Chemical & Microbial Risk Assessment: 
*Case studies to demonstrate similarities and differences*

Jane M. Van Doren  
*Branch Chief, Risk Analysis Branch*

Deborah Smegal  
*Branch Chief, Contaminants Assessment Branch, DRDA*

Sherri Dennis  
*Director, Division of Risk & Decision Analysis*

*Office of Analytics & Outreach*
Safety Assessment and Risk Assessment at FDA

- **Safety assessment**: provides a verdict of what is a ‘safe’ level based on the conventions of the analysis

- **Risk assessment**: quantifies the level of risk associated with specific exposures and degree of uncertainty inherent in the risk estimate. Used to compare options.
  - **Quantitative assessment**: the risk is expressed as a mathematical statement of the chance of illness or death after exposure to a specific hazard, and it represents the cumulative probabilities of certain events happening and the uncertainty associated with those events.
  - **Qualitative risk assessments**: use verbal descriptors of risk and severity (e.g., higher, lower), and often involve the aggregation of expert opinions.

(adapted from “Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food” FDA Threshold Working Group, March 2006)
Various risk assessment questions

- What is the risk to consumers from consumption of rice potentially contaminated with arsenic? Does it vary by rice type and what can we do about it?

- California almonds to be sold in U.S. must undergo treatment to at least 4-log Salmonella reduction. Is this an acceptable “pasteurization” step or is a higher reduction step needed?

- When should we reopen oyster harvest areas following a combined sewer overflow or wastewater treatment plant disinfection failure?

- How do the risks of listeriosis from consumption of soft-ripened cheese made from unpasteurized milk compare with that from pasteurized milk and how might we reduce these risks?

- Which foods should be designated as having potential for high risk in the context of FSMA sect. 204?
Role of Risk Assessment at FDA

- **Informs risk managers of where to look, to:**
  - set priorities / allocate resources
  - identify major risk-contributing events in the farm-to-fork continuum

- **Allows risk managers to evaluate effectiveness of interventions:**
  - potential or equivalent control measures
  - proposed standards and criteria
  - contribution of compliance to risk management

- **Informs risk communicators in:**
  - developing communication/outreach messages
  - determining population sub-groups “at increased risk”
  - assessing uncertainty and variability
Type of Risk Assessment Developed? *Fit for Purpose*

- Quantitative Risk Assessment
- Semi-quantitative risk assessment
- Qualitative Risk Assessment
- Risk Ranking
- Risk Profile
# Quantitative Chemical Risk Assessment vs. Microbial Risk Assessment

<table>
<thead>
<tr>
<th>Chemical RA</th>
<th>Microbial RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chronic or Acute exposure</td>
<td>• Acute exposure</td>
</tr>
<tr>
<td>• No “outbreaks” (chronic)</td>
<td>• Outbreaks - Identified (countable) cases</td>
</tr>
<tr>
<td>• Typically, exposure assessment begins at retail</td>
<td>• Typically, exposure assessment begins at production</td>
</tr>
<tr>
<td>• Dose-Response, can include multiple health endpoints and/or relevant subpopulations</td>
<td>– Bacterial growth, inactivation</td>
</tr>
<tr>
<td>• Many don’t require “What if?” scenarios</td>
<td>• Dose-Response, typically illness as endpoint, sometimes need to differentiate among subpopulations</td>
</tr>
<tr>
<td></td>
<td>• “What if?” scenarios important component</td>
</tr>
<tr>
<td></td>
<td>– Risk management options &amp; exceptional events</td>
</tr>
</tbody>
</table>
Risk Assessment Case Studies

• Inorganic Arsenic in Rice and Rice Products
• *Listeria monocytogenes* in soft-ripened cheese

Focus

• Exposure Assessment
• “What if?” Scenarios & Risk Management Options
• Areas of ongoing development
CONTRIBUTORS

Project Co-Leads:
Sherri Dennis, PhD
Suzanne Fitzpatrick, PhD, DABT

Project Manager:
Dana Hoffman-Pennesi, MS

Risk Modelers:
Clark Carrington, PhD, DABT (Retired April 2015)
Régis Pouillot, DVM, PhD

