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CENTER FOR ADVANCING MICROBIAL RISK ASSESSMENT

ADVANCES IN QMRA

INSIDE:

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CAMRA WIKI UPDATED

Contributing Author: Mark H. Weir, PhD, Michigan State University

The CAMRA wiki is aimed to be an innovative means for QMRA information, instruction and expansion. The new CAMRA wiki's operation is now set up to focus on dose-response data sets. In the next year other models and content will be added.

The CAMRA wiki includes a general overview of QMRA, featuring hazard identification, dose response assessment, exposure assessment, and risk characterization. CAMRA wiki information is searchable by pathogen, disease, and agent type (Category A,B, or C). Background information is currently being provided for a series of pathogens and we are compiling and uploading the largest array of optimized dose response models available. These models are a joint effort between Projects III lead by Dr. Haas at Drexel and Project I lead by Dr. Rose at MSU along with Dr. Weir the Associate Director of CAMRA.

Table 6 Best fitting model determination

Model	Deviance	Δ	$X^2_{0.95,1}$
Exponential	55.19	51.89	3.8
Beta Poisson	3.30		
Exponential is best fitting model			

Table 7 Optimized parameters for the best fitting (beta Poisson), obtained from 10,000 bootstrap iterations

Parameter	MLE Estimate	Percentiles					
		0.5%	2.5%	5%	95%	97.5%	99.5%
α	0.318	--	--	--	--	--	--
N_{50}	6,816	--	--	--	--	--	--
ID_{50}(# org)	869	51	129	156	4,621	6,999	26,859

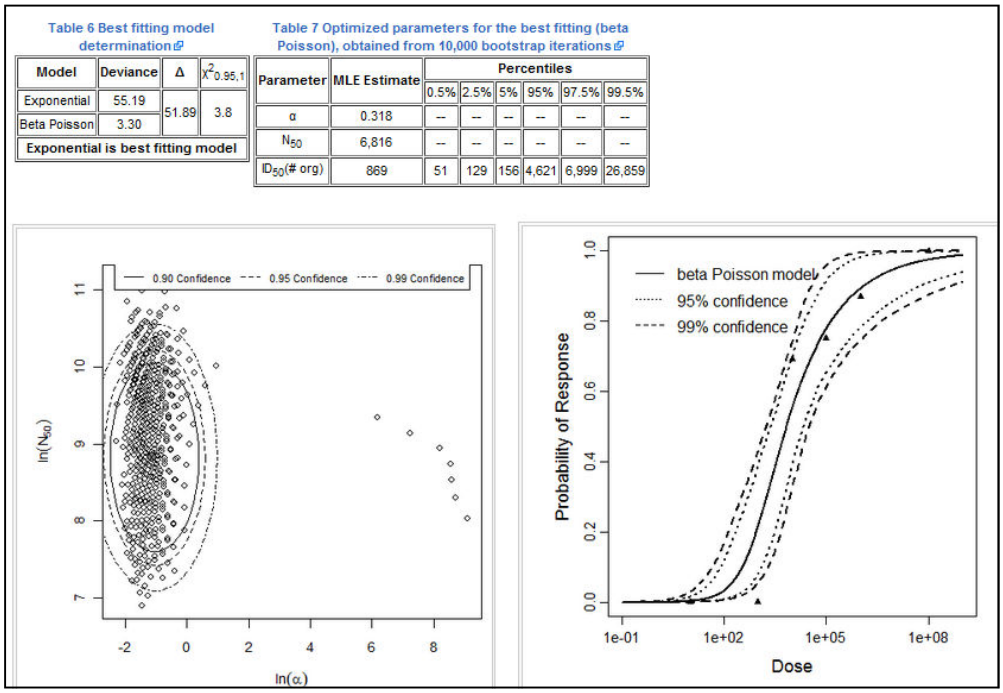

Figure 1. Example of best fit model and optimized parameter data provided on CAMRA wiki.

The wiki will be structured around 6 main pages based on the main steps in the QMRA paradigm as well as the expanded framework and tools CAMRA has developed thus far (or developed outside of CAMRA by collaborators). The wiki not only will provide various tools that have been developed over the years of CAMRA research but also allows CAMRA collaborators to update and upload their work.

The CAMRA wiki is available at http://wiki.camra.msu.edu. For further information please contact Mark Weir (weirma@msu.edu).

