Bad Bug Book

Handbook of Foodborne Pathogenic Microorganisms and Natural Toxins

Introduction

Food safety is a complex issue that has an impact on all segments of society, from the general public to government, industry, and academia. The second edition of the Bad Bug Book, published by the Center for Food Safety and Applied Nutrition, of the Food and Drug Administration (FDA), U.S. Department of Health and Human Services, provides current information about the major known agents that cause foodborne illness. The information provided in this handbook is abbreviated and general in nature, and is intended for practical use. It is not intended to be a comprehensive scientific or clinical reference.

Under the laws administered by FDA, a food is adulterated if it contains (1) a poisonous or otherwise harmful substance that is not an inherent natural constituent of the food itself, in an amount that poses *a reasonable possibility* of injury to health, or (2) a substance that is an inherent natural constituent of the food itself; is not the result of environmental, agricultural, industrial, or other contamination; and is present in an amount that *ordinarily* renders the food injurious to health. The first includes, for example, a toxin produced by a fungus that has contaminated a food, or a pathogenic bacterium or virus, if the amount present in the food *may be* injurious to health. An example of the second is the tetrodotoxin that occurs naturally in some organs of some types of pufferfish and that *ordinarily* will make the fish injurious to health. In either case, foods adulterated with these agents are prohibited from being introduced, or offered for introduction, into interstate commerce.

Our scientific understanding of pathogenic microorganisms and their toxins is continually advancing. When scientific evidence shows that a particular microorganism or its toxins can cause foodborne illness, the FDA may consider that microorganism to be capable of causing a food to be adulterated. Our knowledge may advance so rapidly that, in some cases, an organism found to be capable of adulterating food might not yet be listed in this handbook. In those situations, the FDA still can take regulatory action against the adulterated food.

The agents described in this book range from live pathogenic organisms, such as bacteria, protozoa, worms, and fungi, to non-living entities, such as viruses, prions, and natural toxins. Included in the chapters are descriptions of the agents' characteristics, habitats and food sources, infective doses, and general disease symptoms and complications. Also included are examples of outbreaks, if applicable; the frequency with which the agent causes illness in the U.S.; and susceptible populations. In addition, the chapters contain brief overviews of the analytical methods used to detect, isolate, and/or identify the pathogens or toxins.

However, while some general survival and inactivation characteristics are included, it is beyond the scope of this book to provide data, such as D and z values, that are used to establish

processes for the elimination of pathogenic bacteria and fungi in foods. One reason is that inactivation parameters for a given organism may vary somewhat, depending on a number of factors at the time of measurement. For more information on this topic, readers may wish to consult other resources. One example is the International Commission on Microbiological Specifications for Foods, the source of a comprehensive book (*Microorganisms in Foods 5. Characteristics of Microbial Pathogens*) on the heat resistance (D and z values) of foodborne pathogens in various food matrices, as well as data on survival and growth in many foods, including data on water activity and pH.

The Bad Bug Book chapters about pathogenic bacteria are divided into two main groups, based on the structure of the microbes' cell wall: Gram negative and Gram positive. A few new chapters have been added, reflecting increased interest in certain microorganisms as foodborne pathogens or as potential sources of toxins.

Another new feature is the brief section for consumers that appears in each chapter and is set apart from the main text. These sections provide highlights of information, about the microbe or toxin, that will be of interest to consumers, as well as information and links regarding safe food-handling practices. A glossary for consumers is included at the end of the book, separately from the technical glossary.

Various chapters link readers to Federal agencies with an interest in food safety, including the FDA, the Centers for Disease Control and Prevention (CDC), and the U.S. Department of Agriculture Food Safety Inspection Service. These are the primary agencies that collaborate to investigate outbreaks of foodborne illness, prevent foodborne illness, and advance the field of food safety, to protect the public's health. In addition, some technical terms have been linked to the National Library of Medicine's Entrez glossary.

Links to recent articles from the CDC's Morbidity and Mortality Weekly Reports are provided in selected chapters, to provide readers with current information about outbreaks or incidents of foodborne disease. At the end of selected chapters about pathogenic microorganisms, hypertext links are included to relevant Entrez abstracts and GenBank genetic loci.