Subject Matter Experts:
Katie Egan (Retired July 2013)
Brenna Flannery, PhD
Richard Kanwal, MD
Deborah Smegal, MPH
Judi Spungen, MS
Shirley Tao, PhD

Technical Writer/Editor:
Susan Mary Cahill
Risk Assessment Charge

• Quantitatively evaluate the cancer occurrence from longer-term exposure to inorganic arsenic in rice and rice products and the impact potential risk management options might have on this risk

• Qualitatively evaluate certain non-cancer risks, in certain susceptible life stages, from inorganic arsenic in rice and rice products.
<table>
<thead>
<tr>
<th>Hazard</th>
<th>Inorganic Arsenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food</td>
<td>Rice and foods containing rice</td>
</tr>
<tr>
<td>Population</td>
<td>General population in U.S. Infants Children 0-6 Pregnant women (prenatal exposure)</td>
</tr>
<tr>
<td>Health endpoint</td>
<td>Cancer (quantitative assessment) -Bladder -Lung Adverse pregnancy outcomes (qualitative) Neurodevelopment (qualitative)</td>
</tr>
</tbody>
</table>
Quantitative Risk Assessment

Assess the risk of illness from consumption of a product by a population

Hazard Identification
Describes hazard/host/food/food characteristics that impact the risk

Exposure Assessment
How often is the hazard ingested?
How many are ingested?

Hazard Characterization
For a given ingested dose, how likely is the adverse effect?

Risk Characterization
What is the probability of occurrence of the adverse effect?
What is the impact of interventions to change the risk?
Inorganic Arsenic in rice Exposure Assessment
Hazard Characterization

iAs Dose-Response

Dose-Response Model for Bladder Cancer

Dose-Response Model for Lung Cancer
### Lifetime Cancer (Bladder + Lung) Risk Estimates attributable to inorganic arsenic in rice and rice products

**Cancer Cases per Million for Per Capita Consumption**

<table>
<thead>
<tr>
<th>Rice Type</th>
<th>Median Estimate [90% CI] Infants (&lt;1 y)</th>
<th>Median Estimate [90% CI] Children (0-6 y)</th>
<th>Median Estimate [90% CI] Lifetime (0-50 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Rice Grain &amp; Rice Products</td>
<td>2.3 [0.4.6]</td>
<td>9.1 [0.19]</td>
<td>39 [0.79]</td>
</tr>
<tr>
<td>All White Rice</td>
<td>-</td>
<td>8.0 [0.16]</td>
<td>34 [0.69]</td>
</tr>
<tr>
<td>All Brown Rice</td>
<td>-</td>
<td>1.2 [0.2.4]</td>
<td>5.4 [0.11]</td>
</tr>
<tr>
<td>White Long Grain Rice</td>
<td>-</td>
<td>3.5 [0.7.5]</td>
<td>15 [0.31]</td>
</tr>
<tr>
<td>White Instant/Pre-cooked</td>
<td>-</td>
<td>&lt;1 [0.0.2]</td>
<td>&lt;1 [0.0.97]</td>
</tr>
<tr>
<td>Infant White Rice Cereal</td>
<td>1.6 [0.3.4]</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Infant Brown Rice Cereal</td>
<td>1.9 [0.3.9]</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Inorganic Arsenic in Rice and Rice Products

“What if?” scenarios
Risk Management Options
What is the impact of reducing number of servings?

- **Lifetime (0-50 y), All Brown/White, long grain**
- **Children (0-6 y), All Brown/White, long grain**
- **Infant (<1 y), Brown/White rice Cereal**

**Graph:**
- Y-axis: Median Estimated Cases per Million
- X-axis: Servings/day

- Linear relationships are observed between the number of servings and the estimated cases for each age group.

**Legend:**
- Black line: Children (0-6 y)
- Brown line: Infant (<1 y)
- Green line: Lifetime (0-50 y)

**Key Points:**
- Reducing servings has a significant impact on the number of estimated cases.
- The impact is more pronounced in younger age groups.

