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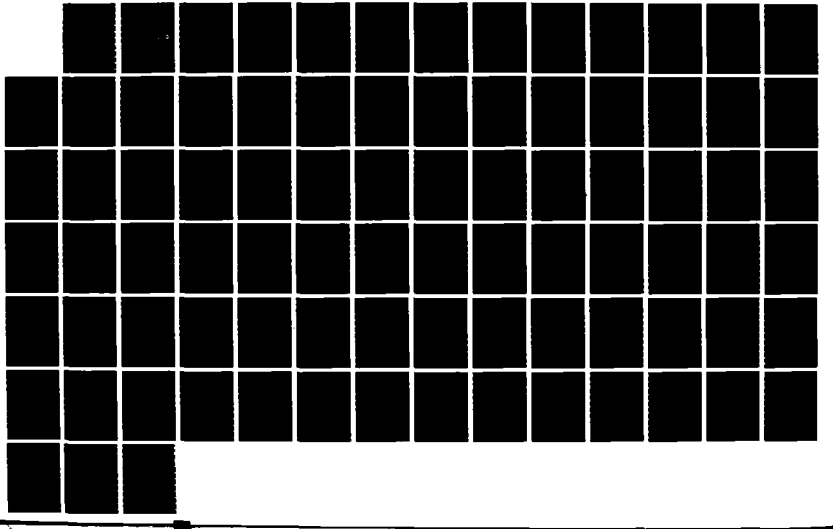

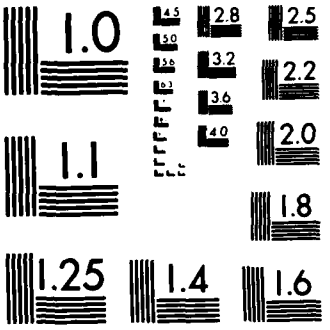

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ABSTRACT

Improving Risk Characterizations Based on Time to Response

(May 1986)

Ronald James Berdine, B. S., Iowa State University;

M. S., Stanford University

Chairman of Advisory Committee: Dr. Robert L. Sielken Jr.

One of the important aspects of quantitative cancer risk assessment is to model the frequency of a carcinogenic response as a function of exposure. Most of the current time-to-response modeling has been done using the "simple" model which does not include the effect of competing risks. As a result, the probabilities which are stated in terms of these models do not correspond to real world occurrences. Rather they correspond to a fictional world where no competing risks exist; that is, a world where only the risk being modeled is present. The cause-specific family of models is preferred since it incorporates the effect of competing risks. A method is presented for utilizing life table data and existing simple model maximum likelihood estimates to obtain cause-specific risk characterizations.

Representations for various risk characterizations (e.g., time-to-response probability, mean response free period, mean free dose, and virtually safe dose) under both models are compared. The results show that the simple model always overstates the effect of the carcinogen. The overstatement can easily be in the 20% - 200% range.

Two alternatives are introduced for modeling time to death from tumor when the cause of death is uncertain. One alternative is to model the time to death irrespective of cause. The other alternative focuses on the increase in the hazard rate due to the presence of a tumor. Thus, deaths caused by this increase in hazard rates are considered as being related to the introduction of the carcinogen. Both alternatives give risk characterizations which may be more relevant to cancer risk assessment.

IMPROVING RISK CHARACTERIZATIONS BASED ON TIME TO RESPONSE

Ronald J. Berdine, Major, USAF

Texas A&M University

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IMPROVING RISK CHARACTERIZATIONS

BASED ON TIME TO RESPONSE

A Dissertation

by

RONALD JAMES BERDINE

Submitted to the Graduate College of
Texas A&M University
in partial fulfillment of the requirement for the degree of

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IMPROVING RISK CHARACTERIZATIONS

BASED ON TIME TO RESPONSE

A Dissertation

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RONALD JAMES BERDINE

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This dissertation is dedicated to

Sharon, Michael and Matthew.

Without their love and support

this work would not have been possible.

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1. INTRODUCTION

One of the important aspects of quantitative cancer risk assessment is to model the frequency of a carcinogenic response as a function of exposure. The type of modeling has generally been of the form where the frequency of response is modeled as a function of dose alone as opposed to including both dose and time. Only recently have researchers attempted to use a time- to-response variable to model more completely the biological development of tumors and associated responses (e.g., Society of Toxicology ED_{01} Task Force (1981)). The response of concern could be death, death caused by tumor, death with tumor, tumor onset or any number of other possibilities. This paper is concerned with effects resulting in observable times to response. Methods for modeling unobservable times are given by McKnight and Crowley (1984) and Kalbfleisch, Krewski and Van Ryzin (1983).

Heretofore, risk characterizations based on time to response have been based on the simple model where the general form of the probability distribution for the time to a specified response is

$$P_s(t;d) = Pr(T \leq t;d)$$

with d being the dose and T being the time to the response of interest. However, $P_s(t;d)$ does not reflect the fact that a competing response might occur before the specified response of interest.

Two models which incorporate times to competing responses are the latent failure time model and the cause-specific model. In Section 2

Citations will follow the format of Biometrics.

these models are discussed and the cause-specific model is shown to be the model of choice. The general form for the cause-specific model is

$$P_{cs}(t,j;d) = Pr(T \leq t, J=j;d)$$

where there are p mutually exclusive and collectively exhaustive responses, J is the indicator of the one response observed, T is the time at which the observation is made and d is the dose.

In Section 3 the formulations of both the simple and cause-specific models and their likelihood functions are given. A relationship exists between the simple and cause-specific likelihood function that allows new risk characterizations to be calculated using results from an experiment where the simple model has been applied. Thus improved risk characterizations can easily be calculated.

Section 4 is concerned with the selection of hazard functions. In the cause-specific model a hazard function for each cause of an observation can be modeled. Most of the results developed do not depend on the parametric form of the specified response's hazard function; however, a very general form is used to generate examples and simulate data. The competing risks' hazard function can be derived from life table data. For many species such data are available.

Sections 5 and 6 are concerned with the impact on certain risk characterizations of using the cause-specific model instead of the simple model. The magnitude of this impact is measured in terms of relative bias. Relative bias is the fraction by which the simple risk characterization overstates or understates a corresponding cause-specific risk characterization. In certain cases, bounds are derived for the

relative bias as well as examples demonstrating the actual relative biases. The risk characterizations to be investigated are the probability that the specified response occurs before a time t, the mean response free period, the mean response free dose and the virtually safe dose. Implementation of the cause-specific model requires that the definitions of these risk characterizations be refined in order to incorporate the impact of competing risks.

In Section 7 two new options for obtaining risk characterizations are investigated. These options are for the special case where the original response of interest is death from tumor but the cause of death is uncertain. Both of the new options rely on a new definition for the response of interest. One option defines the specified response to be death from all causes combined while the second option defines the specified response to be death related to tumor as opposed to death from tumor.

Finally, Section 8 gives the conclusions that can be drawn from the results in Sections 2 through 7. A short discussion as to the utility of the procedures derived in this dissertation and their impact on future risk assessment procedures is also given.

2. REVIEW OF THE LITERATURE

The theory of competing risks was formalized by Chiang (1970) and Moeschberger and David (1971). Both used a model which is referred to as the latent failure time model. This model uses p times to failure, T_1, ..., T_p, each denoting the random "latent" time to failure by one of p competing risks. For each individual only the minimum of T_1, ..., T_p is observed. Thus, if $T = \min(T_1,\ldots,T_p)$, then probability statements giving the probability of survival until a time t are of the form

$$\Pr(T>t).$$

Chiang (1970) defines the crude survival function as

$$Q(t_1,\ldots,t_p) = \Pr(T_1>t_1,\ldots,T_p>t_p) ,$$

and the hazard function for each of the latent times to failure can be defined by

$$\lambda_j(t) = \lim_{\Delta t\to 0} \frac{\Pr(t<T_j\leq t+\Delta t \mid T>t)}{\Delta t}$$

$$= \frac{-d}{dt_j}\{\log[Q(t_1,\ldots,t_p)]\}\Big|_{t_1=\ldots=t_p=t} \quad \text{for } j = 1, \ldots, p. \quad (2.1)$$

Also defined are the marginal survival functions

$$Q_j(t_j) = \Pr(T_1>0,\ldots,T_j>t_j,\ldots,T_p>0) .$$

With the assumption that T_1, ..., T_p are independent random variables equation (2.1) becomes

$$\lambda_j(t) = \frac{-d}{dt_j} \{\log[Q_j(t_j)]\}\Big|_{t_j=t} \qquad \text{for } j = 1, \ldots, p.$$

This is the assumption used throughout the work by Chiang (1970) and Moeschberger and David (1971). In fact, Tsiatis (1975) showed that the latent failure time model is nonidentifiable unless the independence assumption is made. Examples where more than one model lead to the same set of hazard functions when the independence assumption is not assumed are found in both Tsiatis (1975) and Kalbfleisch and Prentice (1980).

Prentice et al. (1978) discussed the latent failure time model before developing the cause-specific model. They noted that besides the assumption of statistical independence there is another

> "...very strong assumption that the time to failure from cause j under one set of study conditions in which all ... causes are operative is precisely the same as under an altered set of conditions in which all causes except the j-th cause have been removed."

Thus, not only is statistical independence required for identifiabilty but a physical independence among causes of death is implied.

As an alternative, Prentice et al. (1978) formulate the cause-specific model. It does not require statistical independence nor does it imply any specified physical relationship among the causes of death. (The cause-specific model formulation is given in Section 3.2.) Moreover, as the likelihood was developed, they noticed that it could be partitioned into multiplicative factors, each depending on a set of mutually exclusive parameters. This property is important in the development of methods used in this dissertation and is discussed more fully in Section 3.

The choice of a parametric form for each cause-specific hazard function has received much attention in the literature. Not only must the resulting parametric model fit the data well, but it must provide an accurate representation of the carcinogenic effect at doses where no data may be available. Armitage (1982) discusses the implications that various parametric models have on risk characterizations in the low dose region. A detailed examination of the effect of the models on a specified risk characterization (i.e., a virtually safe dose which is discussed in Section 6) is given in Krewski et al. (1983). One model which allows considerable flexibility is given by Hartley and Sielken (1977) and Hartley, Tolley and Sielken (1981). This is the Hartley-Sielken model used in Section 4 when a parametric form for the hazard function for the response of interest is specified. A review of several parametric models is given in Kalbfleisch et al. (1983).

Some research has also been done on estimating tumor prevalence when the time to tumor onset is unobservable (e.g., Dinse (1985) and Dewanji and Kalbfleisch (1985)). McKnight and Crowley (1984) showed that the tumor incidence rate for unobservable time to tumor onset cannot be estimated unless interim sacrifices are made. All of the models used in the research cited here use an extension of the cause-specific model as opposed to the latent failure time model.

3. TIME-TO-RESPONSE MODELS

3.1 Simple Time-to-Response Models

Simple time-to-response models focus on the time to a specified response and consider the times to competing responses solely as censoring times and not part of the model. For example, let the specified response be time to death due to a tumor. If a subject dies from some cause other than tumor, then the time of death is treated as a censoring time for the time to death from tumor. In the simple model the probability refers to the anticipated time of death from tumor regardless of whether a competing cause of death might occur prior to that time and the death from tumor not be observed.

3.1.1 Model Formulation

Suppose an experiment is conducted where several doses of a carcinogen are administered to N test subjects. The observations are (T_i, δ_i, d_i), $i = 1, \ldots, N$ where, for the i-th subject

T_i = time to specified response or censoring time,

$$\delta_i = \begin{cases} 1 \text{ if the specified response is observed at } T_i \\ 0 \text{ if the specified response is censored,} \end{cases}$$

d_i = dose.

The hazard function $\lambda(t;d)$ is defined by

$$\lambda(t;d) = \lim_{\Delta t \to 0} \frac{Pr(t<T<t+\Delta t;d \mid T>t)}{\Delta t}$$

$$= \frac{-d}{dt} \{\log[Pr(T>t)]\} ,$$

so that

$$P_s(t;d) \equiv Pr(T \leq t;d) = 1 - \exp[-\int_0^t \lambda(u;d)\, du]$$

$$= \int_0^t \lambda(u;d) \exp[-\Lambda(u;d)]\, du \qquad (3.1)$$

where $\Lambda(u;d) = \int_0^u \lambda(v;d)\, dv$ is called the cumulative hazard function.

The model given by (3.1) will be referred to as the "simple" model herein. Each model is uniquely determined by its hazard function, or equivalently, its cumulative hazard function.

3.1.2 Likelihood

For the i-th individual, the observation can be either the response of interest or a censoring time such as sacrifice or death from some other cause. The possible contributions to the likelihood for the i-th individual are given in Table 1.

Table 1.

