SRA Dose-Response Specialty Group
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Time-dose-response model

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The terror attacks on September 11, 2001 and the subsequent bio-terrorist releases of Bacillus anthracis raised public awareness of the potential bioterrorism. Effective responses to this threat (emergency preparedness, use of detectors, public education) depend on an understanding of the threat and its likelihood. Microbial risk assessment (MRA) is ideally suited for developing this understanding. As a major component of MRA, dose-response analysis which quantifies the hazard posed by an inoculated dose of organisms has been developed and widely used. Although the classical dose response models such as exponential and beta-Poisson models have been important to MRA for many years, they have limitations because they only describe the overall probability of an adverse effect, rather than the distribution of times since dosing that these effects may occur. It is well known that the infection is a time-dependent process and, phenomenologically, responses of animal to bacteria vary not only with the dose, but also with the time post-inoculation (TPI), i.e., incubation time, with infectious agents. TPI is therefore one of the most important factors required for better describing or predicting the long term effects of infectious diseases. For chemicals, the received dose is the total amount available to cause a response. However, bacteria and viruses have the ability to replicate in the host. Thus, a different aspect needs to be considered in microbial risk assessment - that is, not only the ability of the initial dose to survive but the extent to which it multiples in the host species. This resulting body burden may be the ultimate cause of the biological effect. To describe this issue comprehensively, it is desirable to incorporate the factor of time into the classical models. In this analysis, the exponential and beta-Poisson models were modified to allow modeling of survival post-inoculation. In the exponential model, the k parameter is the probability that a single organism can survive and proliferate in order to initiate infection. A single microorganism, having survived, can replicate and colonize, and this process will increase the probability that a response (infection, illness, or death) occurs, so it is reasonable to expect that as TPI increases, the risk will increase. To describe this in the exponential model, it is plausible to regard k as a time-dependent parameter. In the beta-Poisson model, the N50 parameter is the median infective dose (ID50) or median lethal dose (LD50). Just as for the exponential model, the risk of infection at a particular initial dose is expected to increase with TPI. Therefore, the initial dose to elicit response in 50% of the population (N50) is expected to decrease with TPI. To model these observed effects, the parameter k in the exponential dose-response model and the parameter N50 in the beta-Poisson model would be set equal to functions of time. These functions are presumably related to the (generally unobserved) multiplication of pathogens to an in vivo body burden at which response is elicited. Candidate functional forms for the time-dependent parameters would be proposed based on analysis of dose-response data sets in which survival over time was recorded. For the data collection, an extensive search on open literature was conducted and 24 sets of animal survival data administered with graded doses of various pathogens including Bacillus anthracis, Yersina pestis, Francisella tularensis and Mycobacterium tuberculosis were drawn for model fitting. For each survival dose-response data set, exponential and beta-Poisson models were fit to the cumulative dose response on each individual day. The

parameters and deviances were determined. The parameter k in the exponential model and N50 in the beta Poisson model for the cumulative response on each day were plotted as a function of TPI to explore the potential trends via regression functions implemented in the statistical software SPSS. An exponential-power relationship (a cumulative function of inverse Weibull distribution) and its simplified form - exponential-reciprocal dependency (a cumulative function of inverse exponential distribution) between parameters of classical dose-response models and TPI were found when model parameters were plotted against TPI for each survival dose-response data set. By adding these identified TPI dependencies into the classical dose-response models, significantly acceptable fits were achieved. The residual deviances of modified models with additional parameters are all significantly lower than the critical chi-square value. The modified beta-Poisson models with exponential-power or exponential-reciprocal dependency provided statistically acceptable fits for all the data sets. The modified exponential models with exponential-power or exponential-reciprocal dependency provided significantly acceptable fits for most of the data sets. This result shows that the functional form of our modifications to incorporate time-dose-response can be applied to multiple pathogens, routes of exposure and hosts. The narrower applicability of the exponential model is due to its assumption that host-pathogen interaction is a constant, while the beta-Poisson model assumes that host-pathogen interactions can be heterogeneous and described by parameter α in the model. In this study, no TPI dependency of α was found in all sets of data, which indicates that the degree of heterogeneity is independent of time, although it can be affected by the characteristics of pathogen, host, and the infection route. This is the first instance that a time-dose-response model for MRA system was developed and validated with data representing infections initiated by various pathogens. These time dependencies hypothetically reflect the kinetic bacterial growth and quantify the time effect on dose response. The new models described the development of animal infectious response over time and represented observed responses fairly accurately. The success of these models to fit survival data for four disparate pathogens with very different characteristics indicates that the models are of an appropriate form and flexible enough to model the many processes occurring in infections. This study provides an advanced approach for future microbial risk assessment frameworks. The new models can be used practically in areas such as epidemiological study, disaster preparedness, and emergency response.