MULTIPLE INGESTION INNOCULATIONS OF A PRION AGENT

Contributing Author: Yin Huang, PhD, Michigan State University

Prions are 'self-replicating' basic proteins of small molecular weight. Prions form a new class of infectious agents responsible for a number of slow degenerative central nervous system diseases of humans and other animal species. Public awareness of prion diseases had been raised after an outbreak of bovine spongiform encephalopathy (BSE) occurred among cattle in many European countries and scientific evidence indicated the foodborne transmission of BSE to humans. An in-depth understanding of the time course of such disease and its dose dependence is crucial, which makes a time-dose-response model desirable. In prior studies (Huang et al. 2009), we have used quantitative methods and mathematical modeling to devise and verify the time-dose-response model based on clinical, pathophysiological and epidemiological data of various kinds of infectious diseases. However these models are undergoing further modification to describe the multiple dosing challenges and quantify the effect of time intervals between individual challenges on the host response to scrapie agents (a prion agent).

$$P(d,t) = 1 - \{[1 - F(d_1, t - t_1)] \times \cdots \times [1 - F(d_n, t - t_n)]\} \quad (1)$$

$$F(d,t) = 1 - e^{-G(t,\theta,\ldots)k_0 d} \quad (2)$$

$$F(d,t) = 1 - \left[1 + \frac{G(t,\theta,\ldots)d}{N_{50}} \times \left(2^{\frac{1}{\alpha}} - 1\right)\right]^{-\alpha} \quad (3)$$

To investigate the effect of multiple exposures to scrapie agent, data from a large-scale experimental investigation of repeated doses of transmissible spongiform encephalopathies affecting the incidence and incubation time of disease were analyzed. Diringer et al. (1998) investigated hamster response to multiple oral challenges of scrapie agent. Previously proposed time-dose-response model were further modified to fit with the data of repeated dosing. For a multiple dose exposure regime composed of separated challenges, denoting the temporal distribution of cumulative probability of response initiated by a dose d_i inoculated at time t_j as $F(d_i, t- t_j)$, and assuming an independent and identical relationship between multiple doses for each schedule, the overall probability of response caused by the multiple doses can be given as: where; $G(t,\Theta,\ldots)$ is an empirical function or a cumulative distribution function (CDF) that reflects the distribution of time to response from challenge with an infectious agent. The parameter θ is the time parameter. k_0 is the parameter for the exponential model, α and N_{50} are the parameters for and the beta-Poisson model.

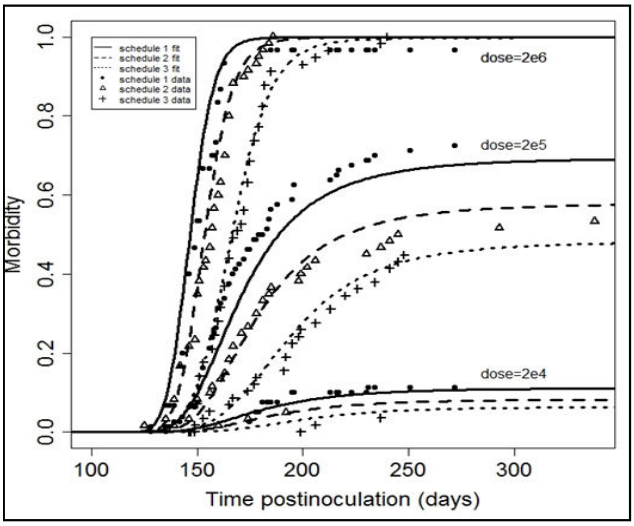

Figure 1. Model with the optimized parameter estimates for pooled

The animal survival data by Diringer et al. (1998) were fit to Equations 1-3 with different candidate distributions. In all cases, the modified beta-Poisson models did not provide a significantly better fit over the modified exponential models. The exponential model incorporating an inverse-Weibull distribution provided the best fits to the data of schedules 1 and 3, while the data of schedule 2 is best fit by the exponential model incorporating a gamma distribution. To show such difference statistically, the pooling of these data with the same dose parameters was conducted but proved unsuccessful. The model with the optimized parameter estimates for the pooled data is plotted with the observed data in Fig. 1 for comparison. It can be seen that the model estimates are closely aligned with the data. It is shown in Fig. 1 that the dosing schedule has significant impact on the response in the intermediate dose range. The exponential parameter (k_0) generally decreases from schedule 1 to 3, which indicates a decreasing probability of infection with increasing interval between individual challenges. The response of fixed total dose was reduced when the material was presented as multiple challenges, and as the time between challenges lengthens. To show such difference statistically, the pooling of these data with the same dose parameters was conducted and proven not successful. It can be seen that probability of infection decreases as the interval between successive challenges increases. It is against the hypothesis that each dose acts independently. This may demonstrate that greater interval between exposures leads to a higher degree of immune response.