Simple model likelihood contributions

Likelihood contribution	Observation
$\lambda(t_i;d_i)\exp[-\Lambda(t_i;d_i)]$	Response of interest
$\exp[-\Lambda(t_i;d_i)]$	Censoring time

Let $\underset{\sim}{\theta}$ be the vector of parameters associated with $\lambda(t;d)$. Also, without loss of generality, assume that the first n_1 observations are the observed responses of interest and the last n_2 observations are the censored observations where $N = n_1 + n_2$. Then the likelihood function is given by

$$L(\underset{\sim}{\theta};\underset{\sim}{t}) = \prod_{i=1}^{n_1} \{\lambda(t_i;d_i) \exp[-\Lambda(t_i;d_i)]\} \prod_{i=n_1+1}^{N} \{\exp[-\Lambda(t_i;d_i)]\}$$

which can be written as

$$L(\underset{\sim}{\theta};\underset{\sim}{t}) = \prod_{i=1}^{N} \{[\lambda(t_i;d_i)]^{\delta_i} \exp[-\Lambda(t_i;d_i)]\} .$$

3.2 Cause-Specific Models

In the formulation of the simple models, the only random variable is the time to the specified response. Thus, $P_s(t;d)$ gives a hypothetical probability of the specified response by time t. The actual frequency of the specified response is never greater than $P_s(t;d)$ but can be less than $P_s(t;d)$ due to competing risk deaths prior to the time of the specified response. The cause-specific model explicitly includes death due to competing risks as well as the time to the specified response.

3.2.1 Model Formulation

For the i-th individual, let T_i be the time to one of p+1 mutually exclusive responses. Let J = 0, ..., p be the indicator of the one response which is observed. Let J = 0 correspond to a scheduled

sacrifice and let J = 1 correspond to the specified response. Often it is not necessary to distinguish among the competing risks, so that p = 2 with J = 2 corresponding to a death or censoring by any competing risk. Also, let d_i be the dose and let

$$\delta_{ij} = \begin{cases} 1 & \text{if the i-th individual's response is response j, } j = 1, \ldots, p \\ 0 & \text{otherwise .} \end{cases}$$

Define the cause-specific hazard function as

$$\lambda_j(t;d) = \lim_{\Delta t \to 0} \frac{Pr(t<T\leq t+\Delta t, J=j;d \mid T>t)}{\Delta t}$$

$$= \frac{-d}{dt} \{\log[Pr(T>t, J=j;d)]\} .$$

The cause-specific model is then given by

$$P_{cs}(t,j;d) = Pr(T\leq t, J=j;d) = \int_0^t \lambda_j(u;d) \exp[-\sum_{k=1}^{p} \Lambda_k(u;d)] \, du .$$

3.2.2 Likelihood

Kalbfleisch and Prentice (1980) give the development of the likelihood for the cause-specific model. The contributions are as follows (Table 2):

Table 2.

Cause-specific likelihood contributions

Likelihood contribution	Observation
$\lambda_j(t_i;d_i)\ \exp[-\sum_{k=1}^{p} \Lambda_k(t_i;d_i)]$	Response of type j j = 1, ..., p
$\exp[-\sum_{k=1}^{p} \Lambda_k(t_i;d_i)]$	Sacrifice (j = 0)

Notice that the i-th contribution can be written as

$$\prod_{j=1}^{p} \{[\lambda_j(t_i;d_i)]^{\delta_{ij}} \exp[-\Lambda_j(t_i;d_i)]\} \ .$$

Let $\underset{\sim}{\theta}_1$, ..., $\underset{\sim}{\theta}_p$ be the vectors of parameters associated with $\lambda_1(t;d)$, ..., $\lambda_p(t;d)$ respectively. Then the likelihood function is

$$L(\underset{\sim}{\theta}_1, \ldots, \underset{\sim}{\theta}_p;\underset{\sim}{t}) = \prod_{i=1}^{N} \{ \prod_{j=1}^{p} [\lambda_j(t_i;d_i)]^{\delta_{ij}} \exp[-\Lambda_j(t_i;d_i)]\}$$

$$= \prod_{j=1}^{p} \{ \prod_{i=1}^{N} [\lambda_j(t_i;d_i)]^{\delta_{ij}} \exp[-\Lambda_j(t_i;d_i)]\}$$

$$= \prod_{j=1}^{p} L_j(\underset{\sim}{\theta}_j;\underset{\sim}{t}) \qquad (3.2)$$

where $L_j(\underset{\sim}{\theta}_j;\underset{\sim}{t})$ is the same likelihood function from a simple model with the j-th response being the specified response of interest and all other responses are treated as censors.

3.2.3 Properties

The cause-specific model is an intuitively appealing model because of its ability to incorporate competing risks. It also has several desirable properties. Naturally, J and T are not necesssarily independent. The simple model is also a special case of the cause-specific model if p = 1. It is very general since the time T does not have to be represented as the minimum of p independent response times as in the latent failure time model.

The tractability of the cause-specific models is facilitated by two characteristics.

(i) In the likelihood function (3.2), the $\underset{\sim}{\theta}_1$, ..., $\underset{\sim}{\theta}_p$ appear in separate multiplicative terms.

(ii) Each of the multiplicative terms in the likelihood (3.2) has the same form as the likelihood corresponding to a simple model.

The maximum likelihood estimates of the cause-specific model parameters in $\lambda_1(t;d)$ are the same estimates that would be obtained using a simple model and treating individuals who succumb to a competing risk as censored. Therefore, if these simple model estimates are available and $\lambda_2(t;d)$ is known, the cause-specific probabilities and other associated risk characterizations can be calculated without making any alterations in the estimates of the parameters in $\lambda_1(t;d)$.

4. CHOICE OF HAZARD FUNCTIONS

4.1 A Form for the Hazard Function of the Specified Response

A parametric form for $\lambda_1(t;d)$ will be used whenever specific examples or simulations are required. Theoretically, any form of $\lambda_1(t;d)$ could be used. A special case of the Hartley-Sielken model will be used with $\Lambda_1(t;d) = H(t)g(d)$ and the dose function, $g(d)$, being a non-negative convex function of dose. In particular, a Weibull form for $H(t)$ will be used; namely $H(t) = \beta t^k$ and $g(d) = \alpha_0 + \alpha_1 d^s$ for $s \geq 1$.

4.2 A Form for the Hazard Function of the Competing Risks

The form for $\lambda_2(t;d)$ will be defined in terms of $S_2(t;d) = \exp[-\Lambda_2(t;d)]$. It is assumed that the hazard function for the competing risks is not dependent on dose. Therefore, the "d" notation will be suppressed from this point on when referring to $\lambda_2(t)$ and $S_2(t)$. Let $S_2(t)$ be a piecewise linear, continuous function not involving dose with

$$S_2(t) = a_i t + b_i \quad \text{for } t_i \leq t \leq t_{i+1}, \quad i = 0, \ldots, m , \qquad (4.1)$$

$$\text{with } a_i \leq 0, \quad b_i > 0.$$

This implies

$$\Lambda_2(t) = -\log (a_i t + b_i) \quad \text{for } t_i \leq t \leq t_{i+1} , \; i = 0, \ldots, m .$$

If the time is scaled such that $t_{i+1} - t_i = 1$, then $a_i = S_2(t_{i+1}) - S_2(t_i)$. The hazard function, $\lambda_2(t)$, can then be expressed as

$$\lambda_2(t) = \frac{d}{dt}[\Lambda_2(t)] = \frac{-a_i}{a_i t + b_i}$$

$$= -\frac{[S_2(t_{i+1}) - S_2(t_i)]}{S_2(t)}, \quad t_i < t \leq t_{i+1}, \; i = 0, \ldots, m.$$

In this formulation, there are $m + 1$ equally spaced points in time where the number of survivors is available.

This form for $\lambda_2(t)$ is convenient when life table data are available. This may often be the case since many experiments have control groups of the species under investigation. These groups are subjected to either none of the carcinogen or the background level of the carcinogen. The observed hazard rate in these groups will be a good approximation for $\lambda_2(t)$ provided that the background contribution of $\lambda_1(t;d)$ is small as will often be the case.

The specific examples used throughout this dissertation use human life table data to obtain $\lambda_2(t)$. The data are from Table 6.2 of Vital Statistics of the United States (National Center for Health Statistics (1984)). The contribution of $\lambda_1(t;d)$ to these mortality data is assumed to be negligible.

The cause-specific probability of succumbing to cause J = 1 before time t is given by

$$P_{cs}(t,1;d) = \int_0^t \lambda_1(u;d) \exp[-\Lambda_1(u;d) - \Lambda_2(u)] \, du ,$$

or equivalently, in a more convenient computational form,

$$P_{cs}(t,1;d) =$$

$$\sum_{i=0}^{m} \{S_2(t_i) \exp[-\Lambda_1(t_i;d)] - S_2(t_{i+1}) \exp[-\Lambda_1(t_{i+1};d)]$$

$$+ [S_2(t_{i+1}) - S_2(t_i)] \int_{t_i}^{t_{i+1}} \exp[-\Lambda_1(u;d)]\, du\} ,$$

with $t = t_{m+1}$. The computational form is obtained by substituting the piecewise continuous form for $\exp[-\Lambda_2(t)]$ from (4.1) and integrating by parts to account for $\lambda_1(t;d)$. Depending upon the parametric form for $\Lambda_1(t;d)$, the integration in the computational form may be done directly, or, a numerical integration routine may be used.

5. RISK CHARACTERIZATIONS INVOLVING TIME TO RESPONSE

In this section risk characterizations obtained from a simple model will be compared to improved characterizations obtained from the cause-specific model. Two risk characterizations involving the time to response are considered; namely, the probability that the time to the response precedes a specified time and the mean response free period in a specified period. The comparisons will be made in terms of relative bias.

5.1 Relative Bias

Relative bias refers to two deterministic representations of a non-random risk characteristic, one of which is assumed to be the true representation.

Definition 5.1 Let Φ_1 and Φ_2 be two representations of a risk characteristic and let Φ_2 be the true representation. The relative bias of Φ_1 with respect to Φ_2 is

$$RB(\Phi_1,\Phi_2) = (\Phi_1 - \Phi_2)/\Phi_2 = \Phi_1/\Phi_2 - 1 .$$

This is the fraction by which Φ_1 overstates or understates Φ_2. Often lower and upper bounds can be calculated for the relative biases.

5.2 Time-to-Response Probability

5.2.1 Bounds on Relative Bias

If the risk characteristic is the probability that the time to a specified response precedes a specified time t at a dose d, then the relative bias of $P_s(t;d)$ with respect to $P_{cs}(t,1;d)$ is

$$RB(P_s,P_{cs}) = \frac{P_s(t;d)}{P_{cs}(t,1;d)} - 1 .$$

In this case, upper and lower bounds on the relative bias may be calculated.

Theorem 5.1 If $\Lambda_1(t;d)$ and $\Lambda_2(t)$ are nondecreasing, nonnegative, continuous cumulative hazard functions such that $\Lambda_1(0;d) = \Lambda_2(0) = 0$, then for all $t \geq 0$

$$0 \leq RB(P_s,P_{cs}) \leq \exp[\Lambda_2(t)] - 1 .$$

Proof. Since $\Lambda_2(t)$ is nonnegative,

$$\exp[-\Lambda_2(t)] \leq 1 \quad \text{for all } t \geq 0 .$$

Therefore,

$$\begin{aligned} P_s(t;d) &= \int_0^t \lambda_1(u;d)\exp[-\Lambda_1(u;d)]\,du \\ &\geq \int_0^t \lambda_1(u;d)\exp[-\Lambda_1(u;d)]\exp[-\Lambda_2(u)]\,du \\ &= P_{cs}(t,1;d) . \end{aligned}$$

This implies $RB(P_s, P_{cs}) \geq 0$.

Also, the hypothesis on $\Lambda_2(t)$ implies that $\exp[-\Lambda_2(t)]$ is non-increasing in t. Therefore,

$$P_{cs}(t,1;d) = \int_0^t \lambda_1(u;d)\exp[-\Lambda_1(u;d)]\exp[-\Lambda_2(u)]\, du$$

$$\geq \exp[-\Lambda_2(t)] \int_0^t \lambda_1(u;d)\exp[-\Lambda_1(u;d)]\, du$$

$$= \exp[-\Lambda_2(t)]\, P_s(t;d) .$$

This implies that

$$\frac{P_s(t;d)}{P_{cs}(t,1;d)} \leq \exp[\Lambda_2(t)] ,$$

and the result follows.

The conclusion from Theorem 5.1 is that the simple model inflates the probability of the time to the specified response preceding t relative to the cause-specific probability. This is true not only for the actual probabilities but also for the estimated probabilities. This is because $\hat{\Lambda}_1(t;d)$ from the simple model is the same as $\hat{\Lambda}_1(t;d)$ from the cause-specific model as shown in Section 3. Thus, the proof is the same with the true cumulative hazard functions replaced by the estimated cumulative hazard functions.

