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Hierarchical models for probabilistic dose–response assessment ☆

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Abstract

Probabilistic risk assessment is gaining acceptance as the most appropriate way to characterize and communicate uncertainties in estimates of human health risk and/or reference levels of exposure such as benchmark doses. Although probabilistic techniques are well established in the exposure-assessment component of the National Research Council's risk-assessment paradigm, they are less well developed in the dose–response-assessment component. This paper proposes the use of hierarchical statistical models as tools for implementing probabilistic dose–response assessments, in that such models provide a natural connection between the pharmacokinetic (PK) and pharmacodynamic (PD) components of dose–response models. The results show that incorporating internal dose information into dose–response assessments via the coupling of PK and PD models in a hierarchical structure can reduce the uncertainty in the dose–response assessment of risk. However, information on the mean of the internal dose distribution is sufficient; having information on the variance of internal dose does not affect the uncertainty in the resulting estimates of excess risks or benchmark doses. In addition, the complexity of a PK model of internal dose does not affect how the variability in risk is measured via the ultimate endpoint.

Keywords: Bayesian; Benchmark dose; Binomial; Internal dose; Michaelis–Menten; Monte Carlo; PBPK; PK/PD; Risk management; Two-stage model; Uncertainty; Weibull

1. Introduction

Hierarchical statistical models can provide useful formulations for facilitating probabilistic risk assessments for adverse human health effects. Bayesian hierarchical models (Carlin and Louis, 1996), in particular, have become increasingly popular for fitting complex physiologically based pharmacokinetic (PBPK) models to produce probabilistic representations of internal dose (Gelman et al., 1996). These complex PBPK models, which practitioners are utilizing more commonly in human health risk assessment (Young et al., 2001; Lipscomb et al., 2003; Clewell and Andersen, 2004), present special challenges for evaluation of model adequacy (Clark et al., 2004; Clewell et al., 2005). It has been suggested that the Bayesian hierarchical framework presents a firm statistical foundation for model calibration to facilitate appropriate characterization of the uncertainty in model outputs (Zeise et al., 2002).

This paper proposes that a hierarchical statistical model is also the most natural and correct way to link the pharmacokinetic (PK) and pharmacodynamic (PD) components of PK/PD dose–response models for probabilistic dose–response assessment, whether or not these components are physiologically based (Andersen, 1995; Schlosser et al., 2003). The extent to which such hierarchical formulations may help to account for uncertainty in the dose–response component of the risk assessment process is explored. Unlike the typical Bayesian hierarchical model used in PBPK analysis, in which the hierarchy arises from the assumption of a prior distribution on the model's parameters, the PK/PD model's hierarchy arises from the fact that the PD model is conditionally dependent on the distribution of the internal dose represented by the PK

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model. To facilitate the exposition, the context will be cancer risk assessment; however, the conclusions apply generally to adverse endpoints in human health risk assessment.

2. Methods

2.1. Hierarchical models

In the general health risk assessment paradigm (NRC, 1983), once a hazard assessment has been conducted and a (potential) carcinogen has been identified, the risk assessment proceeds to an exposure assessment and a dose–response assessment, which are often conducted separately and then linked to produce a risk characterization. The focus of this paper is the dose–response component of the process.

The dose–response assessment often involves fitting a mathematical model in dose (usually, administered dose) to tumorigenicity data from a two-year rodent bioassay. The probability of a tumor at administered dose D is expressed as

$$\Pr(\text{tumor}|D) = F(D), \tag{1}$$

where $F(D)$ may be the multistage model, probit model, or some other dose–response function. With a model such as this, no attempt is made to separate the hidden PK and PD components that might explain the transformation of an external exposure into the development of a tumor.

For some time it has been recognized that PK information on internal dose ought to be incorporated into dose–response models whenever possible (Andersen et al., 1987). One way to do this is to conduct a PK analysis in the rodent species/strain tested in the cancer bioassay to estimate the average internal dose $\mu(d|D)$ at each administered dose D (e.g., the average AUC (area under the blood concentration–time curve) and/or $C_{\max}$ (maximum blood concentration) of parent chemical or metabolite). The estimate, $\bar{d}_D$, is then simply substituted for D in (1) (Gehring et al., 1978; Starr, 1990). Hence, (1) becomes the PD model, $F(\bar{d}_D)$. If this average internal dose can be formulated mathematically as a function of D, say $\mu(d|D) = H(D)$, then $H(D)$ can be substituted functionally for D in the dose–response model in (1) (e.g., Van Ryzin and Rai, 1987).

