INTRODUCTION

Infectious foodborne diseases are of major importance worldwide and of special importance in the United States. Two emerging agents of increasing concern are Listeria monocytogenes (Gellin et al. 1991) and E. coli O157:H7 (Griffin and Tauxe 1991). Up to 25,000 US cases of listeriosis per year have been estimated to occur (Todd 1989). Griffin and Tauxe (Griffin and Tauxe 1991) have estimated the incidence of E. coli O157:H7 illness (laboratory confirmed cases) in Canada to be 5.2 per 100,000 persons per year, which would translate into a total US burden of approximately 14,000 cases per year. Both of these organisms have high severity, particularly in sensitive subpopulations. In addition, the above numbers probably do not reflect a much larger disease burden of mild to moderate symptoms, or undiagnosed illnesses.
In prior work, the authors have developed microbial risk assessment methodology for food and waterborne organisms (Haas 1983, Regli et al. 1991, Haas et al. 1996, Medema et al. 1996). The objective of the present work was to develop and validate dose response models for these two organisms.

Methods

A comprehensive review of literature was conducted to locate dose-response data sets for the two organisms of concern. Unfortunately, no human dose-response data could be located. However, animal dose-response studies were available for both organisms.

Listeria dose-response data was obtained from studies done by (Audurier et al. 1980) and (Donnelly et al. 1989). Audurier et al exposed Swiss conventional female OF1 mice to L.monocytogenes 10401 whereas Donnelly et al exposed C57B1/6J mice with varying concentration of L.monocytogenes F5817. Audurier et al orally dosed the animals using water, while Donnelly et al dosed mice with L.monocytogenes suspended in 11% nonfat milk solids. In both studies, infection was confirmed through enumeration of viable bacteria in the spleen, liver, lungs, brain and kidneys.

E. coli O157:H7 data was obtained from a study done by Pai and co-workers (1986). Pai et al (Pai et al. 1986) studied the pathogenesis of diarrheal disease due to E. coli O157:H7. New Zealand white infant rabbits (2-3 days old) were inoculated with 1 mL of bacterial suspension through a catheter tube passed through the oral route. After inoculation, the animals were observed daily for diarrhea.

These dose response data were fitted to the exponential and beta-Poisson dose-response models that have previously been used to fit microbial data (Haas 1983, Crockett et al. 1996, Haas et al. 1996). Fitting was performed using maximum likelihood, either on a spreadsheet or using the MATLAB(The MathWorks Inc. 1994) programming environment on a Macintosh™ computer(Haas 1994).
To validate the dose-response models, which were obtained on animals, outbreaks in which the exposure and attack rate were both reported were used. One Listeria and one E. coli outbreak are illustrated for this comparison.

An outbreak of listeriosis occurred in rural Illinois in the summer of 1996. An outbreak of gastroenteritis and fever occurred among persons who attended a picnic in Elizabeth, Illinois (Dalton 1997). Forty-five of the 60 people who consumed chocolate milk reported illness that met the case definition, as compared with none of the 22 people who did not drink the contaminated chocolate milk. A total of 5,600 8-oz cartons of chocolate milk were manufactured on June 24, with an expiration of July 12. No defect in pasteurization process was identified. The company log shows that the chocolate milk was transported to Elizabeth, Illinois without refrigeration. Listeria monocytogenes was isolated from multiple unopened products from the dairy. Two unopened cartons of chocolate milk yielded $1.2 \times 10^9$ and $8.8 \times 10^8$ CFU/mL.

In fall of 1995 there was an outbreak of E. coli infection in an Oregon community (Keene and Sazie 1997). Jerky prepared from deer meat was implicated as the source of the outbreak. There were six confirmed cases that were identified from three families and 2 friends who were visiting. Over 500 g of the jerky was consumed in two days. The daily attack rate was determined to be 0.2308. Two pieces of leftover jerky was tested for E.coli O157:H7. They tested positive and a quantitative enumeration revealed E.coli O157:H7 concentrations ranged from 3 to 93 CFU/g.