5.2.2 Attaining the Upper Bound

The attainability of the upper bound on the relative bias will be discussed in terms of $\Lambda_1(t;d)$. That is, $\Lambda_2(t)$ is considered to be a

fixed function of t and the goal is to find $\Lambda_1(t;d)$ such that the upper bound in Theorem 5.1 is attained. The case where t = 0 is trivial since the lower and upper bounds are equal at t = 0. Is there a cumulative hazard function $\Lambda_1(t;d)$ such that the upper bound is attainable for some t > 0?

Consider the case where the carcinogen has no effect until time t_0. Here, t_0 is called the latency period. In this case, let the cumulative hazard function have the form

$$\Lambda_1(t;d) = \begin{cases} \beta(t-t_0)^k g(d) & \text{for } t \geq t_0 \\ 0 & \text{otherwise .} \end{cases}$$

Then let

$$F_1(t;d) = \begin{cases} 1 - \exp[-\beta(t-t_0)^k g(d)] & \text{for } t \geq t_0 \\ 0 & \text{otherwise .} \end{cases}$$

In this formulation, as β increases, the carcinogen's lethality increases. For all $t \geq t_0$,

$$P_{cs}(t,1;d) = \int_0^t \lambda_1(u;d)\exp[-\Lambda_1(u;d)]\exp[-\Lambda_2(u)]\, du$$

$$= \int_0^t \exp[-\Lambda_2(u)]\, dF_1(u;d) .$$

So,

$$RB(P_s,P_{cs}) = \frac{\int_0^t dF_1(u;d)}{\int_0^t \exp[-\Lambda_2(u)]\, dF_1(u;d)} - 1 .$$

Thus, as $\beta \to \infty$,

$$F_1(u;d) \to \begin{cases} 1 & \text{for } u \geq t_0 \\ 0 & \text{otherwise} , \end{cases}$$

the cdf of a point mass at t_0, and

$$\int_0^t \exp[-\Lambda_2(u)]dF_1(u;d) \to \exp[-\Lambda_2(t_0)] .$$

This implies

$$RB(P_s,P_{cs}) \to \exp[\Lambda_2(t_0)] - 1 \quad \text{as } \beta \to \infty .$$

Thus, the relative bias approaches the upper bound at $t = t_0$ as $\beta \to \infty$.

This example shows that for a special form of $\Lambda_1(t;d)$ the relative bias approaches the upper bound at some $t > 0$ in the limiting case. However, if the hypothesis of Theorem 5.1 is changed so that $\Lambda_2(t)$ is additionally required to be strictly increasing then a strict inequality holds for the upper bound. That is

$$RB(P_s,P_{cs}) < \exp[\Lambda_2(t)] - 1 .$$

5.2.3 Effect of Latency Period

Latency period affects relative bias also. To investigate this effect, relative biases were calculated for several latency periods. The models used were

$$P_s(t;d) = \int_{t_0}^t \lambda_1(u;d) \exp[-\Lambda_1(u;d)] \, du$$

and

$$P_{cs}(t,1;d) = \int_{t_0}^{t} \lambda_1(u;d)\exp[-\Lambda_1(u;d) - \Lambda_2(u)]\, du$$

where $\Lambda_1(t;d) = \beta(t-t_0)^k\, g(d)$ for an unspecified $g(d)$ and t_0 is the latency period. For each $t = 60, 65, 70, 75, 80, 85, 90, 95, 100$, all combinations of the parameter k and latency period t_0 were considered where

$$k = 3, 4, 5, 6$$

and

$$t_0 = 0, 10, 20, 30, 40, 50, 60\ .$$

These ranges for the parameters k and t_0 correspond to observed estimates of time-to-response effects.

The life table data were truncated at $t = 85$, so the values of $\Lambda_2(t)$ are extrapolated from $t = 85$ to $t = 100$. The extrapolation was done by fitting a Weibull cumulative hazard function, $\Lambda_2(t) = \gamma t^6$, to the life table data. A least squares fit gives $\hat{\gamma} = 0.3378\times10^{-11}$ so that for $t > 85$, $\Lambda_2(t) = \hat{\gamma}t^6$.

The values of $\beta\times g(d)$ were chosen such that $P_{cs}(75,1;d) = 10^{-6}$. This helps to make the relative biases more comparable across latency periods. Therefore, each t_0, k combination uses a different value of $\beta\times g(d)$.

Tables 3 through 6 give the relative biases. For example when $k = 3$, $t_0 = 60$ and $t = 100$ the relative bias of the simple model representation for the time-to-response probability with respect to the cause-specific model representation is 4.1023 which implies that $P_s(100;d)$ is 5.1023 times greater than $P_{cs}(100,1;d)$, i.e., 5.1023 times

Table 3

Relative bias of time-to-response probability for various latency periods with k = 3

	t_0							
t	0	10	20	30	40	50	60	upper bound
60	0.0901	0.0987	0.1093	0.1227	0.1405	0.1650		0.1990
65	0.1206	0.1327	0.1477	0.1668	0.1922	0.2268	0.2735	0.3062
70	0.1647	0.1820	0.2035	0.2310	0.2671	0.3159	0.3829	0.4742
75	0.2278	0.2527	0.2837	0.3234	0.3756	0.4461	0.5431	0.7719
80	0.3198	0.3566	0.4028	0.4623	0.5414	0.6497	0.8029	1.3875
85	0.4525	0.5080	0.5785	0.6708	0.7957	0.9712	1.2288	2.7151
90	0.6275	0.7098	0.8157	0.9565	1.1505	1.4296	1.8504	5.0207
95	0.8498	0.9694	1.1258	1.3374	1.6358	2.0776	2.7687	10.9788
100	1.1210	1.2907	1.5161	1.8276	2.2787	2.9698	4.1023	28.3121

Table 4

Relative bias of time-to-response probability for various latency periods with k = 4

	t_0							
t	0	10	20	30	40	50	60	upper bound
60	0.1017	0.1103	0.1206	0.1334	0.1497	0.1710		0.1990
65	0.1387	0.1511	0.1662	0.1850	0.2089	0.2400	0.2812	0.3062
70	0.1931	0.2113	0.2335	0.2611	0.2960	0.3410	0.3992	0.4742
75	0.2722	0.2992	0.3322	0.3732	0.4252	0.4923	0.5798	0.7719
80	0.3910	0.4324	0.4835	0.5477	0.6301	0.7385	0.8849	1.3875
85	0.5687	0.6344	0.7166	0.8218	0.9601	1.1473	1.4100	2.7151
90	0.8123	0.9149	1.0451	1.2150	1.4431	1.7592	2.2119	5.0207
95	1.1368	1.2947	1.4991	1.7719	2.1482	2.6872	3.4888	10.9788
100	1.5542	1.7926	2.1082	2.5407	3.1577	4.0797	5.5266	28.3121

Table 5

Relative bias of time-to-response probability for various latency periods with k = 5

	t_0							
t	0	10	20	30	40	50	60	upper bound
60	0.1109	0.1193	0.1293	0.1414	0.1564	0.1751		0.1990
65	0.1534	0.1659	0.1808	0.1989	0.2213	0.2498	0.2852	0.3062
70	0.2166	0.2352	0.2575	0.2846	0.3178	0.3591	0.4105	0.4742
75	0.3099	0.3381	0.3719	0.4130	0.4636	0.5267	0.6061	0.7719
80	0.4533	0.4979	0.5520	0.6185	0.7018	0.8080	0.9466	1.3875
85	0.6749	0.7486	0.8395	0.9536	1.1002	1.2930	1.5536	2.7151
90	0.9891	1.1092	1.2598	1.4528	1.7057	2.0453	2.5098	5.0207
95	1.4259	1.6204	1.8697	2.1973	2.6395	3.2531	4.1241	10.9788
100	2.0164	2.3275	2.7369	3.2921	4.0709	5.2036	6.9065	28.3121

Table 6

Relative bias of time-to-response probability for various latency periods with k = 6

	t_0							
t	0	10	20	30	40	50	60	upper bound
60	0.1184	0.1266	0.1362	0.1476	0.1614	0.1782		0.1990
65	0.1656	0.1780	0.1925	0.2099	0.2308	0.2565	0.2881	0.3062
70	0.2364	0.2551	0.2772	0.3034	0.3349	0.3729	0.4188	0.4742
75	0.3422	0.3710	0.4050	0.4455	0.4942	0.5535	0.6261	0.7719
80	0.5084	0.5551	0.6108	0.6783	0.7609	0.8639	0.9948	1.3875
85	0.7723	0.8522	0.9495	1.0697	1.2211	1.4154	1.6701	2.7151
90	1.1576	1.2927	1.4600	1.6708	1.9411	2.2935	2.7566	5.0207
95	1.7146	1.9433	2.2333	2.6084	3.1039	3.7712	4.6792	10.9788
100	2.5035	2.8892	3.3929	4.0677	4.9969	6.3113	8.2089	28.3121

greater than the actual probability of observing the specified response when there are competing risks. Tables 3 through 6 show the increase in relative bias as the latency period increases, as k increases, and as t increases. For example, the relative bias for $t_0 = 40$ and $k = 5$ increases from 0.1564 for $t = 60$ to 4.0709 for $t = 100$. For fixed t_0 and t, say 40 and 75 respectively, the relative bias increases from 0.3756 for $k = 3$ to 0.4942 for $k = 6$. Similarly, for $k = 5$ and $t = 75$ the relative bias increases from 0.3099 for $t_0 = 0$ to 0.6061 for $t_0 = 60$.

5.2.4 Fitting a Simple Model Without a Latency Period to Data from a Cause-Specific Model with a Latency Period

The relative biases given previously were calculated using the simple hazard function parameters. Since the factor $L_1(\underset{\sim}{\theta},\underset{\sim}{t})$ in the likelihood associated with the cause-specific model has the same form as the likelihood associated with the simple model, the maximum likelihood estimates, $\hat{\underset{\sim}{\theta}}$, are the same under both models. Hence Tables 3 through 6 also give the relative bias of the estimated simple model relative to the estimated cause-specific model. However, if data are from a cause-specific model with the cumulative hazard function for the specified response given by

$$\Lambda_1(t;d) = \begin{cases} \beta(t-t_0)^k g(d) & \text{for } t \geq t_0 \\ 0 & \text{otherwise} , \end{cases}$$

and these data are fit by a simple model with

$$\Lambda_1^*(t;d) = \beta^* t^{k^*} g(d) ,$$

then the likelihoods do not have the same form.

A small Monte Carlo study was conducted to obtain estimates of the relative biases associated with not only using simple models but also omitting the latency period. In this study the probability of the specified response occurring before time t would be of the order 10^{-6} if the dose levels of primary concern were used. This would require that the number of simulations be very large in order to insure that at least a few specified responses occurred. To alleviate this problem, the study was conducted using doses high enough to give moderate to large percentages of the outcomes being the specified response. The estimated probabilities were then extrapolated down to the low dose region. The simulation procedure is as follows:

The experimental data were generated using

$$P_{cs}(t,1;d) = \int_{t_0}^{t} \lambda_1(u;d)\exp[-\Lambda_1(u;d) - \Lambda_2(u)]\, du$$

with

$$\Lambda_1(t;d) = \beta(t-t_0)^k g(d) , \quad t \geq t_0 \text{ and } t_0 = 40 .$$

Also, let

$$P_s(t;d) = \int_0^t \lambda^*(u;d)\exp[-\Lambda_1^*(u;d)]\, du$$

with

$$\Lambda_1^*(t;d) = \beta^* t^{k^*} g(d) .$$

The dose function, g(d), was not specified; however, it was assumed that at the dose level d_0 where the estimated relative bias was to be computed, $g(d_0) = 1$ and $P_{cs}(75,1;d_0) = 10^{-6}$. This implied a value for β. The experimental data were simulated with 1000 observations at each of $d_1, \ldots, d_5$ where

$$P_{cs}(t_{max},1;d_i) = f_i \tag{5.1}$$

with $f_1 = 0.3$, $f_2 = 0.4$, $f_3 = 0.5$, $f_4 = 0.6$, $f_5 = 0.7$ and $t_{max} = 125$ corresponding to a maximum possible lifetime. Equation (5.1) implied the value of $g(d_i)$.

For each of 300 sets of experimental data, the maximum likelihood estimates $\hat{\beta}^*$, and $\hat{k}^*$ were determined as well as $RB(\hat{P}_s,P_{cs})$. Tables 7 through 10 give the sample means of the $RB(\hat{P}_s,P_{cs})$'s. The variances are not given in the tables but they were small. Several 95% confidence intervals were constructed and resulted in interval half-widths which were about 2% of the relative bias estimates. The last column in each of these tables is the corresponding column from Tables 3 through 6 with $t_0 = 40$. This last column shows the actual relative bias of the simple model with latency period relative to the cause-specific model.

