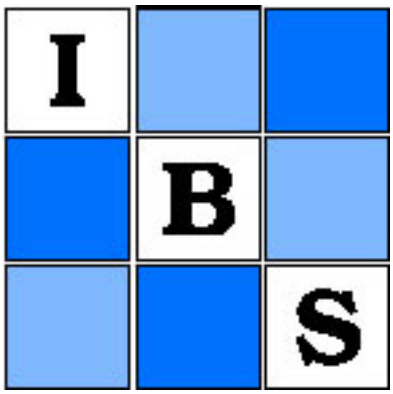

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Model-Based Time Extrapolation for Quantal Response Studies

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SUMMARY

It is often desired to compare chemicals with respect to toxicity for purposes of priority setting in regulation. Long-term carcinogenicity studies are frequently used as the basic data for such exercises. When the results of these studies for different chemicals are compared, many confounders potentially arise. One confounder is that these studies may have been conducted for different study lengths. In this case, converting the results of these studies to a common "standard" time length would be of interest. We propose an adjustment to modify the results of a study with a particular study length to a standard time length. This adjustment is based on a simple stochastic model for carcinogenicity studies. We illustrate the application of this adjustment with an example of a chemical that has been studied by the National Toxicology Program.

1. Introduction

Animal carcinogenicity studies are typically lifetime exposure studies during which an animal is randomly assigned to some dose group and is then exposed to a particular concentration of a compound from the time of weaning until death or study termination. Rodents in these studies are examined after death for the presence of tumors at various sites. Many methods are used to analyze such studies for dose-related increases in tumorigenicity (see, e.g., Hoel and Walburg, 1972; Tarone, 1975; Dinse and Lagakos, 1983; Bailer and Portier, 1988). Data from these studies are also used to derive estimates of the tumorigenic potency of a compound (Sawyer et al., 1984; Finkelstein and Ryan, 1987; Bailer and Portier, 1993). (Potency, in this context, refers to the ability of a compound to induce tumor formation.) Potency estimates have been calculated for the entire set of animal carcinogenicity studies conducted by the National Center Institute/National Toxicology Program (see, e.g., Gold et al., 1984). One problem in interpreting these estimates is that these studies may have been conducted for differing study lengths. A possible solution is to adjust any potency estimator to a "standard lifespan" for purposes of comparison. Peto et al. (1984) suggest an adjustment for experiments that "terminate prior to or after the standard lifespan." They recommend multiplying the potency estimate by a factor equal to

$$(\text{standard lifespan}/\text{experiment duration})^2.$$

This adjustment factor had been suggested by previous experimental work.

Long-term carcinogenicity studies are frequently used as the basis of quantitative risk assessments. In this exercise, the cancer response is modeled as a function of dose, and then this function is used to predict tumor response at specified dose levels. (These doses are often well below the range of the experimental doses but are often in the range of human exposures.) If this function is developed for an experiment that was appreciably shorter than a "standard lifespan," some adjustment would seem necessary. One justification for any adjustment would be that, since cancer tends to be a phenomenon that occurs late in life, any prediction of risk based on a study with shorter than standard lifespan may underestimate risk. This is the context that motivated the development of the methods presented in this paper. In Section 2, we present the notation for the study designs mentioned above, and we provide a description of a simple stochastic model for describing such

Key words: Carcinogenicity; risk assessment.

studies. The derivation of a new time adjustment factor is given in Section 3 with an application of this adjustment factor presented in Section 4. We conclude with observations on the benefits and potential difficulties in applying this adjustment.

2. Study Designs and an Associated Stochastic Model

Consider a carcinogenicity experiment with two or more treated groups and a zero-dose control group that was conducted for some duration t^*. The data associated with each animal include information on dose group, survival time, and some indicator of tumor presence. As mentioned above, these data may be used for tests of increased tumorigenicity, estimates of tumorigenic potency, or as the basic information in developing a dose–response model.

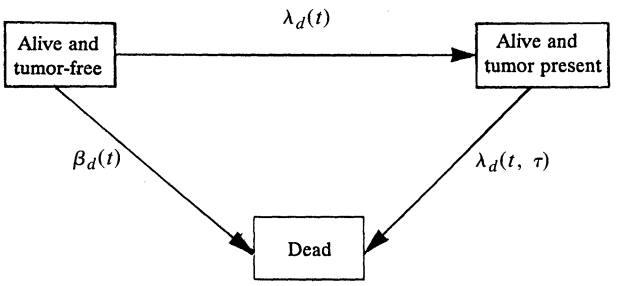

Figure 1. Three-state stochastic model for animal carcinogenicity experiments.

