-3)</td>
<td>5.29(-4)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td></td>
<td>1.79(-2)</td>
<td>1.44(-3)</td>
<td>4.75(-4)</td>
</tr>
</tbody>
</table>

\(^a\) Values in parenthesis are powers of 10.
TABLE A.20
ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS
BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 20

TRUE VSD = 5.220(-6)a

Replicate 1

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
<td>Logit</td>
<td>Weibull</td>
<td></td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>1.70(-2)</td>
<td>1.10(-3)</td>
<td>6.53(-4)</td>
<td></td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>3.23(-2)</td>
<td>3.28(-3)</td>
<td>5.91(-4)</td>
<td></td>
</tr>
<tr>
<td>Unobservables Time to Tumor - Weibull Time Component</td>
<td>2.20(-2)</td>
<td>1.51(-3)</td>
<td>7.25(-4)</td>
<td></td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>2.63(-2)</td>
<td>1.94(-3)</td>
<td>4.59(-4)</td>
<td></td>
</tr>
<tr>
<td>Unobservables Time to Tumor - Nonparametric Time Component</td>
<td>2.97(-2)</td>
<td>2.32(-3)</td>
<td>6.02(-4)</td>
<td></td>
</tr>
</tbody>
</table>

Replicate 2

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
<td>Logit</td>
<td>Weibull</td>
<td></td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>6.71(-3)</td>
<td>2.66(-4)</td>
<td>1.75(-4)</td>
<td></td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>4.02(-2)</td>
<td>4.47(-3)</td>
<td>1.28(-3)</td>
<td></td>
</tr>
<tr>
<td>Unobservables Time to Tumor - Weibull Time Component</td>
<td>1.40(-2)</td>
<td>7.54(-4)</td>
<td>3.96(-4)</td>
<td></td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>3.36(-2)</td>
<td>3.05(-3)</td>
<td>1.15(-3)</td>
<td></td>
</tr>
<tr>
<td>Unobservables Time to Tumor - Nonparametric Time Component</td>
<td>3.29(-2)</td>
<td>2.96(-3)</td>
<td>1.11(-3)</td>
<td></td>
</tr>
</tbody>
</table>

a Values in parentheses are powers of 10.
TABLE A.21

ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS
BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 21

TRUE VSD = 5.220(-6)a

Replicate 1

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
<td>Logit</td>
<td>Weibull</td>
</tr>
<tr>
<td>Total No. of Animals</td>
<td>4.57(-2)</td>
<td>5.75(-3)</td>
<td>3.93(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>4.00(-2)</td>
<td>3.80(-3)</td>
<td>1.02(-3)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>4.31(-2)</td>
<td>4.67(-3)</td>
<td>2.70(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>4.36(-2)</td>
<td>4.59(-3)</td>
<td>1.36(-3)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>3.90(-2)</td>
<td>3.56(-3)</td>
<td>9.66(-4)</td>
</tr>
</tbody>
</table>

Replicate 2

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
<td>Logit</td>
<td>Weibull</td>
</tr>
<tr>
<td>Total No. of Animals</td>
<td>2.36(-2)</td>
<td>1.90(-3)</td>
<td>1.29(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>6.62(-2)</td>
<td>1.07(-2)</td>
<td>2.28(-3)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>4.75(-2)</td>
<td>5.15(-3)</td>
<td>2.02(-3)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>6.16(-2)</td>
<td>8.03(-3)</td>
<td>2.93(-3)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>6.13(-2)</td>
<td>7.78(-3)</td>
<td>2.83(-3)</td>
</tr>
</tbody>
</table>

a Values in parentheses are powers of 10.
TABLE A.22

ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS
BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 22

TRUE VSD = 5.220(-6)\(^a\)

Replicate 1

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>9.84(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>1.13(-1)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>1.13(-1)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>9.83(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>1.01(-1)</td>
</tr>
</tbody>
</table>

Replicate 2

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probit</td>
</tr>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>7.23(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>8.83(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>8.69(-2)</td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>6.86(-2)</td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>7.23(-2)</td>
</tr>
</tbody>
</table>

\(^a\) Values in parentheses are powers of 10.
TABLE A.23

ESTIMATED VIRTUALLY SAFE DOSES FOR RISK OF 1/1,000,000 AT 900 DAYS
BY DOSE COMPONENT AND TIME ENDPOINT ANALYSIS - EXPERIMENT 23

TRUE VSD = 5.220(-6)\textsuperscript{a}

Replicate 1

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>1.08(-2)</td>
<td>6.87(-4)</td>
<td>4.96(-4)</td>
<td></td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>1.84(-2)</td>
<td>1.10(-3)</td>
<td>1.88(-4)</td>
<td></td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>1.59(-2)</td>
<td>9.43(-4)</td>
<td>5.23(-4)</td>
<td></td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>1.85(-2)</td>
<td>1.05(-3)</td>
<td>1.75(-4)</td>
<td></td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>1.96(-2)</td>
<td>1.17(-3)</td>
<td>2.04(-4)</td>
<td></td>
</tr>
</tbody>
</table>

Replicate 2

<table>
<thead>
<tr>
<th>Time Strategy</th>
<th>Dose Component</th>
<th>Probit</th>
<th>Logit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantal Response - Total No. of Animals</td>
<td>2.12(-2)</td>
<td>2.37(-3)</td>
<td>2.03(-3)</td>
<td></td>
</tr>
<tr>
<td>Time to Death with Tumor - Weibull Time Component</td>
<td>3.96(-2)</td>
<td>4.26(-3)</td>
<td>2.05(-3)</td>
<td></td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Weibull Time Component</td>
<td>2.95(-2)</td>
<td>3.28(-3)</td>
<td>2.57(-3)</td>
<td></td>
</tr>
<tr>
<td>Time to Death with Tumor - Nonparametric Time Component</td>
<td>3.80(-2)</td>
<td>3.97(-3)</td>
<td>1.40(-3)</td>
<td></td>
</tr>
<tr>
<td>Unobservable Time to Tumor - Nonparametric Time Component</td>
<td>4.55(-2)</td>
<td>5.40(-3)</td>
<td>2.00(-3)</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Values in parentheses are powers of 10.