Tables 7 through 10 show that the effect of not including a latency period in a simple model when the underlying cause-specific model has a latency period usually increases the relative bias, especially for larger k. The difference is not so great for the middle values of t, say t = 75 or 80, as it is for smaller or larger values of t. For example, for $k = 5$ and $f_3 = 0.5$ the relative bias without a latency period is 0.3684

Table 7

Relative bias of time-to-response probability for $k = 3$ and $t_0 = 40$.

t	Estimated relative bias of the simple model without a latency period					Known relative bias of the simple model with a latency period
	$f_1 = 0.3$	$f_2 = 0.4$	$f_3 = 0.5$	$f_4 = 0.6$	$f_5 = 0.7$	
60	0.2755	0.2257	0.1782	0.1197	0.0671	0.1405
65	0.1553	0.1263	0.1035	0.7447	0.0616	0.1922
70	0.1570	0.1429	0.1397	0.1350	0.1595	0.2671
75	0.2458	0.2457	0.2628	0.2842	0.3533	0.3756
80	0.4306	0.4467	0.4894	0.5446	0.6756	0.5414
85	0.7456	0.7840	0.8634	0.9683	1.1941	0.7957
90	1.2218	1.2932	1.4282	1.6098	1.9848	1.1505
95	1.9231	2.0453	2.2663	2.5687	3.1816	1.6358
100	2.9295	3.1299	3.4842	3.9761	4.9663	2.2787

Table 8

Relative bias of time-to-response probability for $k = 4$ and $t_0 = 40$.

t	Estimated relative bias of the simple model without a latency period					Known relative bias of the simple model with a latency period
	$f_1 = 0.3$	$f_2 = 0.4$	$f_3 = 0.5$	$f_4 = 0.6$	$f_5 = 0.7$	
60	0.5602	0.4642	0.3714	0.2663	0.1666	0.1497
65	0.3068	0.2515	0.2034	0.1491	0.1132	0.2089
70	0.2515	0.2211	0.2031	0.1850	0.2025	0.2960
75	0.3194	0.3097	0.3200	0.3382	0.4179	0.4252
80	0.5154	0.5276	0.5727	0.6381	0.8071	0.6301
85	0.8848	0.9297	1.0267	1.1652	1.4807	0.9601
90	1.4835	1.5784	1.7595	2.0193	2.5848	1.4431
95	2.4334	2.6116	2.9347	3.4034	4.4075	2.1482
100	3.9150	4.2345	4.8000	5.6312	7.4077	3.1577

Table 9

Relative bias of time-to-response probability for k = 5 and t_0 = 40.

t	Estimated relative bias of the simple model without a latency period					Known relative bias of the simple model with a latency period
	f_1 = 0.3	f_2 = 0.4	f_3 = 0.5	f_4 = 0.6	f_5 = 0.7	
60	0.8866	0.7307	0.5867	0.4250	0.2572	0.1564
65	0.4644	0.3818	0.3047	0.2236	0.1556	0.2213
70	0.3428	0.3002	0.2616	0.2316	0.2388	0.3178
75	0.3867	0.3750	0.3684	0.3866	0.4792	0.4636
80	0.5899	0.6117	0.6423	0.7230	0.9422	0.7018
85	1.0133	1.0832	1.1704	1.3525	1.7929	1.1002
90	1.7357	1.8855	2.0696	2.4312	3.2775	1.7057
95	2.9572	3.2497	3.6106	4.3057	5.9278	2.6395
100	5.0116	5.5661	6.2578	7.5852	10.7137	4.0709

Table 10

Relative bias of time-to-response probability for k = 6 and t_0 = 40.

t	Estimated relative bias of the simple model without a latency period					Known relative bias of the simple model with a latency period
	f_1 = 0.3	f_2 = 0.4	f_3 = 0.5	f_4 = 0.6	f_5 = 0.7	
60	1.2522	1.0328	0.7871	0.5755	0.3529	0.1614
65	0.6233	0.5105	0.3856	0.2851	0.1950	0.2308
70	0.4269	0.3656	0.3029	0.2665	0.2677	0.3349
75	0.4436	0.4180	0.4032	0.4250	0.5275	0.4942
80	0.6513	0.6619	0.7017	0.8002	1.0575	0.7609
85	1.1220	1.1847	1.3100	1.5391	2.0820	1.2211
90	1.9608	2.1141	2.3937	2.8675	3.9685	1.9411
95	3.4585	3.7847	4.3654	5.3269	7.5760	3.1039
100	6.1521	6.8226	8.0128	9.9777	14.6566	4.9969

for t = 75 (compared to 0.4636 with a latency period), but 0.5878 for t = 60 compared to 0.1564) and 6.2578 for t = 100 (compared to 4.0709). The relative biases for the simple model without a latency period tend to decrease as the values of f_i increase for smaller t but the relative biases increase as the values of f_i increase for larger t.

5.3 Mean Response Free Period

5.3.1 New Definitions

Mean response free period was introduced as a risk characterization by the Society of Toxicology ED_{01} Task Force (1981). It is defined as follows:

Definition 5.2 The mean response free period, MFP(t;d), is the expected time at dose d without a specified response in the first t units of time. Analytically,

$$MFP(t;d) = t - \int_0^t (t-u) \left[\frac{dP(T;d)}{dt}\right]_{T=u} du \ .$$

Using the simple model, this becomes

$$MFP_s(t;d) = t - \int_0^t (t-u)\lambda_1(u;d)\exp[-\Lambda_1(u;d)] \, du \ . \qquad (5.2)$$

The concept of a mean response free period must be refined to incorporate the multiple possible responses in the cause-specific model.

Definition 5.3 The total mean response free period under the cause-specific model is

$$MFP_{cs}(t;d) = t - \int_0^t (t-u)(\lambda_1(u;d)+\lambda_2(u))\exp[-\Lambda_1(u;d)-\Lambda_2(u)]\,du.$$

This is the expected time without a response due to cause 1 or 2 in the first t units of time at dose d. It is also possible to define mean response free periods associated with each cause.

Definition 5.4 The cause-specific mean response free period associated with cause j is the expected time without a response due to cause j in the first t units of time at dose d. Analytically,

$$MFP_{cs}(t,j;d) = t - \int_0^t (t-u)\lambda_j(u;d)\exp[-\Lambda_1(u;d)-\Lambda_2(u)]\,du\ .$$

The relationship among the mean response free periods under the cause-specific model is

$$MFP_{cs}(t;d) = MFP_{cs}(t,1;d) + MFP_{cs}(t,2;d) - t\ .$$

Since the simple model attempts to model the probability of the specified response, comparisons will be made between $MFP_s(t;d)$ and $MFP_{cs}(t,1;d)$ and measured in terms of relative bias.

5.3.2 Bounds on Relative Bias

From Definition 5.1, the relative bias of the simple mean response free period, equation (5.2), with respect to the cause-specific mean response free period due to cause 1, Definition 5.4, is

$$RB(MFP_s(t;d),MFP_{cs}(t,1;d)) = \frac{MFP_s(t;d)}{MFP_{cs}(t,1;d)} - 1\ .$$

In Section 5.2.1, it was shown that the simple model overstates the probability of a specified response before time t. Therefore, it follows that the simple model should understate the mean response free period associated with cause 1. The following theorem verifies this conjecture.

Theorem 5.2 If $\Lambda_1(t;d)$ and $\Lambda_2(t)$ are nondecreasing, nonnegative cumulative hazard functions such that $\Lambda_1(0;d) = \Lambda_2(0) = 0$. Then for all $t \geq 0$,

$$-1 \leq RB(MFP_s(t;d), MFP_{cs}(t,1;d)) \leq 0 .$$

Proof: Since $\Lambda_2(t)$ is nondecreasing in t,

$$\int_0^t (t-u)\lambda_1(u;d)\exp[-\Lambda_1(u;d)]\, du$$

$$\geq \int_0^t (t-u)\lambda_1(u;d)\exp[-\Lambda_1(u;d)]\exp[-\Lambda_2(u)]\, du ,$$

so that

$$MFP_s(t;d) \leq MFP_{cs}(t,1;d) .$$

This implies

$$RB(MFP_s(t;d), MFP_{cs}(t,1;d)) \leq 0 .$$

Also, $MFP_{cs}(t,1;d)$ may be written as

$$MFP_{cs}(t,1;d) = t[1 - P_{cs}(t,1;d)]$$

$$+ \int_0^t u \times \lambda_j(u;d)\exp[-\Lambda_1(u;d) - \Lambda_2(u)]\, du$$

$$\geq 0$$

since both terms are nonnegative. Similarly $MFP_s(t;d) \geq 0$. Therefore,

$$RB(MFP_s(t;d), MFP_{cs}(t,1;d)) \geq -1 .$$

5.3.3 Examples

Some examples are presented to illustrate the magnitude of the relative bias of the simple mean response free period with respect to the total mean response free period under the cause-specific model. Using the hazard function for the competing risk, described in Section 4, computational forms for $MFP_s(t;d)$, $MFP_{cs}(t;d)$, $MFP_{cs}(t,1;d)$, $MFP_{cs}(t,2;d)$ and $MFP_s(t;d)$ can be obtained in a straightforward manner sometimes including one or two integrations-by-parts. They are

$$MFP_{cs}(t;d) = t - t \sum_{i=0}^{m} \{S_2(t_i)\exp[-\Lambda_1(t_i;d)] - S_2(t_{i+1})\exp[-\Lambda_1(t_{i+1};d)]\}$$

$$+ \sum_{i=0}^{m} \{t_i S_2(t_i)\exp[-\Lambda_1(t_i;d)] - t_{i+1} S_2(t_{i+1})\exp[-\Lambda_1(t_{i+1};d)]\}$$

$$+ \sum_{i=0}^{m} \{a_i \int_{t_i}^{t_{i+1}} u \times \exp[-\Lambda_1(u;d)]\, du\}$$

$$+ \sum_{i=0}^{m} \{b_i \int_{t_i}^{t_{i+1}} \exp[-\Lambda_1(u;d)]\, du\} ,$$

$$MFP_{cs}(t,2;d) = t + t \sum_{i=0}^{m} \{a_i \int_{t_i}^{t_{i+1}} \exp[-\Lambda_1(u;d)]\, du\}$$

$$- \sum_{i=0}^{m} \{a_i \int_{t_i}^{t_{i+1}} u \times \exp[-\Lambda_1(u;d)]\, du\} ,$$

$$MFP_{cs}(t,1;d) = MFP_{cs}(t;d) - MFP_{cs}(t,2;d) + t ,$$

and

$$MFP_s(t;d) = t \times \exp[-\Lambda_1(t;d)]$$

$$+ \sum_{i=0}^{m} \{t_i \exp[-\Lambda_1(t_i;d)] - t_{i+1}\exp[-\Lambda_1(t_{i+1};d)]$$

$$\int_{t_i}^{t_{i+1}} \exp[-\Lambda_1(u;d)]\, du\} ,$$

with $t = t_{m+1}$.

These formulae are used to obtain the mean response free periods used to calculate $RB(MFP_s(t;d), MFP_{cs}(t,1;d))$ in Tables 11 through 14. The form used for the cumulative hazard function due to the cause of interest was the same as in Section 5.2, i.e., $\Lambda_1(t;d) = \beta t^k g(d)$. Tables 11 through 14 correspond to k = 3, 4, 5 and 6, respectively. Each column in these tables is calculated for a different $\beta \times g(d)$ where $\beta \times g(d)$ is chosen so that

$$P_{cs}(75,1;d) = f_0 \quad (= 10^{-6})$$

$$P_{cs}(t_{max},1;d) = f_i, \quad i = 1, \ldots, 5$$

where $f_1 = 0.3$, $f_2 = 0.4$, $f_3 = 0.5$, $f_4 = 0.6$, $f_5 = 0.7$ and $t_{max} = 125$.