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Introduction for Consumers: A Snapshot

Each chapter in this book is about a pathogen – a bacterium, virus, or parasite – or natural toxin that can contaminate food and cause illness. The book was prepared by the Food and Drug Administration (FDA) and contains scientific and technical information about the major pathogens that cause these kinds of illnesses. A separate "consumer box" in each chapter provides non-technical information, in everyday language. The boxes describe plainly what can make you sick and, more important, how to prevent it.

Most foodborne illnesses, while unpleasant, go away by themselves and don't have lasting effects. But you'll read about some pathogens that can be more serious, have long-lasting effects, or cause death. To put these pathogens in perspective, think about how many different foods and how many times you eat each day, all year, without getting sick from the food. The FDA and other Federal agencies work together and with the food industry to make the U.S. food supply one of the safest in the world.

You also play a part in the safety of what you eat. When you read the consumer boxes, you'll see that different pathogens can be risky in different ways, and that a safety step that's effective against one might not be as effective against another. So what should you do? The answer is to follow some simple steps that, together, lower the risk from most pathogens.

- Washing your hands before and after handling food, and in between handling different foods, is one of the most important steps you can take. Do the same with equipment, utensils, and countertops.
- Wash raw fruits and vegetables under running water. These nutritious foods usually are safe, as you probably know from the many times you've eaten them, but wash them just in case they've somehow become contaminated. For the most part, the less of a pathogen on a food – if any – the less chance that it can make you sick.
- Cooking food to proper temperatures kills most bacteria, including *Salmonella*, *Listeria*, and the kinds of *E. coli* that cause illness, and parasites.
- Keep any pathogens that could be on raw, unwashed foods from spreading by keeping raw and cooked foods separate. Keep them in different containers, and don't use the same equipment on them, unless the equipment is washed properly in between. Treat countertops the same way.
- Refrigerate food at 40°F as soon as possible after it's cooked. Remember, the less of a pathogen there is in a food, the less chance that it can make you sick. Proper refrigeration keeps most types of bacteria from growing to numbers that can cause illness (although if a food already has high numbers of bacteria when it's put in the refrigerator, it could still cause illness).

Here are a few examples of why following *all* of these steps is important. Some types of bacteria form spores that aren't killed by cooking. Spores are a survival mode in which those bacteria make an inactive form that can live without nutrition and that develops very tough protection against the outside world. After cooking, the spores may change and grow into bacteria, when the food cools down. Refrigerating food quickly after cooking can help keep the bacteria from multiplying. On the other hand, cooking does kill most harmful bacteria. Cooking is especially important when a pathogen is hard to wash off of a particular kind of food, or if a bacterium can grow at refrigerator temperatures, as is true of *Listeria monocytogenes* and *Yersinia enterocolitica*.

As you read about the differences among the pathogens, remember that there's a common theme: following *all* the safety steps above can help protect you. The exceptions are toxins, such as the poisons in some mushrooms and a few kinds of fish and shellfish. Cooking, freezing, and washing won't necessarily destroy toxins. Avoiding them is your best protection, as you'll see when you read the chapters.

Authorship

The second edition of the Bad Bug Book would not have been possible without the contributions of the many FDA scientists who donated their time and expertise to update the chapters. The result of their efforts is a handbook that can serve as a valuable tool for food-safety professionals and others with an interest in food safety.

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The second edition of the Bad Bug Book would not have been possible without the contributions of the many FDA scientists who donated their time and expertise to update the chapters. The result of their efforts is a handbook that can serve as a valuable tool for food-safety professionals and others with an interest in food safety. Our gratitude is extended to Drs. Mickey Parish and Fred S. Fry Jr., for the insight they offered in their expert reviews of the book. The first edition of the Bad Bug Book was the concept of Dr. Mark Walderhaug, who executed it with the help of the many scientists working with him at the time, and the field is indebted to him and to them for their vision.

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Shellfish toxins (PSP, DSP, NSP, ASP, AZP)

1. Toxins

Shellfish poisoning is caused by a group of toxins produced by planktonic algae (dinoflagellates, in most cases) on which shellfish feed. The toxins are accumulated, and sometimes metabolized by, the shellfish. Numerous shellfish toxins have been described around the world; included here are toxins currently regulated by the FDA.