Results

Dose-Response Models

For the three data sets examined (two Listeria dose response data sets and the E. coli O157:H7 data set), the beta-Poisson dose-response model providing an acceptable fit, which was significantly better than then exponential. The beta-Poisson dose-response equation relating risk on a single exposure ($p$) to dose is written as:
\[ \pi = 1 - \left[ 1 + \frac{d}{N_{50}} \left( 2^{1/\alpha} - 1 \right) \right]^{-\alpha} \]  

(1)

where \( N_{50} \) is the median effective dose (to produce the end-point, e.g., illness) and \( \alpha \) is a shape parameter (as this approaches infinity, the beta-Poisson model approaches the exponential model).

Table 1 summarizes the best-fit dose response parameters, along with the significance level (p value). A p value in excess of 0.05 indicates an acceptable fit, which was determined by evaluating the residual deviance against an appropriate \( \chi^2 \) statistic (Morgan 1992).

<table>
<thead>
<tr>
<th>Data set</th>
<th>Best Fit Dose Response Parameters</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( N_{50} )</td>
<td>( \alpha )</td>
</tr>
<tr>
<td>E. coli O157:H7</td>
<td>596,000</td>
<td>0.49</td>
</tr>
<tr>
<td>Listeria (Audurier)</td>
<td>2,100,000</td>
<td>0.17</td>
</tr>
<tr>
<td>Listeria (Donnelly)</td>
<td>272</td>
<td>0.25</td>
</tr>
</tbody>
</table>

The two Listeria dose-response data sets could not be pooled, i.e., there was a statistically significant difference between the dose-response relationships in the two studies. The difference in dose-response curves in the two studies may be due to a variety of factors. For example, The Donnelly et al. study administered the dose by gavage, while the Audurier et al. study dosed the mice orally. Furthermore, the Donnelly et al. study used milk as the vehicle of exposure, while water was the vehicle of exposure in the Audurier et al, study. Milk could neutralize the stomach acid, thereby minimizing gastrointestinal losses of \( L.\text{monocytogenes} \), thus resulting in lower \( N_{50} \) values.
With reference to the outbreaks described earlier, Table 2 summarizes the observed estimated daily dose of organisms and the observed daily risk of illness. From the dose-response relationships, the imputed daily dose may be computed given the observed daily risk. We also show the 95% confidence region to this computed dose (based on our computations of the confidence region for the dose-response parameters). In the case of Listeria monocytogenes, since there are two dose-response relationships (Table 1), we can compute the imputed dose in two ways.

Examination of Table 2 indicates consistency between the observed and imputed doses in the case of E. coli O157:H7, i.e., the estimates for observed daily dose overlap the imputed dose range. Hence, at least based on this single outbreak, good concordance is exhibited for E. coli O157:H7.

In the case of Listeria monocytogenes, it is clear from Table 2 that there is a substantial difference in estimated exposure using the two dose-response relationships. The Audurier dose-response relationship appears to be more consistent with the observed exposure in this particular outbreak, although the observed exposure is at the upper range of the imputed dose-response.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Observed Estimated Daily Dose</th>
<th>Observed Daily Risk</th>
<th>Imputed Dose Best value (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli O157:H7</td>
<td>750-23,250</td>
<td>23%</td>
<td>1.345 x 10&lt;sup&gt;8&lt;/sup&gt; (1000-1.2 x 10&lt;sup&gt;6&lt;/sup&gt;)</td>
</tr>
<tr>
<td>L. monocytogenes</td>
<td>2.1-2.9 x 10&lt;sup&gt;11&lt;/sup&gt;</td>
<td>75%</td>
<td>4600 (660-1 x 10&lt;sup&gt;6&lt;/sup&gt;) (**)</td>
</tr>
</tbody>
</table>

(*) from Audurier dose-response

(**) from Donnelly dose-response
In the case of both organisms, it is interesting and reassuring that dose-response relationships from animal data appear to provide useful benchmarks for risks to humans. This is the first direct work to address this point for infectious microorganisms, and future studies should examine the utility of animal models for particular organisms in generating dose-response information.

A full report of these studies is contained in the thesis of Aadithya Thayyar-Madabusi (Thayyar-Madabusi 1998), including illustrations of use of these relationships for Monte Carlo calculations, and comparison with additional outbreak situations.

Conclusions

Based on this investigation, it is concluded that:

1) the dose-response relationships for both E. coli O157:H7 and L.monocytogenes can be adequately depicted by the beta-Poisson model.

2) Animal data for the two organisms appears to be in concordance with risk as observed in several outbreaks.

Acknowledgments

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References