Table 11

Relative bias for mean response free period with k = 3

t	$f_0 = 10^{-6}$	$f_1 = 0.3$	$f_2 = 0.4$	$f_3 = 0.5$	$f_4 = 0.6$	$f_5 = 0.7$
60	-0.8427×10^{-8}	-0.2232×10^{-2}	-0.3239×10^{-2}	-0.4468×10^{-2}	-0.6034×10^{-2}	-0.8171×10^{-2}
65	-0.1298×10^{-7}	-0.3392×10^{-2}	-0.4892×10^{-2}	-0.6696×10^{-2}	-0.8950×10^{-2}	-0.1194×10^{-1}
70	-0.2001×10^{-7}	-0.5142×10^{-2}	-0.7356×10^{-2}	-0.9966×10^{-2}	-0.1314×10^{-1}	-0.1721×10^{-1}
75	-0.3076×10^{-7}	-0.7739×10^{-2}	-0.1096×10^{-1}	-0.1466×10^{-1}	-0.1902×10^{-1}	-0.2433×10^{-1}
80	-0.4696×10^{-7}	-0.1151×10^{-1}	-0.1610×10^{-1}	-0.2122×10^{-1}	-0.2700×10^{-1}	-0.3363×10^{-1}
85	-0.7086×10^{-7}	-0.1685×10^{-1}	-0.2324×10^{-1}	-0.3010×10^{-1}	-0.3747×10^{-1}	-0.4529×10^{-1}
90	-0.1048×10^{-6}	-0.2408×10^{-1}	-0.3271×10^{-1}	-0.4157×10^{-1}	-0.5052×10^{-1}	-0.5918×10^{-1}
95	-0.1507×10^{-6}	-0.3338×10^{-1}	-0.4460×10^{-1}	-0.5559×10^{-1}	-0.6594×10^{-1}	-0.7488×10^{-1}
100	-0.2100×10^{-6}	-0.4476×10^{-1}	-0.5882×10^{-1}	-0.7188×10^{-1}	-0.8327×10^{-1}	-0.9182×10^{-1}

Table 12

Relative bias for mean response free period with k = 4

t	$f_0 = 10^{-6}$	$f_1 = 0.3$	$f_2 = 0.4$	$f_3 = 0.5$	$f_4 = 0.6$	$f_5 = 0.7$
60	-0.6494×10^{-8}	-0.1547×10^{-2}	-0.2284×10^{-2}	-0.3217×10^{-2}	-0.4461×10^{-2}	-0.6263×10^{-2}
65	-0.1106×10^{-7}	-0.2601×10^{-2}	-0.3814×10^{-2}	-0.5325×10^{-2}	-0.7297×10^{-2}	-0.1006×10^{-1}
70	-0.1857×10^{-7}	-0.4329×10^{-2}	-0.6290×10^{-2}	-0.8680×10^{-2}	-0.1170×10^{-1}	-0.1575×10^{-1}
75	-0.3146×10^{-7}	-0.7087×10^{-2}	-0.1018×10^{-1}	-0.1383×10^{-1}	-0.1827×10^{-1}	-0.2385×10^{-1}
80	-0.5199×10^{-7}	-0.1135×10^{-1}	-0.1606×10^{-1}	-0.2142×10^{-1}	-0.2758×10^{-1}	-0.3472×10^{-1}
85	-0.8433×10^{-7}	-0.1772×10^{-1}	-0.2461×10^{-1}	-0.3207×10^{-1}	-0.4007×10^{-1}	-0.4841×10^{-1}
90	-0.1330×10^{-6}	-0.2670×10^{-1}	-0.3631×10^{-1}	-0.4610×10^{-1}	-0.5574×10^{-1}	-0.6449×10^{-1}
95	-0.2024×10^{-6}	-0.3859×10^{-1}	-0.5127×10^{-1}	-0.6331×10^{-1}	-0.7402×10^{-1}	-0.8211×10^{-1}
100	-0.2964×10^{-6}	-0.5340×10^{-1}	-0.6924×10^{-1}	-0.8314×10^{-1}	-0.9405×10^{-1}	$-0.1004\times10^{+0}$

Table 13

Relative bias for mean response free period with k = 5

t	$f_0 = 10^{-6}$	$f_1 = 0.3$	$f_2 = 0.4$	$f_3 = 0.5$	$f_4 = 0.6$	$f_5 = 0.7$
60	-0.4980×10^{-8}	-0.1062×10^{-2}	-0.1602×10^{-2}	-0.2315×10^{-2}	-0.3317×10^{-2}	-0.4866×10^{-2}
65	-0.9342×10^{-8}	-0.1967×10^{-2}	-0.2947×10^{-2}	-0.4221×10^{-2}	-0.5971×10^{-2}	-0.8579×10^{-2}
70	-0.1733×10^{-7}	-0.3581×10^{-2}	-0.5313×10^{-2}	-0.7512×10^{-2}	-0.1043×10^{-1}	-0.1455×10^{-1}
75	-0.3154×10^{-7}	-0.6352×10^{-2}	-0.9299×10^{-2}	-0.1292×10^{-1}	-0.1749×10^{-1}	-0.2347×10^{-1}
80	-0.5616×10^{-7}	-0.1092×10^{-1}	-0.1570×10^{-1}	-0.2130×10^{-1}	-0.2793×10^{-1}	-0.3572×10^{-1}
85	-0.9751×10^{-7}	-0.1810×10^{-1}	-0.2543×10^{-1}	-0.3351×10^{-1}	-0.4222×10^{-1}	-0.5113×10^{-1}
90	-0.1634×10^{-6}	-0.2864×10^{-1}	-0.3915×10^{-1}	-0.4983×10^{-1}	-0.6011×10^{-1}	-0.6877×10^{-1}
95	-0.2624×10^{-6}	-0.4294×10^{-1}	-0.5691×10^{-1}	-0.6979×10^{-1}	-0.8053×10^{-1}	-0.8740×10^{-1}
100	-0.4030×10^{-6}	-0.6098×10^{-1}	-0.7817×10^{-1}	-0.9233×10^{-1}	$-0.1022\times10^{+0}$	$-0.1061\times10^{+0}$

Table 14

Relative bias for mean response free period with k = 6

t	$f_0 = 10^{-6}$	$f_1 = 0.3$	$f_2 = 0.4$	$f_3 = 0.5$	$f_4 = 0.6$	$f_5 = 0.7$
60	-0.3816×10^{-8}	-0.7248×10^{-3}	-0.1121×10^{-2}	-0.1669×10^{-2}	-0.2481×10^{-2}	-0.3825×10^{-2}
65	-0.7857×10^{-8}	-0.1475×10^{-2}	-0.2267×10^{-2}	-0.3345×10^{-2}	-0.4907×10^{-2}	-0.7389×10^{-2}
70	-0.1588×10^{-7}	-0.2929×10^{-2}	-0.4455×10^{-2}	-0.6484×10^{-2}	-0.9313×10^{-2}	-0.1354×10^{-1}
75	-0.3127×10^{-7}	-0.5615×10^{-2}	-0.8417×10^{-2}	-0.1200×10^{-1}	-0.1673×10^{-1}	-0.2318×10^{-1}
80	-0.5981×10^{-7}	-0.1033×10^{-1}	-0.1517×10^{-1}	-0.2104×10^{-1}	-0.2817×10^{-1}	-0.3669×10^{-1}
85	-0.1109×10^{-6}	-0.1815×10^{-1}	-0.2592×10^{-1}	-0.3463×10^{-1}	-0.4410×10^{-1}	-0.5349×10^{-1}
90	-0.1971×10^{-6}	-0.3009×10^{-1}	-0.4148×10^{-1}	-0.5303×10^{-1}	-0.6382×10^{-1}	-0.7213×10^{-1}
95	-0.3333×10^{-6}	-0.4666×10^{-1}	-0.6178×10^{-1}	-0.7528×10^{-1}	-0.8570×10^{-1}	-0.9111×10^{-1}
100	-0.5365×10^{-6}	-0.6770×10^{-1}	-0.8582×10^{-1}	-0.9972×10^{-1}	$-0.1081\times10^{+0}$	$-0.1096\times10^{+0}$

The resulting mean response free periods are not given in the tables but both the simple and cause-specific mean response free periods associated with f_0 were very close to the value for t. However, the mean response free periods decreased as f_i increased. For example, $MFP_{cs}(100;d) = 99.9999$ and $MFP_s(100;d) = 99.9999$ for $f_0 = 10^{-6}$ and $k = 3$; but $MFP_{cs}(100;d) = 78.3223$ and $MFP_s(100;d) = 72.6925$ for $f_3 = 0.5$ and $k = 3$.

Some of the conclusions that can be drawn from the tables are as follows:

(i) The magnitude (absolute value) of the relative bias increases as t increases.

(ii) For smaller values of t, the magnitude of the relative bias decreases as k increases, but for large t the magnitude increases as k increases.

(iii) The magnitude of the relative bias tends increases as the probability of a specified response over a lifetime increases.

In comparison to the relative biases in Tables 3 through 6 for the time-to-response probabilty, the relative biases in Tables 11 through 14 for the mean response free period are small. For example, if the probability of a specified response before time $t = 75$ is 10^{-6} then the relative bias in Table 4 for the time-to-response probability for $k = 4$, $t_0 = 40$ and $t = 75$ is 0.4252; but the relative bias in Table 12 for the mean response free period for $k = 4$, and $t = 75$ is only -0.3146×10^{-7}. Thus, $P_s(t;d)$ is 1.4252 times greater than $P_{cs}(t;d)$ but the mean response free periods are almost the same under both models.

6. RISK CHARACTERIZATIONS INVOLVING DOSE

In this section, as in Section 5, risk characterizations obtained from a simple model will be compared to corresponding risk characterizations obtained from a cause-specific model. Two risk characterizations involving dose are considered; namely, mean free dose and virtually safe dose. The comparisons will be made in terms of relative bias.

6.1 Mean Free Dose

6.1.1 Definition

The mean free dose was introduced by the Society of Toxicology ED_{01} Task Force (1981). It is interpreted as the dose which would result in a specified fractional reduction in the mean response free period.

Definition 6.1 The mean free dose at time t is the dose d which satisfies

$$\frac{MFP(t;d)}{MFP(t;0)} = 1 - \varepsilon \ ,$$

with $0 < \varepsilon < 1$ and ε being near 0. The mean free dose at time t is denoted by $MFD(t;\varepsilon)$.

This definition may be used with any of the mean response free periods defined in Section 5.3. The notation for a mean free dose will correspond to the notation used in Section 5.3 for mean response free period. For example, if Definition 6.1 uses $MFP_{cs}(t,1;d)$, then the notation for the corresponding mean free dose would be $MFD_{cs}(t,1;\varepsilon)$.

6.1.2 Approximations of Mean Free Dose

By assuming a fairly general form for $\Lambda_1(t;d)$, simple approximations are available for $MFD_{cs}(t,1;\varepsilon)$ and $MFD_s(t;\varepsilon)$. They can be derived as follows: Let

$$\Lambda_1(t;d) = (1 + d^r)\,\beta t^k \ .$$

Then $MFD_{cs}(t,1;\varepsilon)$ is the dose d that satisfies

$$MFP_{cs}(t,1;d) = MFP_{cs}(t,1;0) - \varepsilon \times MFP_{cs}(t,1;0) \ ,$$

with

$$MFP_{cs}(t,1;d) =$$

$$t - \int_0^t (t-u)(1+d^r)\beta k u^{k-1} \exp[-(1+d^r)\beta u^k - \Lambda_2(u)]\, du \ . \quad (6.1)$$

Using the approximation for small β, $\exp(-d^r \beta u^k) \doteq 1$, equation (6.1) becomes

$$MFP_{cs}(t,1;d) \doteq$$

$$t - \int_0^t (t-u)(1+d^r)\beta k u^{k-1} \exp[-\beta u^k - \Lambda_2(u)]\, du \ .$$

Thus $MFD_{cs}(t,1;\varepsilon)$ is approximately the dose d which satisfies

$$t - \int_0^t (t-u)(1+d^r)\beta k u^{k-1} \exp[-\beta u^k - \Lambda_2(u)]\, du$$

$$\doteq t - \int_0^t (t-u)\beta k u^{k-1} \exp[-\beta u^k - \Lambda_2(u)]\, du$$

$$- \varepsilon \times MFP_{cs}(t,1;0) \ ,$$

which can be rewritten as

$$(1+d^r) \int_0^t (t-u)\beta k u^{k-1} \exp[-\beta u^k - \Lambda_2(u)]\, du$$

$$\doteq \int_0^t (t-u)\beta k u^{k-1} \exp[-\beta u^k - \Lambda_2(u)]\, du$$

$$+ \varepsilon \times MFP_{cs}(t,1;0) \ .$$

Solving for the dose d the result is that

$$MFD_{cs}(t,1;\varepsilon) \doteq \left[\frac{\varepsilon \times MFP_{cs}(t,1;0)}{t - MFP_{cs}(t,1;0)} \right]^{1/r} . \tag{6.2}$$

A similar derivation for $MFD_s(t;\varepsilon)$ yields

$$MFD_s(t;\varepsilon) = \left[\frac{\varepsilon \times MFP_s(t;0)}{t - MFP_s(t;0)} \right]^{1/r} . \tag{6.3}$$

Tables 15 through 22 give examples of the mean free doses calculated from numerical search routines and the approximations (6.2) and (6.3). These mean free doses were calculated for t = 75 and ε's that correspond to losses of 1 hour, 1 day, 1 week and 1 month in a 75 year period. The values of r were r = 1 and r = 3 corresonding to linear and nonlinear dose functions, respectively.