**Conclusion:**
Reducing the number of servings can significantly decrease the estimated cases for all age groups, with the most significant reduction observed in infants.
What is the impact of modified cooking technique?

Baseline cooking technique represents 1:1 rice to water ratio during cooking

Modified cooking technique represents ~1:6 rice to water ratio during cooking (60% reduction in iAs)
What is the impact of setting a limit on iAs in rice?

All rice, per capita consumption

Public Health Impact

Impact on Rice Supply
Why?

Variability of contamination in rice
(weighted distribution)
Joint FDA / Health Canada

Food Directorate / Direction des aliments
Health Canada / Santé Canada

Center for Food Safety and Applied Nutrition
Food and Drug Administration
U.S. Department of Health and Human Services

July 2015

Contributors

Risk Assessment Team
Canada
Mark Smith
William Ross
Loan Nguyen
- United States
- Régis Pouillot
- Sherri Dennis
- Steve Gendel
- Clarence Murray III

Risk Management Team
Canada
Hélène Couture
Jeff Farber
André Jean
- United States
- Vincent Bunning
- Ted Elkin
- Kathy Gombas
- John Sheehan
- Donald Zink

Risk Communication, United States
Susan Cahill

Information Specialist, United States
Lori Papadakis
Risk Assessment Charge

• Evaluate the effect of factors, such as presence and amounts of *L. monocytogenes* in milk, the impact of contamination or manufacturing practices at specific cheese-manufacturing steps, and conditions during distribution and storage, on the overall risk to the consumer; and

• Evaluate the effectiveness of various changes in manufacturing processes and intervention strategies on reducing human illness.
<table>
<thead>
<tr>
<th>Hazard</th>
<th><em>Listeria monocytogenes</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Food</td>
<td>Soft-ripened cheese (e.g., Camembert)</td>
</tr>
<tr>
<td>Population</td>
<td>General population of U.S. and Canada Subpopulations with increased susceptibility (Pregnant Women Immunocompromised individuals, Older adults)</td>
</tr>
<tr>
<td>Health endpoint</td>
<td>Invasive listeriosis</td>
</tr>
</tbody>
</table>
Lm in Soft-Ripened Cheese Exposure Assessment

- On Farm
- Cheese Processing
- Transport & Marketing
- At Retail
- Home storage
- Consumption
Lm in Soft-Ripened Cheese Exposure Assessment: On Farm

Red boxes stand for contaminated units. In this example, the dairy silo is contaminated from the tanker truck. This tanker truck is contaminated from Farm #2 which is contaminated from a mastitic cow with one infected quarter.
Lm in Soft-Ripened Cheese Exposure Assessment: Cheese Processing

Mitigation
- Inactivation
- Removal

Cheese formation
- Partitioning

Ripening
- Inactivation
- Partitioning
- Growth
- Contamination
- Removal

Packaging

Aging
- Growth

Schematic view of the basic steps during soft-ripened cheese processing
Lm in Soft-Ripened Cheese Exposure Assessment: Transport & Marketing, Retail, Home Storage, and Consumption

Schematic view of the basic steps during soft-ripened cheese transport/marketing, retail, home storage, and consumption.

- **Transport**
  - Growth

- **Retail**
  - Growth

- **Home Storage**
  - Growth

- **Consumption**
  - Partitioning
Dose-Response
Invasive Listeriosis

FAO/WHO 2004
- Exponential dose-response functional form
  \[ P(\text{illness}) = 1 - \exp(-r \times \text{Dose}) \]
- Different values for “r”:
  - Susceptible subpopulation
    \[ r = 2.47 \times 10^{-12} \]
  - General population
    \[ r = 6.46 \times 10^{-14} \]
- Uncertainty in mean values of r was also considered
# Risk estimates

