FAO/WHO *Listeria monocytogenes* Quantitative Microbiological Risk Assessment

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Risk assessment of *Listeria monocytogenes* in ready-to-eat foods

5th in the JEMRA series

Background

- Codex Alimentarius Committee on Food Hygiene (CCFH) was developing guidance “Code of Practice for the Control of *Listeria monocytogenes* in Ready-to-eat Foods”

- Included consideration of potential risk management metrics (e.g., microbiological criteria, food safety objectives, performance objectives)

- Asked JEMRA (FAO/WHO) to conduct risk assessment
CCFH posed three questions:

- What would be the impact of varying “criteria” between “absence in 25 g” to 1000 CFU per gram on the risk of listeriosis?
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- What would be the impact of varying “criteria” between absence in 25 g to 1000 CFU per gram on the risk of listeriosis?

- What is the difference in risk associated with foods that do and do not support growth of *L. monocytogenes*?
Background

• CCFH posed three questions:
  ▫ What would be the impact of varying “criteria” between absence in 25 g to 1000 CFU per gram on the risk of listeriosis?
  ▫ What is the difference in risk associated with foods that do and do not support growth of *L. monocytogenes*?
  ▫ What is the relative risk of listeriosis among different subpopulations as compared to the general population?
Since one of the first international JEMRA also used it as an “educational opportunity”

- Strengths and weaknesses of data sources for dose-response modeling
- Approaches to performing exposures assessments
- Role of predictive microbiology
Approach to Developing Risk Assessment
International Risk Assessment Team

- **Drafting Team:**
  - R. Buchanan, Roland Lindqvist, Tom Ross, Mark Smith, Ewen Todd, Richard Whiting

- **Drafting and Review Assistance from:**
  - E.A. Jenkins, M. Vigneault, J. Farber, and W. Ross – Health Canada
  - S. Rasmussen, University of Tasmania
  - FDA/FSIS *Listeria monocytogenes* Risk Assessment Team
  - Meat and Livestock Australia
  - Australian and New Zealand Food Authority
Approach

• Limited time and resources
• Complicated by international nature of risk assessment team
• Extensive hazard characterization with “simplified” dose response model
• Limited exposure assessment
• Used as basis for answering questions as simply as possible
Approach

- Did quantitative risk ranking risk assessment but with four foods only
  - Pasteurized milk
  - Ice cream
  - Smoked fish
  - Fermented meats

- Chosen to represent certain characteristics
Approach

- **Pasteurized Milk**
  - Rarely contaminated, allows growth, high consumption

- **Ice cream**
  - Rarely contaminated, does not allow growth, high consumption

- **Smoked fish**
  - Often contaminated, allows growth, low consumption

- **Fermented meat**
  - Often contaminated, does not allow growth, low consumption
Hazard Identification
Hazard Identification

- Short
- Role as foodborne pathogen well established
- Focused on invasive listeriosis and did not consider listeric gastroenteritis
Hazard Characterization
Hazard Characterization

- Extensive review of information on biological basis of dose-response relations
- Extensive review of dose-response modeling approaches
- Reviewed impact on assumption of maximum levels of *L. monocytogenes* growth in foods
No available model met the all needs of requestors (FAO, WHO, CCFH)

- FDA (2001) approach noteworthy, but mathematically simpler model desirable
- Also asked to provide a more detailed consideration of susceptible subpopulations
Dose Response Relations

- Decided to refine the approach based on annual disease statistics + exposure data
  - Exponential model supported by FDA risk assessment
  - FDA risk assessment provided detailed exposure assessment
  - U.S. FoodNet provided estimate of incidence of listeriosis
  - Developed D-R curves for “more susceptible” and “less susceptible” populations
Effect of Maximum Dose Level

- The calculation of the dose-response is dependent on knowledge of the maximum number of cells consumed in the various RTE foods.