Generally the approximations agree with the mean response free dose obtained by the numerical search technique to about three digits. However as the dose increases the approximation is not as good. For

Table 15

Approximations of mean free dose with k = 3 and linear dose function

	$MFD_s(t;\varepsilon)$		$MFD_{cs}(t,1;\varepsilon)$	
ε	Using Search Technique	Approximation	Using Search Technique	Approximation
1.52×10^{-6}	$0.4955\times10^{+1}$	$0.4955\times10^{+1}$	$0.5507\times10^{+1}$	$0.5505\times10^{+1}$
3.65×10^{-5}	$0.1189\times10^{+3}$	$0.1189\times10^{+3}$	$0.1322\times10^{+3}$	$0.1322\times10^{+3}$
2.55×10^{-4}	$0.8327\times10^{+3}$	$0.8325\times10^{+3}$	$0.9255\times10^{+3}$	$0.9252\times10^{+3}$
1.11×10^{-2}	$0.3624\times10^{+4}$	$0.3620\times10^{+4}$	$0.4028\times10^{+4}$	$0.4023\times10^{+4}$

Table 16

Approximations of mean free dose with k = 3 and nonlinear dose function

	$MFD_s(t;\varepsilon)$		$MFD_{cs}(t,1;\varepsilon)$	
ε	Using Search Technique	Approximation	Using Search Technique	Approximation
1.52×10^{-6}	$0.1705\times10^{+1}$	$0.1705\times10^{+1}$	$0.1766\times10^{+1}$	$0.1766\times10^{+1}$
3.65×10^{-5}	$0.4918\times10^{+1}$	$0.4918\times10^{+1}$	$0.5094\times10^{+1}$	$0.5094\times10^{+1}$
2.55×10^{-4}	$0.9408\times10^{+1}$	$0.9407\times10^{+1}$	$0.9745\times10^{+1}$	$0.9744\times10^{+1}$
1.11×10^{-2}	$0.1536\times10^{+2}$	$0.1535\times10^{+2}$	$0.1591\times10^{+2}$	$0.1590\times10^{+2}$

Table 17

Approximations of mean free dose with k = 4 and linear dose function

	$MFD_s(t;\varepsilon)$		$MFD_{cs}(t,1;\varepsilon)$	
ε	Using Search Technique	Approximation	Using Search Technique	Approximation
1.52×10^{-6}	$0.5978\times10^{+1}$	$0.5978\times10^{+1}$	$0.6821\times10^{+1}$	$0.6821\times10^{+1}$
3.65×10^{-5}	$0.1435\times10^{+3}$	$0.1435\times10^{+3}$	$0.1637\times10^{+3}$	$0.1637\times10^{+3}$
2.55×10^{-4}	$0.1005\times10^{+4}$	$0.1004\times10^{+4}$	$0.1146\times10^{+4}$	$0.1146\times10^{+4}$
1.11×10^{-2}	$0.4374\times10^{+4}$	$0.4367\times10^{+4}$	$0.4991\times10^{+4}$	$0.4983\times10^{+4}$

Table 18

Approximations of mean free dose with k = 4 and nonlinear dose function

	$MFD_s(t;\varepsilon)$		$MFD_{cs}(t,1;\varepsilon)$	
ε	Using Search Technique	Approximation	Using Search Technique	Approximation
1.52×10^{-6}	$0.1815\times10^{+1}$	$0.1815\times10^{+1}$	$0.1897\times10^{+1}$	$0.1897\times10^{+1}$
3.65×10^{-5}	$0.5235\times10^{+1}$	$0.5235\times10^{+1}$	$0.5471\times10^{+1}$	$0.5470\times10^{+1}$
2.55×10^{-4}	$0.1002\times10^{+2}$	$0.1001\times10^{+2}$	$0.1047\times10^{+2}$	$0.1046\times10^{+2}$
1.11×10^{-2}	$0.1635\times10^{+2}$	$0.1635\times10^{+2}$	$0.1709\times10^{+2}$	$0.1708\times10^{+2}$

Table 19

Approximations of mean free dose with k = 5 and linear dose function

	$MFD_S(t;\varepsilon)$		$MFD_{CS}(t,1;\varepsilon)$	
ε	Using Search Technique	Approximation	Using Search Technique	Approximation
1.52×10^{-6}	$0.6967\times10^{+1}$	$0.6967\times10^{+1}$	$0.8144\times10^{+1}$	$0.8144\times10^{+1}$
3.65×10^{-5}	$0.1672\times10^{+3}$	$0.1672\times10^{+3}$	$0.1955\times10^{+3}$	$0.1955\times10^{+3}$
2.55×10^{-4}	$0.1171\times10^{+4}$	$0.1171\times10^{+4}$	$0.1369\times10^{+4}$	$0.1368\times10^{+4}$
1.11×10^{-2}	$0.5099\times10^{+4}$	$0.5090\times10^{+4}$	$0.5961\times10^{+4}$	$0.5949\times10^{+4}$

Table 20

Approximations of mean free dose with k = 5 and nonlinear dose function

	$MFD_S(t;\varepsilon)$		$MFD_{CS}(t,1;\varepsilon)$	
ε	Using Search Technique	Approximation	Using Search Technique	Approximation
1.52×10^{-6}	$0.1910\times10^{+1}$	$0.1910\times10^{+1}$	$0.2012\times10^{+1}$	$0.2012\times10^{+1}$
3.65×10^{-5}	$0.5509\times10^{+1}$	$0.5509\times10^{+1}$	$0.5804\times10^{+1}$	$0.5803\times10^{+1}$
2.55×10^{-4}	$0.1054\times10^{+2}$	$0.1054\times10^{+2}$	$0.1110\times10^{+2}$	$0.1110\times10^{+2}$
1.11×10^{-2}	$0.1721\times10^{+2}$	$0.1720\times10^{+2}$	$0.1831\times10^{+2}$	$0.1812\times10^{+2}$

Table 21

Approximations of mean free dose with k = 6 and linear dose function

	$MFD_s(t;\varepsilon)$		$MFD_{cs}(t,1;\varepsilon)$	
ε	Using Search Technique	Approximation	Using Search Technique	Approximation
1.52×10^{-6}	$0.7932\times10^{+1}$	$0.7932\times10^{+1}$	$0.9478\times10^{+1}$	$0.9478\times10^{+1}$
3.65×10^{-5}	$0.1904\times10^{+3}$	$0.1904\times10^{+3}$	$0.2275\times10^{+3}$	$0.2275\times10^{+3}$
2.55×10^{-4}	$0.1333\times10^{+4}$	$0.1333\times10^{+4}$	$0.1593\times10^{+4}$	$0.1592\times10^{+4}$
1.11×10^{-2}	$0.5807\times10^{+4}$	$0.5795\times10^{+4}$	$0.6940\times10^{+4}$	$0.6924\times10^{+4}$

Table 22

Approximations of mean free dose with k = 6 and nonlinear dose function

	$MFD_s(t;\varepsilon)$		$MFD_{cs}(t,1;\varepsilon)$	
ε	Using Search Technique	Approximation	Using Search Technique	Approximation
1.52×10^{-6}	$0.1994\times10^{+1}$	$0.1994\times10^{+1}$	$0.2116\times10^{+1}$	$0.2116\times10^{+1}$
3.65×10^{-5}	$0.5753\times10^{+1}$	$0.5753\times10^{+1}$	$0.6105\times10^{+1}$	$0.6104\times10^{+1}$
2.55×10^{-4}	$0.1101\times10^{+2}$	$0.1100\times10^{+2}$	$0.1168\times10^{+2}$	$0.1168\times10^{+2}$
1.11×10^{-2}	$0.1797\times10^{+2}$	$0.1796\times10^{+2}$	$0.1907\times10^{+2}$	$0.1906\times10^{+2}$

example at $k = 4$ and $\varepsilon = 1.52\times10^{-6}$ with a linear dose function both the approximation and the search method yield a simple mean response free dose of $0.5978\times10^{+1}$ but at $\varepsilon = 1.11\times10^{-2}$ the approximation is $0.4367\times10^{+4}$ while the search technique gives a simple mean response free dose of $0.4374\times10^{+4}$. This is as expected since the approximation of $\exp(-d^{r}\beta u^{k}) \doteq 1$ is better for low doses.

For the same reason the approximation is not as good as k increases. This can be seen by comparing the approximation and search values at $\varepsilon = 1.11\times10^{-2}$ in Table 15 with the corresponding values in Table 21.

Also, the approximation is better for the nonlinear dose function. This is because the nonlinear dose function results in a lower mean response free dose which in turn makes the approximation $\exp(-d^{r}\beta u^{k}) \doteq 1$ better.

6.1.3 Relative Bias

The relative bias will depend upon which form of the mean free dose is considered. Since any change in the total mean response free period due to the introduction of a carcinogen would be of concern, the total mean free dose is explicitly considered in this subsection. The mean free doses are calculated from the simple mean response free period, equation (5.2), and the total mean response free period under the cause-specific model, Definition 5.3. The relative bias of simple mean free dose with respect to total mean free dose under the cause-specific model is

$$RB(MFD_s, MFD_{cs}) = \frac{MFD_s(t;\varepsilon)}{MFD_{cs}(t;\varepsilon)} - 1 \ .$$

The form of the specified response's cumulative hazard function used to calculate the mean free dose is

$$\Lambda_1(t;d) = (1 + d^r)\beta t^k \ , \qquad (6.4)$$

with r = 1 and r = 3 corresponding to linear and nonlinear dose functions, respectively. The value of β is such that $P_{cs}(75,1;0) = 10^{-6}$, and the mean free doses are calculated at t = 75. Tables 23 and 24 give the relative biases for the linear and nonlinear dose functions with k = 3, 4, 5 and 6. The same values of ε as those in Tables 15 through 22 were used to compute the relative biases.

Tables 23 and 24 show the following:

(i) All relative biases are negative, indicating that $MFD_s(t;\varepsilon)$ understates $MFD_{cs}(t;\varepsilon)$.

(ii) Relative biases are virtually unaffected by changes in ε. This is expected since ε cancels when the relative bias is calculated using the approximation.

(iii) Relative biases have greater absolute values as k increases.

(iv) The magnitude of the relative bias is greater when the dose function is linear than when it is nonlinear.

The effect of using the simple model instead of the true cause-specific model is larger when the dose function is linear. For k = 6 and a linear dose function the relative bias is -0.1925. This means that the

Table 23

Relative bias for mean free dose with linear dose function

	k			
ε	3	4	5	6
1.52×10^{-6}	-0.1301	-0.1551	-0.1755	-0.1925
3.65×10^{-5}	-0.1301	-0.1551	-0.1755	-0.1925
2.55×10^{-4}	-0.1302	-0.1552	-0.1756	-0.1925
1.11×10^{-2}	-0.1302	-0.1553	-0.1757	-0.1927

Table 24

Relative bias for mean free dose with nonlinear dose function

	k			
ε	3	4	5	6
1.52×10^{-6}	-0.04541	-0.05464	-0.06231	-0.06878
3.65×10^{-5}	-0.04541	-0.05465	-0.06231	-0.06878
2.55×10^{-4}	-0.04542	-0.05465	-0.06232	-0.06880
1.11×10^{-2}	-0.04544	-0.05469	-0.06238	-0.06887

$MFD_s(t;\varepsilon)$ is about 0.8 times as large as $MFD_{cs}(t;\varepsilon)$. That is, the mean response free dose calculated under the simple model is only 0.8 times as large as the true mean response free dose when competing risks are considered.

6.2 Virtually Safe Dose

6.2.1 Definition

The virtually safe dose was considered in Hartley and Sielken (1977) but was used with quantal response models prior to 1977. It is interpreted as the dose which would result in a specified slight increase in the probability of the specified response occurring before time t over this probability at dose 0.

Definition 6.2 The virtually safe dose at time t is the dose d that satisfies

$$P(t;d) = P(t;0) + \pi \ ,$$

with $0 < \pi < 1$ and π near 0. The virtually safe dose is denoted by $VSD(t;\pi)$.

Since the probabilities that were compared under the simple and cause-specific models were $P_s(t;d)$ and $P_{cs}(t,1;d)$, in Section 5, the virtually safe doses are calculated in terms of these two probabilities using Definition 6.2 and the corresponding virtually safe doses will be $VSD_s(t;\pi)$ and $VSD_{cs}(t,1;\pi)$ respectively. The $VSD_{cs}(t,1;\pi)$ refers to increasing the cause-specific probability of the specified response as opposed to the total probability of some response.