References:

Huang, Y., Bartrand, T.A., Haas, C.N. and Weir, M.H. (2009) Incorporating time postinoculation into a dose-response model of yersinia pestis in mice. Journal of Applied Microbiology 107, 727-735.

Diringer, H., roehmel, J. and Beekes, M. (1998) Effect of repeated oral infection of hamsters with scrapie. Journal of General Virology 79, 609-612.

EXPANDING OUR UNDERSTANDING IN THE ROLE FOMITES PLAY IN RISK

Contributing Author: Mark H. Weir, PhD, Michigan State University

While QMRA is extremely useful there are significant data gaps in understanding the true nature of risks to users of indoor spaces after a release of pathogens. One of the major data gaps for indoor air environments is the interaction between fomite, pathogen concentration and human interaction with fomites. Therefore an investigation into the recovery efficiencies from various non-porous fomites was initiated to address the pathogen concentration on fomites. Non-porous fomites were chosen since in earlier studies it was found that the porous nature of the fomites had a significant effect on the associated fomite to hand transfer efficiency (Rusin *et al*. 2002).

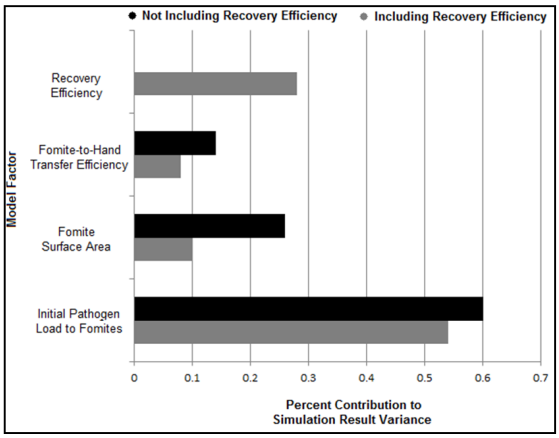

Figure 3. Sensitivity of risk estimate using recovery efficiency

Multiple fomites were evaluated as well as, fomite surface area, elution technique and eluates. This was performed for a non-spore forming bacterial surrogate, *Staphylococcus aureus* (*S. aureus*), and a virus surrogate, bacteriophage P22 (P22). When the best elution and eluate combination was determined, this combination was used. Looking at figure 2 one can see that the recovery efficiency from the fomites decrease significantly as the surface area was increased initially, however this tended to level off at the much larger surface area. In the mid ranged surface area, the overall variance from the mean was also reduced.

These recovery efficiencies were then used to develop a fomite QMRA, where the dose estimated from a topical pathogen, similar to *S. aureus* had contaminated the workspace of a shared office. A Markov chain model was used to simulate office use by a contaminator who used the office first adding bacteria to aluminum, wood laminate and plastic fomites for two hours of office use. Then two subsequent users entered and used the same workspace individually for two hours each, thus contaminating themselves due to the presence of *S. aureus* on the fomites. These subsequent users are the at risk group, however overall the risks were quite low. The sensitivity chart in figure 3, shows that recovery efficiency demonstrates a significant impact on the risk assessed to the office community. Overall we found that recovery efficiency is dependent on the measurement technique as well as the fomite material and surface area, and demonstrated the impact on the associated risk estimate. Further work is needed to understand the role of fomites in disease transmission.