- Substantial uncertainty about the maximum level obtained in foods.
# Dose Response Models Used

<table>
<thead>
<tr>
<th>Increased Susceptibility Population</th>
<th>Median R-value</th>
<th>5&lt;sup&gt;th&lt;/sup&gt; Percentile R-value</th>
<th>95&lt;sup&gt;th&lt;/sup&gt; Percentile R-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$1 \times 10^{-12}$</td>
<td>$3 \times 10^{-13}$</td>
<td>$9 \times 10^{-12}$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Decreased Susceptibility Population</th>
<th>Median R-value</th>
<th>5&lt;sup&gt;th&lt;/sup&gt; Percentile R-value</th>
<th>95&lt;sup&gt;th&lt;/sup&gt; Percentile R-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$2 \times 10^{-14}$</td>
<td>$4 \times 10^{-15}$</td>
<td>$3 \times 10^{-13}$</td>
</tr>
</tbody>
</table>
Exposure Assessment
Exposure Assessment

• Used FDA/FSIS data for the four selected foods
  ▫ *L. monocytogenes* contamination
  ▫ Storage times and temperatures
  ▫ Serving sizes and frequencies

• Also used FDA/FSIS distributions for all RTE food values and distributions
Risk Characterization

Answering the CCFH Questions
Question 1: “Regulatory Criteria”

• What would be the impact of varying “criteria” between “absence in 25 g” to 1000 CFU per gram on the risk of listeriosis?

• In answering this question considered:
  ▫ Distribution of *L. monocytogenes* levels using concentrations from FDA/FSIS risk assessment
  ▫ Potential for level of *L. monocytogenes* to increase if a standard was put into place
  ▫ Role of compliance to a criterion
**Question #1: Role of Compliance**

<table>
<thead>
<tr>
<th>% Defectives (10^6 CFU/g)</th>
<th>Criteria: 0.04 CFU/g</th>
<th>Criteria: 100 CFU/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.000000</td>
<td>0.5*</td>
<td>5.7</td>
</tr>
<tr>
<td>0.000001</td>
<td>1.7</td>
<td>6.9</td>
</tr>
<tr>
<td>0.000010</td>
<td>12.3</td>
<td>17.4</td>
</tr>
<tr>
<td>0.000100</td>
<td>119</td>
<td>124</td>
</tr>
<tr>
<td>0.001000</td>
<td>1,185</td>
<td>1,191</td>
</tr>
<tr>
<td>0.010000</td>
<td>2,133</td>
<td>2,133</td>
</tr>
<tr>
<td><strong>0.018000</strong></td>
<td><strong>2,133</strong></td>
<td><strong>2,133</strong></td>
</tr>
<tr>
<td>0.100000</td>
<td>11,837</td>
<td>11,848</td>
</tr>
<tr>
<td>1.00000</td>
<td>117,300</td>
<td>117,363</td>
</tr>
</tbody>
</table>

* Annual cases
Question 2: Increase in Risk Due to Growth

• What is the difference in risk associated with foods that do and do not support growth of *L. monocytogenes*?

• In addressing question #2, had to consider
  ▫ Conditions between purchase and consumption
  ▫ Variability in those conditions
  ▫ Shelf-life of the product
  ▫ Rate of growth for *L. monocytogenes* to grow under those conditions
  ▫ Differences in final level of exposure
Question 2: Increase in Risk Due to Growth

- Used data from FDA/FSIS risk assessment for the four at retail
  - Distribution of *L. monocytogenes* levels
  - Time and temperature of storage between purchase and consumption
  - Growth rates values

- Used calculated levels at consumption to determine risk per serving and risk per annum
# Question 2: Increase in Risk Due to Growth

<table>
<thead>
<tr>
<th>Food</th>
<th>Cases per 100,000 people</th>
<th>Cases per 1,000,000 servings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>0.0910000</td>
<td>0.0050000</td>
</tr>
<tr>
<td>Ice Cream</td>
<td>0.0001200</td>
<td>0.0000140</td>
</tr>
<tr>
<td>Smoked Fish</td>
<td>0.0046000</td>
<td>0.0210000</td>
</tr>
<tr>
<td>Fermented Meats</td>
<td>0.0000066</td>
<td>0.0000025</td>
</tr>
</tbody>
</table>
Question #3: Relative Susceptibility

• What is the relative risk of listeriosis among different subpopulations as compared to the general population?