It is suggested here that the most natural and correct way to link the PK and PD components directly in the dose–response assessment is via a hierarchical model. Let $f(d|D)$ be the rodent probability density function of internal dose, d, for administered dose, D, where f is obtained by PK analysis. Let $g(\text{tumor}|d)$ be a dose–response model representing the PD model for development of a tumor from exposure to internal dose, d. The hierarchical formulation is

$$\Pr(\text{tumor}|D) = P_0 + (1 - P_0)\int g(\text{tumor}|x) f(x|D)\,\mathrm{d}x, \tag{2}$$

where P_0 is the background tumor risk and x is simply a variable of integration. The expected value (mean) of $f(d|D)$ is $\mu(d|D) = H(D)$ defined above. To determine $f(d|D)$ from a PK experiment with rats, for example, an internal dose (e.g., AUC) can be determined for each of several animals all having the same administered dose, D, and the sample mean and standard deviation can be used to formulate $f(d|D)$. It is customary to assume a normal distribution for $f(d|D)$ based on the similarity of the shapes of the blood concentration-time curves of individual animals. The PK analysis might be somewhat simple, reflecting variation only in physiological parameters that control uptake, distribution, etc.; however, it could involve fitting a complex, PBPK model, perhaps a model that itself has a (Bayesian) hierarchical structure (e.g., Hack, 2006), to account for prior information on parameter values. If there is sufficient information on mechanism of action, then the PD model $g(\text{tumor}|d)$ would reflect that mechanism (e.g., Kodell et al., 2001). Most often, however, g is likely to be a common dose–response model like the multistage, probit or Weibull. Nonetheless, the integral expression (2) with the hierarchical formulation provides a direct linkage of PK and PD components, such that the probability of developing a tumor is the expected value of the PD model over the PK-derived internal-dose distribution. That is, the hierarchical model represents $E_f[g(\text{tumor}|d)|D]$. Simply substituting the mean internal dose, as described above (Van Ryzin and Rai, 1987), represents $g[\text{tumor}|E_f(d|D)]$. (In many contexts, using the simpler $g[E_f(x)]$ in place of the more complex $E_f[g(x)]$ is often motivated by a first-order Taylor series approximation.)

If informative data on mechanism of action are available, then the expression for the probability of a tumor at dose D might look like

$$\Pr(\text{tumor}|D) = P_0 + (1 - P_0)\int g(\text{tumor}|y)\int h(y|x) f(x|D)\,\mathrm{d}x\,\mathrm{d}y, \tag{3}$$

where $h(y|x)$ represents a function that relates internal dose x to a tissue response y, that is a precursor to the formation of a tumor. For example, x might be the level of a key metabolite in a target tissue determined by PBPK analysis and y might be the proliferation rate of preneoplastic cells in the target tissue determined by PCNA analysis. The function, g, could be a two-stage, clonal-growth model that links the growth of preneoplastic cells to the development of the ultimate tumor. Changing the order of integration, expression (3) can be rewritten as

$$\Pr(\text{tumor}|D) = P_0 + (1 - P_0)\int \left[\int g(\text{tumor}|y) h(y|x)\mathrm{d}y\right] f(x|D)\,\mathrm{d}x. \tag{4}$$

Hence, the PD model of expression (2), $g(\text{tumor}|x)$, has been expanded to $\int g(\text{tumor}|y)h(y|x)\mathrm{d}y$ in the brackets in expression (4). Note that the functions f, g, and h may themselves have arisen from hierarchical models. For example, $f(x|D)$ might be the Bayesian posterior distribution of internal dose, if prior information on internal dose is available to utilize a Bayesian hierarchical structure in the PK analysis.

2.2. Fitting models to data

It is helpful to use specific examples to convey ideas. Table 1 gives hypothetical tumor dose–response data from a typical 2-year rodent bioassay with four administered doses and 50 animals per group. Two distinct PK/PD scenarios are illustrated initially, with variations on these discussed subsequently. First, assume that a PK analysis in rodents has indicated that, for any administered dose D, the internal dose distribution is approximately normal with mean, $\mu = 0.1\,D$, and standard deviation, $\sigma = 0.2\,\mu$. Thus,

$$f(d|D) = (1/(0.02D\sqrt{2\pi}))\exp(-(1/2)((d - 0.1D)/(0.02D))^2). \tag{5}$$

Suppose further that a simple 2-stage PD model links the internal dose to the tumor response, i.e.,

$$g(\text{tumor}|d) = 1 - \exp(-(\beta_1 d + \beta_2 d^2)). \tag{6}$$

The probability of a tumor is given by expression (2) with f and g given by (5) and (6), respectively.

Alternatively, assume that PK analysis has indicated that, for any administered dose D, the internal dose distribution is approximately normal with a Michaelis–Menten type mean, $\mu = 2\,D/(10 + D)$, and standard deviation, $\sigma = 0.2\mu$. Thus,

$$f(d|D) = (1/((0.4\,D/(10 + D))\sqrt{2\pi})) \times \exp(-(1/2)((d - 2D/(10 + D))/(0.4D/(10 + D)))^2) \tag{7}$$

Suppose further that in this case a simple Weibull PD model links the internal dose to the tumor response, i.e.,

$$g(\text{tumor}|d) = 1 - \exp(-\beta d^k). \tag{8}$$

Table 1
Hypothetical tumor dose–response data from a 2-year rodent bioassay

Dose	Group size	Number with tumors	Proportion with tumors
0	50	5	0.10
10	50	7	0.14
20	50	13	0.26
40	50	20	0.40