Hazard Analysis and Risk-Based Preventive Controls for Human Food: Draft Guidance for Industry[1]

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Chapter 3: Potential Hazards Associated with the Manufacturing, Processing, Packing, and Holding of Human Food

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3.1 Purpose of this Chapter

The guidance in this chapter is intended to help you consider the biological, chemical, and physical hazards that are commonly of concern in food plants and that should be addressed in a hazard analysis. It addresses ingredient-related hazards, process-related hazards, and hazards that may be introduced from the food-production environment (facility-related hazards). It does not provide an exhaustive compendium of hazards or details about each hazard. Where possible, we cite scientific literature, regulations, and/or guidance (issued by FDA or our food safety regulatory partners) that may provide useful detailed discussion or analysis of hazards of concern. See the definition of "hazard" in 21 CFR 117.3.

It is important for you to understand the potential hazards that may be associated with your products using the raw materials and other ingredients, processes, and equipment specific for those products, as well as the environment of your specific facility. If you identify hazards requiring a preventive control, you will then have to determine what preventive controls are needed to reduce food safety risks and ensure the safety of your products for human consumption. See 21 CFR 117.130 and 117.135. Although this chapter briefly describes the types of preventive controls that may be appropriate for you to implement to control certain hazards, see Chapter 4 and Chapters 6 through 13 of this guidance for more detailed discussion of applicable preventive controls.

3.2 Potential Hazards

Food products can become contaminated with biological, chemical (including radiological), or physical hazards. Table 3-1 provides examples of potential hazards and is not exhaustive.

Table 3-1 Examples of Potential Hazards

Hazard Category	Hazard Sub-category	Examples
Biological	Bacteria	• *Bacillus cereus* (*B. cereus*) • *Campylobacter jejuni* (*C. jejuni*) • *Clostridium botulinum* (*C. botulinum*) • *Clostridium perfringens* (*C. perfringens)* • Shiga-toxin producing *Escherichia coli* such as O157:H7 (*E. coli* O157:H7) • *Listeria monocytogenes* (*L. monocytogenes*) • *Salmonella* spp. • *Shigella* spp. • *Staphylococcus aureus* (*S. aureus*)

Hazard Category	Hazard Sub-category	Examples
Biological	Protozoa and Parasites	• *Cryptosporidium parvum* • *Cyclospora cayetanensis* • *Giardia lamblia (G. intestinalis)* • *Trichinella spiralis*
Biological	Viruses	• Norovirus • Hepatitis A • Rotavirus
Chemical	Pesticide residues	• Organophosphates • Carbamates • Chlorinated hydrocarbons • Pyrethroids
Chemical	Heavy Metals	• Lead • Arsenic • Cadmium • Mercury
Chemical	Drug residues (veterinary antibiotics)	• Chloramphenicol • Beta- Lactams
Chemical	Industrial chemicals	• Ammonia
Chemical	Environmental contaminants	• Dioxins
Chemical	Mycotoxins	• Aflatoxin • Patulin • Ochratoxin • Fumonisin • Deoxynivalenol
Chemical	Allergens	• Milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, and soybeans (commonly called “the Big 8”)
Chemical	Unapproved colors and additives	• FD&C Red #4 • Melamine

Hazard Category	Hazard Sub-category	Examples
Chemical	Substances associated with a food intolerance or food disorder	• Lactose • Yellow #5 • Sulfites • Carmine and Cochineal • Gluten
Chemical	Radionuclides	• Radium 226 and 228 • Uranium 235 and 238 • Strontium 90 • Cesium 137 • Iodine 131
Physical	N/A	• Metal • Glass • Hard plastic

As discussed in Chapter 2 of this guidance, when conducting your hazard analysis you must consider the potential for biological, chemical, and physical hazards to be related to raw materials and other ingredients (ingredient-related hazards), processes (process-related hazards), and the food-production environment (facility-related hazards) (21 CFR 117.130). In Chapter 2 we also provide examples of questions to be considered when identifying potential hazards in the following areas:

- Ingredients;
- Intrinsic factors;
- Processing procedures;
- Microbial content of the food;
- Facility design;
- Equipment design and use;
- Packaging;
- Employee health, hygiene, and education; and
- Storage conditions between packaging and the end user.