For Consumers: A Snapshot

Algae are plant-like life-forms that float or move on their own in water. They vary in size from very small (microscopic) to very large (for example, seaweed, such as kelp). Some marine and freshwater algae make toxins (poisons). Many of the toxins that build up in shellfish – seafood such as oysters, clams, and mussels, to name a few – are made by a small type of algae called "dinoflagellates," which swim and have characteristics of both plants and animals. When shellfish eat these algae, the poisons can build up in the shellfish and sicken people who eat them. The kind of illness depends on the poison. Some can be deadly, like **paralytic shellfish poisoning (PSP)**. Others, like **diarrhetic shellfish poisoning** and **azaspiracid shellfish poisoning**, mostly cause symptoms like nausea, vomiting, diarrhea, and stomach pain. Besides these kinds of symptoms, some shellfish poisonings, like **neurotoxic shellfish poisoning**, also cause neurologic effects, such as tingling or numbness of lips and throat, dizziness, and muscle aches. In extreme cases, **amnesic shellfish poisoning** has resulted in severe neurologic disorders, such as loss of short-term memory, in some people. These poisons aren't destroyed by cooking, freezing, or other food preparation. This highlights the importance of FDA's seafood-safety programs, guidance to industry, and close working relationships with state regulators. For example, the levels of saxitoxins (which cause PSP) often become high in shellfish in New England waters at certain times of the year when the toxin-producing algae are present. When the level becomes too high for safety, state health agencies follow FDA guidance and ban shellfish harvesting, and PSP outbreaks from commercial products are very rare in the U.S.

Paralytic shellfish poisoning (PSP) is caused by water-soluble alkaloid neurotoxins that are collectively referred to as saxitoxins or paralytic shellfish toxins (PSTs). To date 57 analogs have been identified, although not all are always present, and they vary greatly in overall toxicity. In addition to saxitoxin (the parent compound), monitoring laboratories typically analyze for approximately 12 other analogs that may contribute measurably to toxicity.

Diarrhetic shellfish poisoning (DSP) is caused by a group of lipid-soluble polyether toxins that includes okadaic acid, the dinophysistoxins, and a series of fatty acid esters of okadaic acid and the dinophysistoxins (collectively known as DSTs).

Neurotoxic shellfish poisoning (NSP) is caused by a group of lipid-soluble polyether toxins called brevetoxins. NSP-causing toxins in shellfish include intact algal brevetoxins and their metabolites (collectively known as NSTs).

Amnesic shellfish poisoning (ASP) is caused by the neurotoxin domoic acid (DA), a water-soluble, non-protein, excitatory amino acid. Isomers of domoic acid have been reported, but are less toxic than domoic acid itself.

Azaspiracid shellfish poisoning (AZP) is caused by the lipid-soluble toxin azaspiracid and several derivatives (AZAs). To date, more than 30 AZA analogs have been identified, with three analogs routinely monitored in shellfish.

2. Diseases

Human ingestion of contaminated shellfish results in a wide variety of symptoms, depending on the toxin(s) present, their concentrations in the shellfish, and the amount of contaminated shellfish consumed.

Note: The specific seafood with which each toxin generally is associated is included in this "Disease" section, to help readers link symptoms to potential sources. However, all shellfish (filter-feeding mollusks, as well as the carnivorous grazers that feed on these mollusks, such as whelk, snails, and, in some cases, even lobster and octopus) may become toxic in areas where the source algae are present. In most cases, the toxin has no effect on the shellfish itself, and how long each shellfish vector remains toxic depends on the individual species in question. Additionally, there are non-traditional and emerging vectors of these toxins that also are potentially toxic foods. One example is that pufferfish, which typically is associated with tetrodotoxin (see chapter on Tetrodotoxin), may also contain saxitoxin (e.g., puffers from coastal waters of Florida).

Paralytic Shellfish Poisoning

- ***Mortality:*** Death has been reported to occur as soon as 3 to 4 hours after the contaminated food has been consumed.

- ***Onset:*** Symptoms can generally occur within 30 minutes of consuming contaminated seafood, although reports have indicated that symptoms can even ensue within a few minutes, if high enough toxin concentrations are present.