A simple three-state stochastic model for animal carcinogenicity experiments provides the basis for the time adjustment derivation (see Figure 1). In this model, an animal starts alive and tumor-free in dose group d and experiences competing risks of tumor onset and tumor-free death governed by the hazards $\lambda_d(t)$ and $\beta_d(t)$, respectively. Given tumor onset at time τ, an animal has hazard of tumor-bearing death $\gamma_d(t, \tau)$. A complete description of this model is given in Bailer and Portier (1988).

3. Derivation of the Time Adjustment

The hazard functions that govern transition in this stochastic model can be used to obtain the adjustment for differential study length. Before the time adjustment is derived, the probability of tumor onset during a study of standard duration (TS) must be expressed in terms of λ_d and β_d. As noted in Bailer and Portier (1988), this expression is simply

$$P(d, \text{TS}) = \int_0^{\text{TS}} f_d(u)\, du, \tag{1}$$

where

$$f_d(u) = \lambda_d(u) \exp\left(- \int_0^u (\lambda_d(x) + \beta_d(x))\, dx \right).$$

(Note that the hazard of tumor-bearing death $\gamma_d(t, \tau)$ is not influential when considering quantal response probabilities.) Now suppose that we have a study that has been terminated prior to the standard study time, say at time $t^* < \text{TS}$. By partitioning (1) into two time intervals, $[0, t^*]$ and $(t^*, \text{TS}]$, the adjustment $(a(t^*, \text{TS}, d, \lambda_d, \beta_d))$ can be derived. This manipulation is given below:

$$\begin{aligned} P(d, \text{TS}) &= \int_0^{t^*} f_d(u)\, du + \int_{t^*}^{\text{TS}} f_d(u)\, du = P(d, t^*) + \int_{t^*}^{\text{TS}} f_d(u)\, du \\ &= P(d, t^*)\left(1 + \frac{\int_{t^*}^{\text{TS}} f_d(u)\, du}{P(d, t^*)}\right) \\ &= P(d, t^*) \times a(t^*, \text{TS}, d, \lambda_d, \beta_d). \end{aligned} \tag{2}$$

The first term in the product (2) is simply the probability of tumor onset before t^* in dose group d, say $P(d, t^*)$. The second term is the adjustment to extend this result from a study of length t^* to a study of length TS.

The time adjustment factor possesses the following properties. First, $a(\text{TS}, \text{TS}, d, \lambda_d, \beta_d) = 1$, which is a sensible property for any time adjustment. Second, this adjustment depends on dose through its effects on tumor onset and competing risks when $t^* \neq \text{TS}$. Third, if the hazard functions $\lambda_d(t)$ and $\beta_d(t)$ are correctly specified, this method will never adjust a quantal response probability to exceed 1. Incorrect specification of these hazard functions or errors in the estimation of these functions may lead to adjusted probabilities that exceed 1. Other features of this adjustment that are of interest include the easy incorporation of interim sacrifices or modifications for $t^* > \text{TS}$.

This adjustment contains many unknowns, including the functional form of λ_d and β_d. One strategy for addressing this concern is to parametrically specify λ and β. Functional forms for the tumor-onset hazard $\lambda_0(\cdot)$ and an all-causes mortality hazard $\psi_0(\cdot)$ have been suggested by Portier, Hedges, and Hoel (1986). The tumor-free death hazard $\beta_d(\cdot)$, which is needed in the time adjustment, can be obtained from $\lambda_0(\cdot)$ and $\psi_d(\cdot)$. Combining these parametric forms for the control hazards with a linear proportional hazards framework for the effects of exposure on these hazards yields $\lambda_d(t) = (1 + \theta_0 d)\theta_1\theta_2 t^{\theta_2 - 1}$ and $\psi_d(t) = (1 + \alpha_0 d)(\alpha_1 + \alpha_2\alpha_3 t^{\alpha_3 - 1})$. Other parameterizations of the effect of dose on the baseline hazard might be considered. Natural alternatives in this proportional hazards framework are $\lambda_d(t) = e^{\theta_0 d}\lambda_0(t)$ and $\psi_d(t) = e^{\alpha_0 d}\psi_0(t)$.