6.2.2 Approximations of Virtually Safe Dose

As with the mean response free dose, simple approximations for the virtually safe doses are available if a fairly general form for $\Lambda_1(t;d)$ is assumed. Let

$$\Lambda_1(t;d) = (1 + d^r)\,\beta t^k \ .$$

Then $VSD_{cs}(t,1;\pi)$ is the dose d that satisfies

$$\int_0^t (1+d^r)\beta k u^{k-1} \exp[-(1+d^r)\beta u^k - \Lambda_2(u)]\, du$$

$$= \int_0^t \beta k u^{k-1} \exp[-\beta u^k - \Lambda_2(u)]\, du + \pi \ .$$

Using the approximation, for small β, $\exp(-d^r \beta u^k) \doteq 1$ this becomes

$$(1+d^r) \int_0^t \beta k u^{k-1} \exp[-\beta u^k - \Lambda_2(u)]\, du$$

$$\doteq \int_0^t \beta k u^{k-1} \exp[-\beta u^k - \Lambda_2(u)]\, du + \pi \ .$$

Solving for the dose d the result is that

$$VSD_{cs}(t,1;\pi) = \left[\frac{\pi}{P_{cs}(t,1;0)}\right]^{1/r} \ . \qquad (6.5)$$

A similar derivation for VSD_s yields

$$VSD_s(t;\pi) = \left[\frac{\pi}{P_s(t;0)}\right]^{1/r} \ . \qquad (6.6)$$

Tables 25 through 32 give examples of the virtually safe doses calculated from a numerical search routine and the approximations (6.5) and (6.6). The virtually safe doses are calculated for t = 75, $\pi = 10^{-7}$, 10^{-6}, 10^{-5} and 10^{-4}. The values of r were the same as for the mean response free dose; namely, r = 1 and r = 3.

Table 25

Approximations of virtually safe dose with k = 3

and linear dose function

	$VSD_s(t;\pi)$		$VSD_{cs}(t,1;\pi)$	
π	Using Search Technique	Approximation	Using Search Technique	Approximation
10^{-7}	0.8145×10^{-1}	0.8145×10^{-1}	$0.1000\times10^{+0}$	$0.1000\times10^{+0}$
10^{-6}	$0.8145\times10^{+0}$	$0.8145\times10^{+0}$	$0.1000\times10^{+1}$	$0.1000\times10^{+1}$
10^{-5}	$0.8145\times10^{+1}$	$0.8145\times10^{+1}$	$0.1000\times10^{+2}$	$0.1000\times10^{+2}$
10^{-4}	$0.8145\times10^{+2}$	$0.8145\times10^{+2}$	$0.1000\times10^{+3}$	$0.1000\times10^{+3}$

Table 26

Approximations of virtually safe dose with k = 3

and nonlinear dose function

	$VSD_s(t;\pi)$		$VSD_{cs}(t,1;\pi)$	
π	Using Search Technique	Approximation	Using Search Technique	Approximation
10^{-7}	$0.4335\times10^{+0}$	$0.4335\times10^{+0}$	$0.4642\times10^{+0}$	$0.4642\times10^{+0}$
10^{-6}	$0.9339\times10^{+0}$	$0.9339\times10^{+0}$	$0.1000\times10^{+1}$	$0.1000\times10^{+1}$
10^{-5}	$0.2012\times10^{+1}$	$0.2012\times10^{+1}$	$0.2154\times10^{+1}$	$0.2154\times10^{+1}$
10^{-4}	$0.4335\times10^{+1}$	$0.4335\times10^{+1}$	$0.4642\times10^{+1}$	$0.4642\times10^{+1}$

Table 27

Approximations of virtually safe dose with k = 4

and linear dose function

	$VSD_s(t;\pi)$		$VSD_{cs}(t,1;\pi)$	
π	Using Search Technique	Approximation	Using Search Technique	Approximation
10^{-7}	0.7860×10^{-1}	0.7860×10^{-1}	$0.1000\times10^{+0}$	$0.1000\times10^{+0}$
10^{-6}	$0.7860\times10^{+0}$	$0.7860\times10^{+0}$	$0.1000\times10^{+1}$	$0.1000\times10^{+1}$
10^{-5}	$0.7860\times10^{+1}$	$0.7860\times10^{+1}$	$0.1000\times10^{+2}$	$0.1000\times10^{+2}$
10^{-4}	$0.7861\times10^{+2}$	$0.7860\times10^{+2}$	$0.1000\times10^{+3}$	$0.1000\times10^{+3}$

Table 28

Approximations of virtually safe dose with k = 4

and nonlinear dose function

	$VSD_s(t;\pi)$		$VSD_{cs}(t,1;\pi)$	
π	Using Search Technique	Approximation	Using Search Technique	Approximation
10^{-7}	$0.4284\times10^{+0}$	$0.4284\times10^{+0}$	$0.4642\times10^{+0}$	$0.4642\times10^{+0}$
10^{-6}	$0.9229\times10^{+0}$	$0.9229\times10^{+0}$	$0.1000\times10^{+1}$	$0.1000\times10^{+1}$
10^{-5}	$0.1988\times10^{+1}$	$0.1988\times10^{+1}$	$0.2154\times10^{+1}$	$0.2154\times10^{+1}$
10^{-4}	$0.4284\times10^{+1}$	$0.4284\times10^{+1}$	$0.4642\times10^{+1}$	$0.4642\times10^{+1}$

Table 29

Approximations of virtually safe dose with k = 5

and linear dose function

	$VSD_s(t;\pi)$		$VSD_{cs}(t,1;\pi)$	
π	Using Search Technique	Approximation	Using Search Technique	Approximation
10^{-7}	0.7634×10^{-1}	0.7634×10^{-1}	$0.1000\times10^{+0}$	$0.1000\times10^{+0}$
10^{-6}	$0.7634\times10^{+0}$	$0.7634\times10^{+0}$	$0.1000\times10^{+1}$	$0.1000\times10^{+1}$
10^{-5}	$0.7634\times10^{+1}$	$0.7634\times10^{+1}$	$0.1000\times10^{+2}$	$0.1000\times10^{+2}$
10^{-4}	$0.7635\times10^{+2}$	$0.7634\times10^{+2}$	$0.1000\times10^{+3}$	$0.1000\times10^{+3}$

Table 30

Approximations of virtually safe dose with k = 5

and nonlinear dose function

	$VSD_s(t;\pi)$		$VSD_{cs}(t,1;\pi)$	
π	Using Search Technique	Approximation	Using Search Technique	Approximation
10^{-7}	$0.4242\times10^{+0}$	$0.4242\times10^{+0}$	$0.4642\times10^{+0}$	$0.4642\times10^{+0}$
10^{-6}	$0.9140\times10^{+0}$	$0.9140\times10^{+0}$	$0.1000\times10^{+1}$	$0.1000\times10^{+1}$
10^{-5}	$0.1969\times10^{+1}$	$0.1969\times10^{+1}$	$0.2154\times10^{+1}$	$0.2154\times10^{+1}$
10^{-4}	$0.4242\times10^{+1}$	$0.4242\times10^{+1}$	$0.4642\times10^{+1}$	$0.4642\times10^{+1}$

Table 31

Approximations of virtually safe dose with k = 6

and linear dose function

	$VSD_s(t;\pi)$		$VSD_{cs}(t,1;\pi)$	
π	Using Search Technique	Approximation	Using Search Technique	Approximation
10^{-7}	0.7450×10^{-1}	0.7450×10^{-1}	$0.1000\times10^{+0}$	$0.1000\times10^{+0}$
10^{-6}	$0.7450\times10^{+0}$	$0.7450\times10^{+0}$	$0.1000\times10^{+1}$	$0.1000\times10^{+1}$
10^{-5}	$0.7450\times10^{+1}$	$0.7450\times10^{+1}$	$0.1000\times10^{+2}$	$0.1000\times10^{+2}$
10^{-4}	$0.7451\times10^{+2}$	$0.7450\times10^{+2}$	$0.1000\times10^{+3}$	$0.1000\times10^{+3}$

Table 32

Approximations of virtually safe dose with k = 6

and nonlinear dose function

	$VSD_s(t;\pi)$		$VSD_{cs}(t,1;\pi)$	
π	Using Search Technique	Approximation	Using Search Technique	Approximation
10^{-7}	$0.4208\times10^{+0}$	$0.4208\times10^{+0}$	$0.4642\times10^{+0}$	$0.4642\times10^{+0}$
10^{-6}	$0.9065\times10^{+0}$	$0.9065\times10^{+0}$	$0.1000\times10^{+1}$	$0.1000\times10^{+1}$
10^{-5}	$0.1953\times10^{+1}$	$0.1953\times10^{+1}$	$0.2154\times10^{+1}$	$0.2154\times10^{+1}$
10^{-4}	$0.4208\times10^{+1}$	$0.4208\times10^{+1}$	$0.4642\times10^{+1}$	$0.4642\times10^{+1}$

The approximations agree almost always with the virtually safe doses obtained from the numerical search technique to at least four digits. The values of the virtually safe doses appear to be changing by exactly a factor of 10 as π increases when the dose function is linear. This is because π is increasing by a factor of 10 also. These approximations appear to be much more accurate than those for the mean free dose.

6.2.3 Relative Bias

The relative bias of the simple virtually safe dose with respect to the cause-specific virtually safe dose is given by

$$RB(VSD_s, VSD_{cs}) = \frac{VSD_s(t;\pi)}{VSD_{cs}(t;\pi)} - 1 \ .$$

The form of the specified response's cumulative hazard function is the same as it is in the discussion of the mean free dose and is given by equation (6.4). The values of r, β and k were chosen in the same manner. The relative biases were calculated for $\pi = 10^{-7}$, 10^{-6}, 10^{-5} and 10^{-4} and are given in Tables 33 and 34.

Tables 33 and 34 provide conclusions analogous to those drawn from Tables 23 and 24:

(i) All relative biases are negative, indicating that $VSD_s(t;\pi)$ understates $VSD_{cs}(t;\pi)$.

(ii) Relative biases are virtually unaffected by changes in π. This is expected since π cancels when the relative bias is calculated using the approximation.

Table 33

Relative bias for virtually safe dose with linear dose function

	k			
π	3	4	5	6
10^{-7}	-0.1855	-0.2140	-0.2366	-0.2550
10^{-6}	-0.1855	-0.2140	-0.2366	-0.2550
10^{-5}	-0.1855	-0.2140	-0.2366	-0.2550
10^{-4}	-0.1855	-0.2140	-0.2366	-0.2550

Table 34

Relative bias for virtually safe dose with nonlinear dose function

	k			
π	3	4	5	6
10^{-7}	-0.06612	-0.07712	-0.08605	-0.09345
10^{-6}	-0.06612	-0.07712	-0.08605	-0.09346
10^{-5}	-0.06612	-0.07712	-0.08605	-0.09346
10^{-4}	-0.06613	-0.07712	-0.08605	-0.09346

(iii) Relative biases have greater absolute values as k increases.

(iv) The magnitude of the relative bias is greater when the dose function is linear than when it is nonlinear.

The relative biases for the virtually safe dose are about the same as for the mean free dose. Again the relative bias increases with k and

is larger when the dose function is linear rather than nonlinear. For $k = 6$ and a linear dose function, the relative bias of $VSD_s(t;\pi)$ with respect to $VSD_{cs}(t,1;\pi)$ is -0.2550. Thus, $VSD_s(t;\pi)$ is about 0.75 times as large as $VSD_{cs}(t,1;\pi)$. That is, the virtually safe dose calculated under the simple model is only 0.75 times as large as the true virtually safe dose when competing risks are considered.

7. ESTIMATION OF HAZARD FUNCTIONS WHEN THE CAUSE OF DEATH IS UNCERTAIN

The results in the preceding section were developed with the assumption that the specified response of interest is observable, e.g., death with tumor, observable tumor onset, or death from tumor (when the cause of death can be determined). In the last case, death from tumor, a common problem that arises is that the cause of death cannot be determined accurately. This section describes two risk assessment options when the cause of death is unknown, but it is known whether an individual died with a tumor or not.

7.1 Option One: All Causes of Death Combined

Option one is to consider the difference in the survival function (or the corresponding cdf) for a specified dose $d=d^*$ versus the survival function (or cdf) for the dose $d=0$. That is, compare

$$\Pr(T \leq t \mid d=d^*) \quad \text{versus} \quad \Pr(T \leq t \mid d=0) \ .$$

Here, the time to death (from all causes combined) is the specified response. If the zero dose level is taken to be the level naturally occurring in the environment, then $\Pr(T \leq t \mid d=0)$ can be obtained from life tables or estimated from the experimental data. The probability $\Pr(T \leq t \mid d)$ can be estimated as a function of d from the experimental data. An acceptable dose $d=d^*$ could then be defined as the dose at which $\Pr(T \leq t \mid d=d^*)$ exceeds $\Pr(T \leq t \mid d=0)$ by no more than a specified amount, say 10^{-6}, for any value of t in a specified time interval. This approach assumes that the dose's effect on the combination of all causes of death

is of interest. If only the dose's effect on death related to carcinogenicity is considered to be important, then option two is more appropriate.

7.2 Option Two: Death Related to Tumor

Option two is derived from a model discussed in both McKnight and Crowley (1984) and Kalbfleisch et al. (1983) but utilizes a new definition for the specified response. The model is given as follows: Let

τ^* = time to tumor onset ,

τ = time to death .

The hazard rates to follow use the notation given by Table 35 as subscripts.