Throughout this chapter, we discuss potential biological, chemical, and physical hazards from the perspective of ingredient-related hazards, process-related hazards, and facility-related hazards, considering the issues and factors listed immediately above.

3.3 Biological Hazards

You must conduct a hazard analysis to identify and evaluate known or reasonably foreseeable biological hazards, including microbiological hazards such as parasites, environmental pathogens, and other pathogens. See 21 CFR 117.130(b)(1)(i). When your hazard analysis identifies a known or reasonably foreseeable biological hazard that requires a preventive control, you must identify and implement a preventive control for the biological hazard. See 21 CFR 117.135(a)(1).

The biological hazards that are the focus of this guidance are bacterial pathogens (e.g., *Salmonella* spp., *Listeria monocytogenes*, *Clostridium botulinum*, and Shiga-toxin producing *Escherichia coli* (STEC) such as O157:H7) that may be associated with foods or food processing operations and can cause consumer illness or disease. The other biological hazards, viruses (e.g., norovirus and hepatitis A) and parasites (e.g., *Cryptosporidium* spp. and *Giardia intestinalis*), are also known to cause illness or disease, but these would generally be addressed by following Current Good Manufacturing Practice (e.g., worker hygiene and disease control) in facilities and our regulation entitled "Standards for the Growing, Harvesting, Packing, and Holding of Produce for Human Consumption" (21 CFR part 112) (e.g., worker hygiene and disease control, water safety) on farms that supply raw agricultural commodities to facilities.

Food products can become contaminated with bacterial pathogens that can be:

- Ingredient-related hazards - i.e., introduced from raw materials and other ingredients;
- Process-related hazards - e.g., if the pathogens:
    - Survive processing that was intended to significantly minimize the pathogen;
    - Increase in number due to lack of time/temperature control or due to the food's formulation; or
    - Selectively grow, and/or produce toxin, in a food as a result of using reduced oxygen packaging;
- Facility-related hazards – e.g., if the pathogens are introduced from:
    - Food processing equipment (e.g., insanitary equipment and utensils);
    - Cross-contamination between raw and cooked products;
    - Air; or
    - Contaminated water or sewage; or
- People-related hazards – e.g., due to people handling the product during packing or processing. (Such people-related hazards are sometimes controlled by following Current Good Manufacturing Practice (e.g., worker hygiene and disease control)).

For further details on the sources of biological hazards that can be introduced into food products, see Tables 1A through1Q and Tables 3A through 3- of Appendix 1 of this guidance.

Bacterial pathogens can be classified based on whether they form spores ("sporeformers") or whether they only exist as vegetative cells and do not form spores ("non-sporeformers"). Spores are not hazardous as long as they remain in the spore state. Unfortunately, spores are very resistant to heat, chemicals, and other treatments that would normally kill vegetative cells of both sporeformers and non-sporeformers. As a result, when spores are a concern, the process steps used to kill them are often much more severe than those necessary to kill vegetative cells.

When spores survive a processing step designed to kill vegetative bacteria, they may become a hazard in the food if they are exposed to conditions that allow germination and growth as vegetative cells. This can be particularly serious when a processing step has removed most of their competition. Thus, other controls such as reduced pH or water activity (a_w) or temperature control (refrigeration or freezing) may be needed to control sporeformers that remain after a kill step.

Because the characteristics of foodborne pathogens differ, the preventive controls that you identify and implement to control specific pathogens should be based on the characteristics of those specific pathogens. In the remainder of this section on biological hazards, we briefly review characteristics of common vegetative and sporeforming foodborne pathogens. For more detailed information, see FDA's *Bad Bug Book* (FDA 2012c).