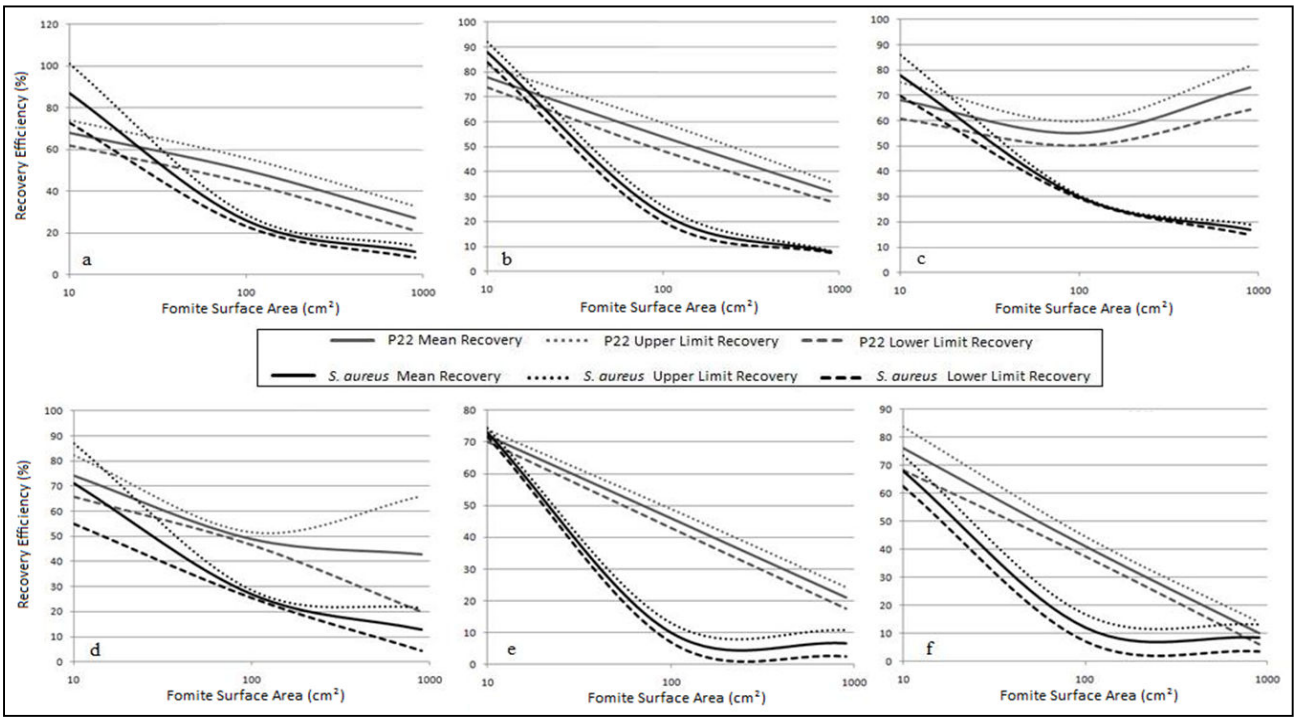

Figure 2. Recovery efficiencies for: aluminum (a), ceramic (b), glass (c), plastic (d), steel (e), wood laminate (f), where the lower and upper limit is from one standard deviation.

References:

Rusin, P., Maxwell, S. and Gerba, C.P. 2002. Comparative surface to hand and finger to mouth transfer efficiency of gram-positive, gram-negative bacteria and phage. *J. Appl. Microbiol*. 93:585-592

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DR. JOAN B. ROSE ELECTED TO NATIONAL ACADEMY OF ENGINEERING

Contributing Author: Rachel McNInch, M.S., Michigan State University

CAMRA co-director, Dr. Joan B. Rose was recently elected as a member of the National Academy of Engineering (NAE) for her contributions to improving water quality safety and public health. NAE membership is one of the highest professional distinctions awarded to engineers, honoring those who have made outstanding contributions to the field through research, practice, education, innovation, and publications. Dr. Rose is among 68 new members and nine foreign associates honored in February and among 2,290 total U.S. members. Of the total U.S. members, she joins an elite team of only 107 females, 7 of whom were honored this year.

All though a distinction for all members, this NAE honor is quite unique to Dr. Rose, a microbiologist by training receiving both her M.S., and PhD in Microbiology from the University of Wyoming and University of Arizona, respectively. Since starting her career she has become an international expert in water microbiology, water quality and public health safety publishing more than 300 manuscripts. She has been involved in the investigation of numerous waterborne outbreaks world-wide, examining new molecular methods for waterborne pathogens, zoonotic agents (such as *Cryptosporidium*), enteric viruses and source tracking. Her career has advanced the information needed to establish science-based quantitative microbial risk assessments.

Other career distinctions include recipient of the Clarke Water Prize in 2001 (one of 5 international awards for contributions to water science and technology), the first Hei-jin Woo Award in 2008 for Achievements of Women in the Water Profession from the International Water Association, and the Public Service Medal from the Singapore Ministry of Environment and Water Resources in 2009 for her work on water and health.

Link to press release: http://www.nae.edu/Activities/MediaRoom/20095/42133.aspx

2011 CAMRA SUMMER INSTITUTE

Contributing Author: Mark H. Weir, PhD, Michigan State University

The 2011 CAMRA Quantitative Microbial Risk Assessment (QMRA) Summer Institute will be held August 21-26 at Michigan State University in East Lansing, Michigan. Our previous institutes have been greatly successful, due primarily to our network members our student base has made this possible. We invite all CAMRA Listserv members to inform their colleagues who may be interested in improving or developing their QMRA knowledge and skills. Details and application materials are available on the CAMRA website (camra.msu.edu). Funding opportunities are also available. Please visit the CAMRA website or contact Mark Weir (weirma@msu.edu) for further information.

2009 CAMRA QMRA Summer Institute participants and leaders.