- ***Symptoms and course of illness:*** Effects of PSP are predominantly neurologic and include tingling of the lips, mouth, and tongue; numbness of extremities; paresthesias; weakness; ataxia; floating/dissociative feelings; nausea; shortness of breath; dizziness; vomiting; headache; and respiratory paralysis.

  Medical treatment consists of providing respiratory support, and fluid therapy can be used to facilitate toxin excretion. For patients surviving 24 hours, with or without respiratory support, the prognosis is considered good, with no lasting side effects. In fatal cases, death is typically due to asphyxiation. In unusual cases, death may occur from cardiovascular collapse, despite respiratory support, because of the weak hypotensive action of the toxin.

- ***Food Sources:*** PSP generally is associated with bivalves, such as mussels, clams, cockles, oysters, and scallops (excluding the scallop adductor muscle).

Diarrhetic Shellfish Poisoning

- ***Mortality:*** This disease generally is not life-threatening.

- ***Onset:*** Onset of the disease, depending on the dose of toxin ingested, may be as little as 30 minutes to 3 hours.

- ***Symptoms and course of illness:*** DSP is primarily observed as a generally mild gastrointestinal disorder; i.e., nausea, vomiting, diarrhea, and abdominal pain, accompanied by chills, headache, and fever. Symptoms may last as long as 2 to 3 days, with no chronic effects.

- ***Food Sources:*** DSP generally is associated with mussels, oysters, and scallops.

Neurotoxic Shellfish Poisoning

- ***Mortality:*** No fatalities have been reported.

- ***Onset:*** Onset of this disease occurs within a few minutes to a few hours.

- ***Symptoms and course of illness:*** Both gastrointestinal and neurologic symptoms characterize NSP, including tingling and numbness of lips, tongue, and throat; muscular aches; dizziness; diarrhea; and vomiting. Duration is fairly short, from a few hours to several days. Recovery is complete, with few after-effects.

- ***Food Sources:*** NSP generally is associated with oysters and clams harvested along the Florida coast and the Gulf of Mexico. In 1992 / 1993, NSP was linked to shellfish harvested from New Zealand.

Amnesic Shellfish Poisoning

- ***Mortality:*** All fatalities, to date, have involved elderly patients.

- ***Onset:*** The toxicosis is characterized by onset of gastrointestinal symptoms within 24 hours; neurologic symptoms occur within 48 hours.

- ***Symptoms and course of illness:*** ASP is characterized by gastrointestinal disorders (vomiting, diarrhea, abdominal pain) and neurological problems (confusion, short-term memory loss, disorientation, seizure, coma). Human clinical signs of domoic acid toxicity are reported as mild gastrointestinal symptoms, from an oral dose of 0.9-2.0 mg domoic acid (DA)/kg body weight. Neurologic effects, such as seizure and disorientation, are reported from an oral dose of 1.9-4.2 mg DA/kg body weight. The toxicosis is particularly serious in elderly patients, and includes symptoms reminiscent of Alzheimer's disease.

- ***Food Sources:*** ASP generally is associated with mussels. Other taxa of interest include scallops, razor clams, market squid, and anchovy.

Azaspiracid Shellfish Poisoning

- ***Mortality:*** No known fatalities to date.

- ***Onset:*** Symptoms appear in humans within hours of eating AZA-contaminated shellfish.

- ***Symptoms and course of illness:*** Symptoms are predominantly gastrointestinal disturbances resembling those of diarrhetic shellfish poisoning and include nausea, vomiting, stomach cramps, and diarrhea. Illness is self-limiting, with symptoms lasting 2 or 3 days.

- ***Food Sources:*** AZAs have been detected in mussels, oysters, scallops, clams, cockles, and crabs.

3. Diagnosis

Diagnosis of shellfish poisoning is based entirely on observed symptomatology and recent dietary history.

4. Frequency

Good statistical data on the occurrence and severity of shellfish poisoning are largely unavailable, which undoubtedly reflects the inability to measure the true incidence of the disease. Cases are frequently misdiagnosed and, in general, infrequently reported. The proliferation (sometimes referred to as "blooms") of the toxin-producing algae and subsequent toxin events or outbreaks of illness appear to be increasing around the world. To combat this, seafood monitoring programs enforce harvesting bans when toxins exceed their respective regulatory action levels. In many countries, including the United States, this has resulted in protection of public health. Additional information on the frequency and severity of outbreaks for the various shellfish toxins around the world can be found in the Resources section, below.

