The Impact of Harmful Algal Blooms on the Health of Humans and Marine Mammals: An Immunotoxicological Approach

Milton Levin, MS, PhD

Department of Pathobiology and Veterinary Science
University of Connecticut, Storrs, CT
**Issue**

- Harmful algal bloom (HAB) frequency and global distribution in coastal ecosystems have increased
  - Pollution runoff
  - Global warming

- Toxins produced/released associated with
  - Human illness and death
  - Marine mammal stranding events and mortality

- Low-level, life-long exposure on health is not well-understood
What are HABs?

- Commonly referred to as “red tide”
- Events involving microscopic algae which grow quickly in water
- Form visible or invisible patches
- Produce potent biotoxins
<table>
<thead>
<tr>
<th>Agent</th>
<th>Domoic Acid</th>
<th>Brevetoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marine diatom</td>
<td><em>Pseudo-nitzschia</em></td>
<td>Dinoflagellate</td>
</tr>
<tr>
<td></td>
<td><em>Karenia brevis</em></td>
<td><em>K. brevis</em></td>
</tr>
<tr>
<td>Route of exposure</td>
<td>Shellfish</td>
<td>Shellfish</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhalation of aerosol</td>
</tr>
<tr>
<td>Disease (human)</td>
<td>Amnesic shellfish poisoning (ASP)</td>
<td>Neurotoxic shellfish poisoning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(NSP)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Gastrointestinal</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td>Neurological</td>
<td>Neurological</td>
</tr>
<tr>
<td></td>
<td>Memory loss</td>
<td></td>
</tr>
<tr>
<td>Affected species</td>
<td>Humans</td>
<td>Humans</td>
</tr>
<tr>
<td></td>
<td>CA sea lions</td>
<td>Manatees</td>
</tr>
<tr>
<td></td>
<td>Southern sea otters</td>
<td>Dolphins</td>
</tr>
<tr>
<td></td>
<td>Marine birds</td>
<td></td>
</tr>
</tbody>
</table>
HAB events in the US

Source: NOAA & D. Anderson
So What?

• HAB toxins can enter food chain…
  • Biomagnify and bioaccumulate
  • Acute illness or death in humans who consume contaminated shellfish
  • Mortality events in marine mammals, fish and marine birds
HABs & Unusual Mortality Events

http://www.nmfs.noaa.gov/pr/health/mmume/
Economic effects of HABs in the U.S. are at least $82 million/year*

Commercial Fisheries Impacts: $38 million/year

Public Health Costs of Illness: $37 million/year

Recreation and Tourism Impacts: $4 million/year

Coastal Monitoring and Management: $3 million/year


http://www.cop.noaa.gov/stressors/extremeevents/hab/current/HAB_Econ.html
Rationale

• **What we know?**
  – Acute, high level exposure causes food poisoning (neurological and gastrointestinal) and sometimes death

• **What we need to know?**
  – Adverse health effects associated with life-long, low level exposure
  – Specifically, effects on immune system
Immune System

Health

Biotoxins

Infectious Disease

Immune System
Hypothesis

Brevetoxin and DA are immunotoxic in humans and marine mammals upon \textit{in vitro} exposure and intracellular toxin levels can be correlated with changes in immune function.

These data can be used for mechanistically-based risk assessment to link environmental exposure and immunotoxic effects.
Specific Aims

1. Measure changes in immune functions upon *in vitro* exposure to HAB toxins and compare among mice, humans and marine mammals

2. Identify/assess pathways and mechanisms of action mediating HAB-induced immunotoxicity

2. Develop a statistical model to predict the impact of HAB on the health in exposed populations
Methods

1. Collect whole blood and isolate immune cells
   - Mouse
   - Humans
   - California sea lions
   - Bottlenose dolphins

1. Expose cells *in vitro* to increasing concentrations of DA or brevetoxin

2. Measure changes in immune cell functions
Immune functions

• **Innate**
  – Phagocytosis
    • Engulf extracellular material
  – Respiratory burst
    • Generate reactive oxygen species (ROS) to kill intracellular pathogens

• **Acquired**
  – Lymphocyte proliferation
    • Generate effector and memory B and T lymphocytes
Research Aim Summary

1. DA and brevetoxin modulate immune functions in mice, CA sea lions, and dolphins
   - Not all species equally sensitive

2. Kainate receptors appear to mediate DA-induced immunotoxicity (in mice)
   - Brevetoxin receptors yet to be investigated on immune cells
   - Role of calcium yet to be investigated

3. Intracellular brevetoxin can be detected
   - Need to correlate with changes in immune functions

4. Statistical models will be developed over next year
Consequences of immunomodulation

• Phagocytosis
  – **Decreased**, reduced pathogen clearance

• Respiratory burst
  – **Increased**, release of free radicals, local tissue inflammation

• Lymphocyte proliferation
  – **Increased**, dysregulated proliferation, cancer
  – **Decreased**, reduced pathogen clearance

• Immunomodulation may increase individual’s susceptibility to bacterial, viral, protozoal or fungal pathogens
Risk Assessment Approach

1. Hazard identification
2. Dose-response assessment
3. Exposure assessment
4. Risk characterization
1. Hazard Identification

- 1998 and 2000
  - DA blooms sickens/kills over 500 California sea lions

- 1987
  - 4 humans die after eating DA-contaminated shellfish
2. Dose-Response

Non-lethal blood collection  \textit{In vitro} immunotoxicology

![Diagram showing dose-response relationship with statistical significance markers.](image)
3. Exposure Assessment

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>Sample Matrix</th>
<th>DA Equivalents</th>
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<tbody>
<tr>
<td>CSL 3734 22 May 1998</td>
<td>Sea lion serum</td>
<td>0.20 mg ml-1</td>
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<tr>
<td>CSL 3724 21 May 1998</td>
<td>Sea lion serum</td>
<td>0.17 mg ml-1</td>
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4. Risk Characterization

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Probability curve ‘example’
Benefits

• Contribute to NOAA/OHII mission
  – Providing tools, technologies and environmental information to resource and public health managers and the public

• ‘Bench to bedside’
  – Transfer of knowledge to public/wildlife health officials
  – Provide appropriate treatment to those suffering adverse health effects
    • humans and marine mammals
**Take Home Message**

- HAB frequency is increasing along coastal ecosystems

- Need to better understand the risk of low-level, life-long HAB exposure on human and marine mammal health

- Help law makers, risk managers, and public/wildlife health managers to establish policies to prevent and/or mitigate the risk for adverse health effects in humans and marine mammals
Acknowledgements

• I-RICH Mentors
  – Sylvain De Guise
  – Ann Ferris

• University of Connecticut Research Foundation

• California Department of Fish & Game
• The Marine Mammal Center
• Monterey Bay Aquarium
• US Navy Marine Mammal Program

• Heather Leibretch
• Erika Gebhard
• Andrea Bogomolni

• Elizabeth Frame, NOAA NWFSC
• Kathi Lefebvre, NOAA NWFSC
• James Ryan, NOAA NOS
• Lori Schwacke, NOAA NOS
• Frances Van Dolah, NOAA NOS

• Frances Gulland, TMMC
• Jerome Naar, UNCW
This study was funded by **Morris Animal Foundation**—the world’s largest nonprofit that supports animal health studies to protect, treat and cure animals.

Morris Animal Foundation funds research at veterinary colleges around the world. Its funding facilitates medical breakthroughs that help animals enjoy longer, healthier lives and trains the next generation of veterinary scientists.
Acknowledgements