The relationships between $\beta_d(t)$ and $\lambda_d(t)$, $\psi_d(t)$ are complex in general but simplify under assumptions about tumor lethality (see, e.g., Bailer and Portier, 1988). When tumor-bearing and tumor-free animals die at the same rate, i.e., $\gamma_d(t, \tau) = \beta_d(t)$, tumors are said to be incidental and $\beta_d(t) = \psi_d(t)$. Rapidly lethal tumors lead to death immediately after onset. This gives $\beta_d(t) = \psi_d(t) - \lambda_d(t)$.

The adjustment factor can now be written incorporating these parametric forms. Unfortunately, these forms involve too many parameters and cannot be estimated using data from a typical bioassay. Estimates for the parameters in the baseline hazards (θ_1, θ_2, α_1, α_2, and α_3) can be obtained for male and female B6C3F$_1$ mice and Fischer 344 rats from Portier et al. (1986). Estimates of dose effects are more elusive.

A possible strategy for obtaining estimates of the dose effects on the hazards (i.e., α_0 and θ_0) is now outlined. This strategy is based on using a nonparametric estimate of the survival distribution in a dose group and in the control group in conjunction with the linear dose effect in the proportional hazards framework. Denote the probability of being alive at time t in dose group d by $S_d(t)$. Clearly $S_d(t) = [S_0(t)]^{1+\alpha_0 d}$ because of the proportional hazards assumption. Given estimates of $S_d(t)$ and $S_0(t)$ ($\neq 1$) at some time t, the dose effect of the death hazards could be estimated by

$$\hat{\alpha}_0 = \left(\frac{1}{d}\right)\left[\frac{\ln S_d(t)}{\ln \hat{S}_0(t)} - 1\right]$$

where ln denotes the natural logarithm. Nonparametric methods, such as the Kaplan–Meier estimate, can be used to obtain an estimate $\hat{S}_d(t)$ of $S_d(t)$. One selection for the time point for obtaining the estimate of α_0 is the study duration t^*. Estimation of θ_0 depends on the tumor lethality assumption. When tumors are rapidly lethal, a similar approach based on Kaplan–Meier estimates is possible. Tumor-free death and sacrifice times effectively right censor the corresponding tumor-onset times. When tumors are incidental, $S_d(t)$ is the prevalence of *tumor-free* animals among those alive at time t. This can be estimated by the prevalence of tumor-free animals observed at the terminal sacrifice. Estimates of the dose parameter in the exponential dose effects model could be obtained in an analogous manner.

4. Example

We applied this adjustment method to lung tumor response in female B6C3F$_1$ mice exposed to 1,3-butadiene. These data were obtained in a long-term carcinogenicity study in which groups of 50 mice were exposed to 0, 625, or 1,250 ppm (NTP, 1984). The study was scheduled to continue for 2 years; however, the study was terminated at 61 weeks due to rapidly declining survival of the groups exposed to 1,3-butadiene.

For the purpose of exposition, we assume that the biologically active dose is proportional to the exposure concentration. We note that other relationships between exposure and dose could reasonably be assumed to hold. Applications of this adjustment to other representations of dose are similar.

We assume that lung tumor status does not affect survival, i.e., tumors of the lung in mice are incidental. The results of Portier et al. (1986) suggest that this is a reasonable assumption. Assuming lung tumors are fatal is problematic for these data since 28 of 91 mice had lung tumors detected by terminal sacrifice. Tumor onset immediately leads to death when this assumption holds; hence, such

tumors should not be detected by sacrifice. We tentatively assume that the time of death of these 28 mice preceded the time of sacrifice by a negligible amount for estimating α_0, θ_0. We did this in order to examine the sensitivity of the results to tumor lethality assumptions and since tumors detected by terminal sacrifice are counted in the quantal framework for which this adjustment was developed.

The Kaplan–Meier estimates of survival, tumor-free prevalence, and tumor-onset survival for

Table 1

Kaplan–Meier estimates of survival and lung tumor-free prevalence observed at 61 weeks for female mice exposed to 1,3-butadiene

Concentration (ppm)	Survival	Tumor-free prevalence	All-causes[a] survival	Tumor-onset survival
0	.92	.9348	.86	.9348
625	.30	.4667	.14	.3832
1,250	.60	.4333	.26	.3641

[a]All occurrences of lung tumors counted as deaths.