Predicted number of servings resulting in 1 case of invasive listeriosis

<table>
<thead>
<tr>
<th>Population</th>
<th>Canada</th>
<th>Canada</th>
<th>United States</th>
<th>United States</th>
</tr>
</thead>
<tbody>
<tr>
<td>type of milk used</td>
<td>Pasteurized</td>
<td>Raw</td>
<td>Pasteurized</td>
<td>Raw</td>
</tr>
<tr>
<td>Elderly</td>
<td>138 million</td>
<td>2.6 million</td>
<td>136 million</td>
<td>1.2 million</td>
</tr>
<tr>
<td>Pregnant</td>
<td>56 million</td>
<td>1.1 million</td>
<td>55 million</td>
<td>570,000</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>163 million</td>
<td>2.4 million</td>
<td>193 million</td>
<td>1.2 million</td>
</tr>
<tr>
<td>General population</td>
<td>7,290 million</td>
<td>105 million</td>
<td>8,644 million</td>
<td>55 million</td>
</tr>
</tbody>
</table>

Predicted X-fold increased risk of invasive listeriosis, per serving, if raw-milk (vs. pasteurized) used in soft-ripened cheese

<table>
<thead>
<tr>
<th>Population</th>
<th>Canada</th>
<th>United States</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly</td>
<td>53-fold higher risk</td>
<td>112-fold higher risk</td>
</tr>
<tr>
<td>Pregnant</td>
<td>52</td>
<td>96</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>69</td>
<td>157</td>
</tr>
<tr>
<td>General population</td>
<td>69</td>
<td>157</td>
</tr>
</tbody>
</table>
Characterizing **Variability & Uncertainty**

Variability >> (considered) Uncertainty in this model
Characterize influence of variability on risk estimate

*Spearman’s rank correlations between various inputs & the risk per serving of soft-ripened cheese at random, pasteurized-milk cheese, for the Elderly population*

- Time of room storage at home
- Temperature during aging
- Storage time during transport and marketing
- Storage time at retail
- Temperature during transport and marketing
- Time to 1st consumption
- Time of aging
- Temperature at retail
- Serving size
- Temperature of home refrigerator
- Time of storage at home
- Number of Lm, Environmental contamination
- Time when environmental contam. occurs
- $T_{\text{min}}$ in cheese
- EGR20
- Parameter $K_x$ for Lm growth lag

*Spearman’s rank correlation alternatives:*
Risk management options for cheese made with raw milk

- No required 60-d aging
- Apply process with 3log reduction
- Test raw-milk in farm bulk tank (100% production) - remove all milk in bulk tank when tests positive
- Test raw-milk cheese (100% lots) – remove entire lots with positive samples
What are the impacts of selected risk management options?

Log$_{10}$ mean risk per serving-Elderly population in Canada

- Baseline (raw milk)
- No 60-day restriction
- 3-log reduction
- Farm milk tested, every milking
- Cheese lot tested

Pasteurized milk
Scenarios – Implementation of Intervention

Testing for *Listeria monocytogenes* in Raw Milk cheese (Older adult population)

Mean Risk Higher than Pasteurized-milk

Mean Risk Lower than Pasteurized-milk

Joint FDA / Health Canada Quantitative Assessment of the Risk of Listeriosis from Soft-Ripened Cheese Consumption in the United States and Canada
Areas of Ongoing Development

• Risk-Risk Assessments (dietary shifts)
• Risk-Benefit Assessments (dietary shifts, nutrition)
• Risk Ranking/Prioritization
• For Microbial Risk Assessment
  – Multi-food & Total Diet Risk Assessments
  – Multi-hazard Risk Assessments
  – Incorporating WGS-specific information in Exposure assessment & Dose-response for microbial hazards
• Transparency – interactive models
Acknowledgements

**iAs-Rice RA**
- Risk Management Team (FDA)
- Risk Communication Team (FDA)
- FDA-CFSAN Lab & Statistical Scientists
- FDA Total Diet Study Experts
- NCTR
- EPA
- NIEHS
- USDA-ARS
- Expert Consultants
- External Peer Reviewers

**Lm Cheese RA**
- FDA & Health Canada
  - Risk Management Team
  - Risk Communication Team
- Former FDA Risk Managers
  - David Carlson, Richard Whiting, & Robert Buchanan
- International Dairy Foods Association Training (Greg Paoli, RSI)
- External Peer Reviewers
- FDA/OAO/Division of Risk & Decision Analysis Staff

Régis Pouillot
Amir Mokhtari
Yuhuan Chen