• Required that the risk assessment consider different dose-response relations for different subpopulations
Developed dose-response model for each of a series of more susceptible subpopulations based on relative susceptibility values

Based on extensive epidemiological data available from France and United States
Question #3: Dose-Response Curves

- Developed Relative Susceptibility values based on frequency of listeriosis among different subpopulations versus size of that population and then comparing that to healthy population

\[ RS = \frac{\text{Cases/Subpopulation Size}}{\text{Cases/Healthy Population}} \]

\[ RS = \frac{P_{\text{subpopulation}}}{P_{\text{healthy}}} \]
## Question #3: Relative Susceptibility

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant</td>
<td>2584</td>
</tr>
<tr>
<td>AIDS</td>
<td>865</td>
</tr>
<tr>
<td>Dialysis</td>
<td>476</td>
</tr>
<tr>
<td>Cancer-Pulmonary</td>
<td>229</td>
</tr>
<tr>
<td>Cancer-Bladder and prostate</td>
<td>112</td>
</tr>
<tr>
<td>Cancer-Gynaecological</td>
<td>66</td>
</tr>
<tr>
<td>Cancer-Blood</td>
<td>1364</td>
</tr>
<tr>
<td>Cancer-Gastrointestinal and liver</td>
<td>211</td>
</tr>
<tr>
<td>Non-cancer liver disease</td>
<td>143</td>
</tr>
<tr>
<td>Diabetes, non-insulin dependent</td>
<td>25</td>
</tr>
<tr>
<td>Diabetes, insulin dependent</td>
<td>30</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>18</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>14</td>
</tr>
<tr>
<td>Over 65 years old</td>
<td>8</td>
</tr>
<tr>
<td>Less than 65 years, no other condition</td>
<td>1</td>
</tr>
</tbody>
</table>
Question #3: Dose-Response Curves

• Generate dose-response curves taking advantage of single parameter Exponential model
  ▫ $RS = \frac{P_{subpopulation}}{P_{healthy}}$
  ▫ $RS = \frac{1 - \exp(-r_{subpopulation} \times N)}{1 - \exp(-r_{healthy} \times N)}$

• Generate dose-response curve for subpopulation by rearranging
  ▫ $r_{subpopulation} = -\ln[RS \times \exp(r_{healthy} \times N) - (RS - 1)] / N$
## Question #3: Relative Susceptibility

<table>
<thead>
<tr>
<th>Condition</th>
<th>r-value</th>
</tr>
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<tbody>
<tr>
<td>Transplant</td>
<td>$1.41 \times 10^{-10}$</td>
</tr>
<tr>
<td>AIDS</td>
<td>$4.65 \times 10^{-11}$</td>
</tr>
<tr>
<td>Dialysis</td>
<td>$2.55 \times 10^{-11}$</td>
</tr>
<tr>
<td>Cancer-Pulmonary</td>
<td>$1.23 \times 10^{-11}$</td>
</tr>
<tr>
<td>Cancer-Bladder and prostate</td>
<td>$5.99 \times 10^{-12}$</td>
</tr>
<tr>
<td>Cancer-Gynaecological</td>
<td>$3.53 \times 10^{-12}$</td>
</tr>
<tr>
<td>Cancer-Blood</td>
<td>$7.37 \times 10^{-11}$</td>
</tr>
<tr>
<td>Cancer-Gastrointestinal and liver</td>
<td>$1.13 \times 10^{-11}$</td>
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<tr>
<td>Non-cancer liver disease</td>
<td>$7.65 \times 10^{-12}$</td>
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<tr>
<td>Diabetes, insulin dependent</td>
<td>$1.60 \times 10^{-12}$</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>$9.60 \times 10^{-13}$</td>
</tr>
<tr>
<td>Over 65 years old</td>
<td>$4.01 \times 10^{-13}$</td>
</tr>
<tr>
<td>Less than 65 years old</td>
<td>$5.34 \times 10^{-14}$</td>
</tr>
</tbody>
</table>
Question #3: Dose-Response Curves for Different Sub-populations

Dose-response curves based on French relative susceptibility data

-15.0
-10.0
-5.0
0.0
0 5 10
Log (L. monocytogenes per serving)

Log (Risk per serving)

-15.0
-10.0
-5.0
0.0
0

Transplant
AIDS
Dialysis
Cancer--Pulmonary, etc
Bladder
Gynecological
Diabetes, hep. Alcohol
Over 65 years
Less than 65, no other
Summary: FAO/WHO Risk Assessment

- Developed a quantitative risk assessment that built on the concepts of the FDA/FSIS assessment, but focused on a somewhat simpler evaluation.
- Successfully addressed CCFH questions.
- Demonstrated that can “internationalize” risk assessments done by national governments.