Table 2

Observed proportions of female mice with lung tumors, adjustment factors, and resulting adjusted proportions for a 104-week experiment assuming linear dose effects in a proportional hazards framework

		Derived using 0 and 625 ppm		Derived using 0 and 1,250 ppm	
Conc. (ppm)	Observed proportion	Adjustment factor	Adjusted proportion	Adjustment factor	Adjusted proportion
0	.061	3.83[a] (3.95)[b]	.234 (.242)	3.83 (3.95)	.234 (.242)
625	.250	1.67 (1.99)	.418 (.499)	2.71 (2.90)	.677 (.724)
1,250	.469	1.29 (1.52)	.605 (.714)	2.12 (2.34)	.997 (1.00)[c]

[a]Analysis assuming tumor was incidental.
[b]Analysis assuming tumor was fatal.
[c]Rounded down to 1.

Table 3

Observed proportions of female mice with lung tumors, adjustment factors, and resulting adjusted proportions for a 104-week experiment assuming exponential dose effects in a proportional hazards framework

		Derived using 0 and 625 ppm		Derived using 0 and 1,250 ppm	
Conc. (ppm)	Observed proportion	Adjustment factor	Adjusted proportion	Adjustment factor	Adjusted proportion
0	.061	3.83[a] (3.95)[b]	.234 (.242)	3.83 (3.95)	.234 (.242)
625	.250	1.67 (1.99)	.418 (.499)	3.15 (3.33)	.788 (.833)
1,250	.469	1.00 (1.01)	.470 (.473)	2.12 (2.34)	.997 (1.00)[c]

[a]Analysis assuming tumor was incidental.
[b]Analysis assuming tumor was fatal.
[c]Rounded down to 1.

Table 4

Ratio of time adjustment after ±10% changes to baseline parameters to original time adjustment. Lung tumors are assumed incidental, and a linear dose effect on baseline hazards is assumed.

	Derived using 0 and 625 ppm						Derived using 0 and 1,250 ppm					
	0 ppm		625 ppm		1,250 ppm		0 ppm		625 ppm		1,250 ppm	
	−10%	+10%	−10%	+10%	−10%	+10%	−10%	+10%	−10%	+10%	−10%	+10%
α_1	1.00	1.00	1.01	.99	1.01	.99	1.00	1.00	1.00	1.00	1.00	1.00
α_2	1.01	.99	1.03	.97	1.02	.98	1.01	.99	1.02	.98	1.02	.98
α_3	1.08	.47	1.58	.60	1.50	.78	1.08	.47	1.24	.44	1.32	.51
θ_1	1.00	1.00	1.01	.99	1.01	.99	1.00	1.00	1.02	.98	1.02	.98
θ_2	.89	1.04	1.02	.81	1.05	.85	.89	1.04	1.00	.74	1.07	.69

each dose at the termination of the study ($t^* = 61$ weeks) are given in Table 1. If lung tumors are assumed to be incidental, the estimates of the dose effects on tumor onset and tumor-free death are $\hat{\theta}_0 = .0165$ and $\hat{\alpha}_0 = .0215$ when based on data from the 0 and 625 ppm groups, and $\hat{\theta}_0 = .00912$ and $\hat{\alpha}_0 = .0041$ when based on data from the 0 and 1,250 ppm groups. If lung tumors are assumed to be fatal, the estimates of the dose effects on tumor onset and tumor-free death are $\hat{\theta}_0 = .0212$ and $\hat{\alpha}_0 = .0193$ when based on data from the 0 and 625 ppm groups, and $\hat{\theta}_0 = .0112$ and $\hat{\alpha}_0 = .0063$ when based on data from the 0 and 1,250 ppm groups.

Estimates of the parameters in the baseline hazards are needed for the calculation of the adjustment factor. From Portier et al. (1986), estimates (and standard errors) for θ_1 and θ_2 for alveolar/bronchiolar adenomas and carcinomas in $B6C3F_1$ female mice were .101 (.0125) and 3.05 (1.38), respectively. The estimates of the parameters for the death hazard in $B6C3F_1$ female mice, i.e., $\hat{\alpha}_1$, $\hat{\alpha}_2$, $\hat{\alpha}_3$, were 2.8678×10^{-4}, 1.4206×10^{-14}, and 6.4978, respectively. [No standard errors for the α_i estimates were given in Portier et al. (1986).]