Table 3-2 is a Quick Reference Guide to help you identify potential pathogens by biological classification and potential sources or entry points in your facility. The potential hazards listed in Table 3-2 will not apply to all facilities.

Table 3-2 Quick Reference Guide for Common Sources of Biological Hazards

Primary Source	Bacteria	Parasites	Viruses
Ingredient-related (e.g., contamination of raw materials and other ingredients)	*Salmonella* spp. (e.g., poultry, produce, nuts) *E. coli* O157:H7 & similar STEC (e.g., ruminant animals, dropped fruit, sprouts) *Campylobacter* spp. (e.g., poultry and raw milk) *B. cereus* (e.g., rice and other grains) *C. botulinum* (spores may be found in soil and on certain root crops.) *C. perfringens* (e.g., spices, may come in soil on produce) *L. monocytogenes* (e.g., raw agricultural commodities, other contaminated products used as ingredients)	*Cryptosporidium parvum* (contaminated water used as an ingredient) *Cyclospora cayetanensis* (berries) *Toxoplasma gondii* (meat)	Norovirus (produce, shellfish) Hepatitis A virus (produce, fruits)
Process-related (e.g., poor or ineffective process controls, including by a supplier)	*Salmonella* spp. survive inadequate heat treatment *C. perfringens* (improperly cooled cooked foods) *L. monocytogenes* (raw agricultural commodities, contaminated products)	*Cryptosporidium parvum* (contaminated water source)	N/A

Primary Source	Bacteria	Parasites	Viruses
Facility-related (may be caused by poor sanitation practices (e.g., inadequate cleaning and sanitizing of potential harborage sites), poor plant and equipment design, and poor pest management practices)	*L. monocytogenes* (e.g., reservoirs include floors, cold wet areas, equipment, drains, condensate, coolers, and soil) *Salmonella* spp. (pests)	N/A	Norovirus (only when active shedding occurs in facility through vomiting and diarrhea)
People-related (individuals who are carriers, showing no signs of disease, who are shedding the hazard, or who are infected and are actively ill)	*S. aureus* *Shigella* spp. *Salmonella* spp.	*Cryptosporidium parvum*	Hepatitis A virus Norovirus Rotavirus

3.3.1 Characteristics of Vegetative Foodborne Pathogens

Table 3-A in Appendix 3 of this guidance contains information on the physical conditions (i.e., a_w, acidity (pH), temperature, and oxygen requirements) that will limit growth for most of the vegetative pathogens that are of greatest concern in food processing. Data shown are the minimum or maximum values - i.e., the extreme limits reported among the references cited. These values may have been obtained in laboratory media, which may be more favorable to growth than many foods. These values may not apply to your specific processing conditions.

***Brucella* spp.** is the bacterium responsible for brucellosis. An estimated 840 foodborne cases of brucellosis occur annually in the United States (Scallan et al., 2011) When sheep, goats, cows, or camels are infected with the pathogen, their milk becomes contaminated with the bacteria. The most common way for humans to be infected is by eating or drinking unpasteurized/raw dairy products from infected animals. *Brucella* can also enter the body through skin wounds or mucous membranes following contact with infected animals. Symptoms include: fever; sweats; malaise; anorexia; headache; pain in muscles, joints and/or back; and fatigue. Some signs and symptoms may persist for prolonged periods of time or may never go away.

***Campylobacter jejuni* (*C. jejuni*)** is the bacterium responsible for campylobacteriosis. An estimated 845,000 foodborne cases of campylobacteriosis occur annually in the United States (Scallan et al., 2011). Symptoms include diarrhea, fever, abdominal pain, nausea, headache, and muscle pain. Symptoms start from 2 to 5 days after consumption of contaminated food and last from 7 to 10 days. A small percentage of patients develop complications that may be severe. These include bacteremia and infection of various organ systems, such as meningitis, hepatitis, cholecystitis, and pancreatitis. Autoimmune disorders are another potential long-term complication associated with campylobacteriosis; for example, Guillain-Barré syndrome (GBS). Everyone is susceptible to infection by *C. jejuni.* Campylobacteriosis occurs more frequently in the summer months than in the winter.