5. Target Populations

All humans are susceptible to shellfish poisoning. A disproportionate number of shellfish-poisoning cases occur among (1) tourists or others who are not native to the location where the toxic shellfish are harvested and (2) fishermen and recreational harvesters. This may be due to disregard for either official quarantines or traditions of safe consumption.

6. Food Analysis

According to the 4th edition of the FDA Fish and Fisheries Products Hazards and Controls Guidance, regulatory action levels for the shellfish toxins are as follows:

- **PSP** – 0.8 ppm (80 µg/100 g) saxitoxin equivalents
- **NSP** – 0.8 ppm (20 mouse units/100 g) brevetoxin-2 equivalents
- **DSP** – 0.16 ppm total okadaic acid equivalents (i.e., combined free okadaic acid, dinophysistoxins, acyl-esters of okadaic acid and dinophysistoxins)
- **ASP** – 20 ppm domoic acid (except in the viscera of Dungeness crab, for which the action level is 30 ppm)
- **AZP** – 0.16 ppm azaspiracid 1 equivalent

The mouse bioassay historically has been the most universally applied technique for examining shellfish toxins. Other bioassay procedures have been developed and are becoming more generally applied. In recent years, considerable effort has been applied to development of chemical analyses to replace or provide alternatives to *in-vivo* (live animal) bioassays. Examples are included below.

Paralytic Shellfish Poisoning (PSP): The mouse bioassay is still the most widely accepted detection method for the **saxitoxins** around the world and has been shown to

adequately protect the public's health. However, a pre-column oxidation, high-performance liquid chromatography (HPLC) with fluorescence detection (FD) method has received AOAC approval and has become a regulatory tool in some countries. This method is the only one currently listed for **saxitoxins** in the Codex Alimentarius "Standard for Live and Raw Bivalve Molluscs." In 2009 the Interstate Shellfish Sanitation Conference approved a post-column oxidation HPLC-FD approach as a Type IV NSSP (National Shellfish Sanitation Program) method, making it the newest regulatory method available for **PSP** toxins in the U.S. This method also gained AOAC approval in 2011. The receptor binding assay, a competition assay whereby radiolabeled saxitoxin competes with unlabeled saxitoxin for a finite number of available receptor sites as a measure of native saxitoxin concentrations in a sample, was also approved as an official AOAC method in 2011.

Diarrhetic Shellfish Poisoning (DSP): Until recently, **DSP** toxins were not monitored in the U.S. In other parts of the world, a mouse bioassay was used to assess **diarrhetic shellfish toxins (DST)** presence, but this assay was neither sensitive nor specific enough to adequately protect public health. The dose-survival times for the **DSP** toxins in the mouse assay fluctuate considerably, and fatty acids and other co-occurring non-diarrhetic compounds interfere with the assay, giving false-positive results. Consequently, a suckling mouse assay that measures fluid accumulation after injection of a shellfish extract was developed and used for control of DSP. Due to a mandate to eliminate *in-vivo* mouse assays for lipophilic toxins in the European Union (EU), numerous alternative methods are in various stages of development and validation around the world. These include liquid chromatography / mass spectrometry (LC/MS), antibody-based commercial kits, and several *in-vitro* bioactivity assays based on phosphatase inhibition.

Neurotoxic Shellfish Poisoning (NSP): Toxicity of shellfish exposed to the dinoflagellate *Karenia brevis* has been historically assessed by mouse bioassay in the U.S. Mouse bioassay is not very specific for **NSP** toxins. Thus, efforts are underway to validate *in-vitro* methods for detection of **brevetoxins** in shellfish. For example, rapid, sensitive ELISA test kits already are commercially available for this purpose. Biomarkers of **brevetoxin** contamination in shellfish have been identified by using LC/MS. Structural confirmation of these metabolites and brevetoxins in shellfish can be made by LC/MS, a method that offers high sensitivity and specificity.