Tables 2 and 3 present the resulting adjustment factors required to obtain estimates of the expected proportion responding during a 2-year (104-week) study. These are applied to the observed proportions from the $t^* = 61$-week study to estimate the proportions expected in the TS = 104-week study. The linear dose effect proportional hazards framework is given in Table 2 while the experimental dose effect parameterization is given in Table 3. The sensitivity of the time adjustment to tumor lethality assumptions can be explored within these two tables. For the linear dose effect calculations, the lethality assumption most affected the time adjustment for the highest concentration group. For the exponential dose effect calculations, the lethality assumption most affected the time adjustment for the middle concentration group. In both dose parameterizations, the time adjustment differed by less than 30% when the lethality assumptions were varied. The sensitivity of the time adjustment to differing dose parameterizations can be explored by comparing across Tables 2 and 3. The time adjustment differed by less than 30% as the dose parameterization was changed from linear to exponential.

The sensitivity of the time adjustment to changes in the baseline hazards, λ_0 and β_0, can be explored in Table 4. Parameter estimates from Portier et al. (1986) were varied by $\pm 10\%$ and the effects of these changes on the adjustment were determined. The scale parameters of these models (α_1, α_2, θ_1) had very little effect on the adjustment (<2% change). The shape parameters (α_3, θ_2) had a much greater effect on the adjustment with changes of up to 60% in the time adjustment observed. It is not too surprising that the shape parameter, an exponent associated with a time variable, would exert fairly strong influence on a time adjustment.

The $a(61, 104, d, \lambda_d, \beta_d)$ adjustment factor obviously differs from the more commonly applied constant time adjustment factor. The $a(\cdot)$ adjustment differs as a function of dose, whereas the constant time adjustment factor, (standard lifespan/experiment duration)$^2 = (104/61)^2 = 2.907$, is a constant multiplier of the quantal response probability associated with each dose group. (Note that time adjustments other than squared ratio of lifespan to experiment duration are used. A cube of this ratio leads to an adjustment of 4.956.) In both cases, the constant time adjustment overadjusts the quantal response probability in the 1,250 ppm group, leading to an estimate greater than 1. The model-based time adjustment reflects the fact that animals in the control group have much greater risk of lung tumor onset in the time interval (61, 104] weeks than animals in the two dosed groups. This follows since the number of animals at risk of tumor onset in the control group (i.e., alive and tumor-free at $t^* = 61$ weeks) was much larger than the number of animals at risk of lung tumor onset in the 625 and 1,250 ppm groups.

5. Conclusion

A general model-based time adjustment has been presented and illustrated with a typical carcinogenicity experiment. Various assumptions are necessary for applying this adjustment. For the application illustrated in this manuscript, two assumptions were made. First, parametric forms for the hazards of tumor onset and death are assumed, and estimates for the parameters in the control hazard functions are obtained from the literature. Second, a proportional hazards relationship between dose and these control hazards is assumed with dose effects in the example estimated by simple methods. If the data are available, fully parametric or semiparametric methods might be used to estimate dose effects.

Even with all of these unknowns, we believe this is a promising adjustment. This adjustment reflects the observed strength of the dose–tumor response relationship as well as the presence of competing risks in addition to the differences in the study duration and standard lifespan, whereas the constant time adjustment reflects only the differences in the study duration and the standard lifespan. The differential adjustment is reasonable in the context of modifying quantal response

probabilities in long-term carcinogenicity studies. It is not unusual for high-dose groups in these studies to experience increased hazard of death due to toxicity in addition to increased hazard of tumorigenesis. This suggests that a reasonable time adjustment for modifying results from a study of shorter duration to a greater standard lifespan (i.e., $t^* < TS$) would adjust higher doses less dramatically than lower doses. This is exactly what the proposed adjustment does.

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Résumé

II est souvent souhaité de comparer la toxicité de produits chimiques à des fins règlementaires. Les études de cancérogénicité à long-terme sont souvent utilisées dans ce but. Lorsque l'on compare les résultats de ces études pour différents produits chimiques, on se trouve confronté à des facteurs de confusion potentiels. L'un de ces facteurs est que ces études ont pu être conduites sur des durées variables. Dans ce cas, il serait intéressant de pouvoir ramener les résultats de ces études à une durée standard commune. Nous proposons une méthode pour ajuster les résultats d'une étude à une durée standard. Cet ajustement repose sur un modèle stochastique simple. Nous illustrons l'application de cette méthode à l'exemple d'un produit chimique étudié dans le cadre du Programme National de Toxicologie.

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