Table 35

Notation for hazard functions used for death related to tumor

Subscript	Denotes:
T	presence of a tumor
NT	no tumor present
D	death
DFT	death from tumor
DCR	death from competing risk
DRT	death related to tumor

Define the hazard rate for tumor onset to be

$$\lambda_T(t) = \lim_{\Delta t \to 0} \frac{Pr(t<\tau^* \leq t+\Delta t \mid \tau>t, \tau^*>t)}{\Delta t} ,$$

the conditional hazard rate for death given that a tumor has occurred to be

$$\lambda_{D|T}(t) = \lim_{\Delta t \to 0} \frac{Pr(t<\tau\leq t+\Delta t \,|\, \tau>t, \tau^{*}\leq t)}{\Delta t} ,$$

and the conditional hazard rate for death given that no tumor has occurred to be

$$\lambda_{D|NT}(t) = \lim_{\Delta t \to 0} \frac{Pr(t<\tau\leq t+\Delta t \,|\, \tau>t, \tau^{*}>t)}{\Delta t} .$$

Also let

$$J = \begin{cases} 1 & \text{if the death is due to tumor} \\ 2 & \text{if the death is due to competing risks.} \end{cases}$$

Then the hazard rate $\lambda_{D|T}(t)$ can be partitioned as follows:

$$\lambda_{D|T}(t) = \lim_{\Delta t \to 0} \frac{Pr(t<\tau\leq t+\Delta t, J=1 \,|\, \tau>t, \tau^{*}\leq t)}{\Delta t}$$

$$+ \lim_{\Delta t \to 0} \frac{Pr(t<\tau\leq t+\Delta t, J=2 \,|\, \tau>t, \tau^{*}\leq t)}{\Delta t}$$

$$= \lambda_{DFT|T}(t) + \lambda_{DCR|T}(t) , \qquad (7.1)$$

where the last two hazard rates are the hazards corresponding to death from tumor given that a tumor has occurred and death from a competing risk given that a tumor has occurred, respectively. Notice that the conditional hazard rates do not depend on the time of the tumor onset rather they depend only on the existence of the tumor prior to time t. McKnight and Crowley (1984) discuss this situation with respect to

$\lambda_{D|T}(t)$. If this hazard rate is written as being conditional on the time of tumor onset, then it is not identifiable. Therefore, $\lambda_{D|T}(t)$ is regarded as a marginal hazard function that averages the risk over the distribution of τ^*.

If the cause of death can be determined, then $\lambda_T(t)$, $\lambda_{DCR|T}(t)$, $\lambda_{DFT|T}$ and $\lambda_{D|NT}(t)$ can be estimated provided interim sacrifices are made (see McKnight and Crowley (1984)). Kalbfleisch et al. (1983) give the likelihoods for this case. However, if the cause of death cannot be determined, then the hazard functions $\lambda_{DFT|T}(t)$ and $\lambda_{DCR|T}(t)$ are not identifiable and only $\lambda_{D|T}(t)$ can be estimated.

Assuming that the cause of death cannot be determined, the focus is now shifted to a new specified response - death related to tumor. This response has meaning only for the case where the hazard rate in the presence of a tumor exceeds the hazard rate in the absence of a tumor. A death related to a tumor is defined to be a death caused by the increase in $\lambda_{D|T}(t)$ relative to $\lambda_{D|NT}(t)$. This implies that the hazard rate for the specified response is

$$\lambda_{DRT|T}(t) = \lambda_{D|T}(t) - \lambda_{D|NT}(t) \ . \tag{7.2}$$

A death related to tumor may be a death caused by a tumor directly or a death resulting from an increase in the hazard rate for a competing risk. Since a death related to tumor is not necessarily clinically differentiable from other deaths with tumor, it is important that the estimation procedure for $\lambda_{DRT|T}(t)$ does not require that such differentiations be made.

If $\lambda_{D|T}$ is replaced by its equivalent expression in (7.1), then

$$\lambda_{DRT|T}(t) = \lambda_{DFT|T}(t) + \lambda_{DCR|T}(t) - \lambda_{D|NT}(t) ,$$

which futher emphasizes that a death related to tumor is not just a death from tumor but refers to the increase in all causes of death in the presence of a tumor relative to all causes of death in the absence of a tumor.

To estimate the desired risk characterizations, it is necessary to first estimate $\lambda_T(t)$, $\lambda_{D|T}(t)$ and $\lambda_{D|NT}(t)$. This is done by using the likelihoods from Kalbfleisch et al. (1983) which simplify when the cause of death is unknown. The resulting likelihood contributions are

$$L_I = \lambda_{D|NT}(t) \exp[-\int_0^t (\lambda_{D|NT}(u) + \lambda_T(u)) du] ,$$

$$L_{II} = \exp[-\int_0^t (\lambda_{D|NT}(u) + \lambda_T(u)) du] ,$$

$$L_{III} = \int_0^t \lambda_T(u) \times \exp[-\int_0^u (\lambda_T(v) + \lambda_{D|NT}(v)) dv - \int_u^t \lambda_{D|T}(v) dv] du,$$

and

$$L_{IV} = \int_0^t \lambda_T(u) \times \exp[-\int_0^u (\lambda_T(v) + \lambda_{D|NT}(v)) dv]$$

$$\times \lambda_{D|T}(t) \times \exp[-\int_u^t \lambda_{D|T}(v) dv] du ,$$

where Table 36 gives the situation governing each of the contributions. Using these contributions, the maximum likelihood estimates $\hat{\lambda}_T(t)$, $\hat{\lambda}_{D|T}(t)$ and $\hat{\lambda}_{D|NT}(t)$ can be obtained and $\hat{\lambda}_{DRT|T}(t)$ is obtained by

Table 36

Situations for the likelihood contributions when the cause of death is uncertain

Contribution	Situation
L_I	death at time t with no tumor present
L_{II}	sacrifice at time t with no tumor present
L_{III}	sacrifice at time t with a tumor present
L_{IV}	death at time t with a tumor present

applying equation (7.2). Thus, the time-to-response probabilities and other risk characterizations for the time to death related to tumor can be estimated.

The dependence of the hazard functions on dose has been suppressed in this discussion. A natural experimental situation would be to estimate the probability of death related to tumor at dose d and compare this to the probability of death related to tumor at dose 0. Also, other risk characterizations based on dose, such as mean free dose and virtually safe dose, can be estimated.

These two options provide the researcher and risk assessor with alternatives when the cause of death is unknown. Both options require that a new specified response be determined. The first option gives risk characterizations when death from all causes combined is the specified response. The second option gives a method for estimating risk characterizations when death related to tumor is the specified response.

8. CONCLUSIONS

This dissertation has demonstrated a method for improving risk characterizations from a simple model by incorporating competing risks via the cause-specific model. Two aspects of this method arise which make the incorporation of the cause-specific model desirable; they are increased accuracy and ease of implementation.

The cause-specific model give more accurate representations of risk characteristics than the simple model in two ways.

(i) The cause-specific model reflects the possibility of a competing response occurring before the specified response whereas the simple model does not.

(ii) The cause-specific model implies more relevant risk characterizations.

The difference between the two models was discussed in terms of relative bias. In Sections 5 and 6, bounds are obtained for various risk characterizations and examples are given that demonstrate how the simple model overstates the effect of the carcinogen. If the risk characterization is a time-to-response probability, the simple model can overstate the probability by as much as 800% depending on latency period, time, and parameter values of the specified response's hazard function. However, most overstatements are of the order of 50% - 60% for middle values of time, latency period and parameter values.

Additionally, if the data are generated from a cause-specific model with a latency period but fit by a simple model without a latency period, then the overstatement of the carcinogenic effect is usually increased.

This was demonstrated by a simulation study in Section 5. It shows that the simple time-to-response probability may be as much as 1400% larger than the true time-to-response probability under the cause-specific model.

The magnitude of the relative bias for mean response free period was not as large as it was in the case of time-to-response probability. In fact, if the probability of the specified response occurring before time t is of the order 10^{-6} then the relative bias for mean response free period is almost negligible; however, if the risk characterization is given in terms of dose, the relative bias may be larger. For example, if the dose function is linear, the virtually safe dose under the simple mmodel may only be 75% of the virtually safe dose under the cause-specific model. The same order of magnitude holds for the relative bias of the mean free dose. This percentage increases to about 90% if the dose function is nonlinear (e.g., cubic).

The risk characteristics under consideration have different representations under the simple and cause-specific models. By using the new definitions of the risk characterization under the cause-specific model the researcher is required to be more precise in his definition of the specified response and the health effects to be measured. These risk characteristics under the cause-specific model are easily interpreted.

Accuracy is just one advantage of the cause-specific model; implementation is another. As shown in Section 3, the relationship between the cause-specific and simple likelihood functions allows the use of existing simple model maximum likelihood estimates to develop cause-specific maximum likelihood estimates. Also, the approximation for

the competing risks' hazard function, $\lambda_2(t)$, given in Section 4 is both reasonable and convenient. Thus, the procedure given in Sections 3 and 4 for incorporating the cause-specific model can be implemented using either the experimental data alone or the simple model estimates and a life table approximation for the competing risks' hazard function.

Finally, when the cause of death is uncertain, the framework of the cause-specific model allows the estimation of time-to-response probabilities for the specified response, death related to tumor. Using this new response is reasonable and may be more relevant to the risk assessment than defining the response to be death from tumor when the cause of death is unknown or subjectively assigned.

In the area of quantitative cancer risk assessment many modeling problems occur such as low dose extrapolation, interspecies extrapolation and the incorporation of competing risks. These are, by no means, easy problems to solve. They should each be considered by risk managers, risk assessors and researchers with the attitude that accuracy in all aspects of the modeling process is important. This dissertation provides these people with the necessary information to decide if the simple model is sufficient in a particular situation, and if it is not, it provides a method for improving the risk characterizations by utilizing existing results without setting up new experiments.

REFERENCES

Armitage, P. (1982). The assessment of low-dose carcinogenicity. Biometrics 38 (Supplement on Current Topics in Biostatistics and Epidemiology), 119-129.

Chiang, C.L. (1970). Competing risks and conditional probabilities. Biometrics 26, 767-776.

Dewanji, A. and Kalbfleisch, J. D. (1985). Non-parametric methods for survival/sacrifice experiments. Proceedings of the Symposium on Long-Term Animal Carcinogenicity Studies: A Statistical Prospective, 100-106.

Dinse, G. E. (1985). Estimating tumor prevalence, lethality and mortality. Proceedings of the Symposium on Long-Term Animal Carcinogenicity Studies: A Statistical Prospective, 91-99.

Hartley, H. O. and Sielken, R. L. Jr. (1977). Estimation of "safe doses" in carcinogenic experiments. Biometrics 33, 1-20.

Hartley, H. O., Tolley, H. D. and Sielken, R. L. Jr. (1981). The product form of the hazard rate in carcinogenic testing. Current Topics in Probability and Statistics. M. Csörgö, D. Dawson, J. N. K. Rao and E. Saleh (eds.). North Holland, NY, 185.

Kalbfleisch, J. D., Krewski, D. R. and Van Ryzin, J. (1983). Dose-response models for time-to-response toxicity data. The Canadian Journal of Statistics 11, 25-49.

Kalbfleisch, J. D. and Prentice, R. L. (1980). The Statistical Analysis of Failure Time Data. John Wiley & Sons, New York.

Krewski, D., Crump, K. S., Farmer, J. H., Gaylor, D. W., Howe, R., Portier, C., Salsburg, D., Sielken, R. L. Jr. and Van Ryzin, J. (1983). A comparison of statistical methods for low dose extrapolation utilizing time-to-tumor data. Fundamental and Applied Toxicology 3, 140-146.

McKnight, B. and Crowley, J. (1984). Tests for differences in tumor incidence based on animal carcinogenesis experiments. Journal of the American Statistical Association 79, 639-648.

Moeschberger, M. L. and David, H. A. (1971). Life tests under competing causes of failure and the theory of competing risks. Biometrics 27, 909-933.

National Center for Health Statistics: Vital Statistica of the United States, 1979, Vol. II, Mortality, Part A. DHHS Pub No. (PHS) 84-1101. Publich Health Service, Washington. U. S. Government Printing Office, 1984.

Prentice, R. L., Kalbfleisch, J. D., Peterson, A. V., Flournoy, N., Farewell, V. T., and Breslow, N. E. (1978). The analysis of failure times in the presence of competing risks. Biometrics 34, 541-554.

Society of Toxicology ED_{01} Task Force (1981). Re-examination of the ED_{01} study: Risk assessment using time. Fundamental and Applied Toxicology 1, 88-123.

Tsiatis, A. (1975). A nonidentifiability aspect of the problem of competing risks. Proceedings of the National Academy of Science, USA, 72, 20-22.

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He received a Bachelor of Science degree in mathematics from Iowa State University in 1971 and a Master of Science degree in Operations Research from Stanford University in 1980. From 1980 to 1983 he was an instructor and assistant professor of mathematics at the United States Air Force Academy. In May of 1986 he expects to receive a Doctor of Philosophy degree in Statistics from Texas A&M University.

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