Amnesic Shellfish Poisoning (ASP): The mouse bioassay for **domoic acid** is not sufficiently sensitive and does not provide a reliable estimate of potency. The most accepted regulatory method for detecting **domoic acid** in seafood is a reversed-phase HPLC method with ultraviolet (UV) detection. There is also an AOAC approved ELISA for the detection of **domoic acid**.

Azaspiracid Shellfish Poisoning (AZP): AZAs are not routinely monitored in shellfish harvested in the U.S., but, in the EU, the mouse bioassay has been used. As for many of the lipophilic toxins, the mouse assay is not adequately sensitive or specific for public-health purposes. *In-vitro* assays and analytical methods are now available to assess the toxicity of AZA-contaminated shellfish and to confirm the presence of AZA analogs in shellfish. These methods are in various stages of validation for regulatory use around the world. LC/MS is used as a confirmatory method for AZA, providing unambiguous structural confirmation of AZA analogs in shellfish samples.

7. Examples of Outbreaks

PSP – Despite widespread PSP closures, poisoning events still occur and are generally associated with recreational harvest. For example, in July 2007, a lobster fisherman harvested mussels from a floating barrel off Jonesport, ME (an area that was currently open to shellfish harvesting), and he and his family ate them for dinner. All four consumers became ill with PSP symptoms, and three of them were admitted to the hospital. It was apparent that the barrel of mussels had originated further up the coast in an area that had been banned to commercial harvest.

DSP – Although there have been numerous outbreaks of diarrhetic shellfish poisoning around the world, until recently there were no confirmed cases of DSP in the U.S. that were due to domestically harvested shellfish. However, in 2008, a large portion of the Texas Gulf Coast was closed to the harvesting of oysters due to the presence of okadaic acid in excess of the FDA guidance level. Although no illnesses were reported, these were the first closures in the U.S. due to confirmed toxins. In 2011, approximately 60 illnesses occurred in British Columbia, Canada, and 3 illnesses occurred in Washington State due to consumption of DSP-contaminated mussels. Subsequent harvesting closures and product recalls were issued.

NSP – Until NSP toxins were implicated in more than 180 human illnesses in New Zealand, in 1992/1993, NSP was considered to be an issue only in the U.S. Outbreaks of NSP are rare where programs for monitoring *K. brevis* blooms and shellfish toxicity are implemented. An NSP outbreak involving 48 individuals occurred in North Carolina, in 1987. A series of NSP cases occurred along the southwest coast of Florida, in 2006, after people consumed recreationally-harvested clams from waters unapproved for shellfish harvesting.

ASP - The first human domoic acid poisoning events were reported in 1987, in Canada. While domoic acid exposure still exists, there have been no documented ASP cases since 1987, following implementation of effective seafood toxin-monitoring programs.

AZP – There have been no confirmed cases of AZP in the U.S. from domestically harvested product. Examples from around the world include: (1) Several AZP intoxications (20 to 24) were reported in Ireland, in 1997, following consumption of mussels harvested from Arranmore Island. (2) An AZP outbreak involving 10 people was reported in Italy, after they consumed contaminated mussels produced in Clew Bay, Ireland. (3) In 1998, in France, 20 to 30 AZP illnesses were attributed to scallops that originated in Ireland. (4) In 2008, the first recognized outbreak of AZP in the U.S. was reported, but was associated with a mussel product imported from Ireland.

CDC/MMWR: Various Shellfish-Associated Toxins provides a list of Morbidity and Mortality Weekly Reports related to these toxins.

NIH/PubMed: Various Shellfish-Associated Toxins provides a list of research abstracts in the National Library of Medicine's MEDLINE database.

8. Resources

Food and Agriculture Organization of the United Nations Paper 80: Marine Biotoxins

Paralytic Shellfish Poisoning

Diarrheic Shellfish Poisoning

Neurotoxic Shellfish Poisoning

Amnesic Shellfish Poisoning

Azaspiracid Shellfish Poisoning

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Additional Resources [open access]

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9. Molecular Structure

Azaspiracid (AZA analogs produced by the dinoflagellate Azadinium spinosum: AZA1, AZA2, and an isomer of AZA2. Major analogs found in shellfish are AZA1, AZA2, and AZA3.)

Brevetoxin and related compounds

Saxitoxin and related compounds

Okadaic acid and related compounds

Domoic acid