Pathogenic strains of *Escherichia coli* (*E. coli*) are responsible for four types of illness: gastroenteritis or infantile diarrhea, caused by enteropathogenic *E. coli* (EPEC); travelers' diarrhea, caused by enterotoxigenic *E. coli* (ETEC); bacillary dysentery, caused by enteroinvasive *E. coli* (EIEC); and hemorrhagic colitis, caused by enterohemorrhagic *E. coli* (EHEC). EHEC is the most severe, with potential for serious consequences such as hemolytic uremic syndrome, particularly in young children. An estimated 205,800 foodborne cases from all four types of *E. coli* occur annually in the United States (Scallan et al., 2011). Symptoms vary for the different forms of illness, but include abdominal pain, diarrhea, vomiting, fever, chills, dehydration, electrolyte imbalance, high body fluid acidity, and general discomfort. Symptoms start from 8 hours to 9 days after consumption of contaminated food and last from 6 hours to 19 days, with both periods varying significantly between the illness types. Everyone is susceptible to all forms of infection from *E. coli*, but EPEC is most commonly associated with infants, and all types tend to result in more severe symptoms in the very young and elderly.

***Listeria monocytogenes* (*L. monocytogenes*)** is the bacterium responsible for listeriosis. An estimated 1,600 foodborne cases of listeriosis occur annually in the United States (Scallan et al., 2011). *L. monocytogenes* produces mild flu-like symptoms in many individuals. However, in susceptible individuals, including pregnant women, newborns, and the immunocompromised, it can result in more severe symptoms, including septicemia, meningitis, encephalitis, spontaneous abortion, and stillbirth. Symptoms start from 3 days to 3 weeks after consumption of contaminated food. Mortality is high (approximately 25%) in those that display the more severe symptoms.

***Salmonella* spp.** is the bacterium responsible for salmonellosis. An estimated 1,029,000 cases of foodborne salmonellosis occur annually in the United States (Scallan et al., 2011). Symptoms include: nausea, vomiting, abdominal cramps, diarrhea, fever, and headache. Symptoms start from 6 hours to 2 days after consumption of contaminated food and generally last from 4 to 7 days. The most severe form, typhoid fever, is caused by *Salmonella* Typhi. Everyone is susceptible to infection by *Salmonella* spp*.,* but symptoms are most severe in the elderly, infants, and the infirmed. Infections by *Salmonella* spp*.* and other closely related bacterial pathogens, such as *Shigella* spp*., E. coli*, and *Yersinia enterocolitica,* can lead to chronic reactive arthritic symptoms in pre-disposed individuals.

Shigella spp. is the bacterium responsible for shigellosis. Shigella infections may be acquired from eating contaminated food. Foods may become contaminated by infected food handlers who do not wash their hands before handling food. An estimated 131,000 foodborne cases of shigellosis occur annually in the United States (Scallan et al., 2011). Symptoms include: abdominal pain; cramps; diarrhea; fever; vomiting; blood, pus, or mucus in stools; continuous or frequent urges for bowel movement; and death. Symptoms start from 12 hours to 2 days after consumption of contaminated food and last from 1 to 2 weeks. Everyone is susceptible to infection by *Shigella* spp*.*

***Staphylococcus aureus* (*S. aureus*)** is a common bacterium found on the skin and in the noses of many healthy people and animals. The bacterium is responsible for producing toxins as it grows in foods, causing staphylococcal food poisoning. An estimated 241,000 foodborne cases of staphylococcal food poisoning occur annually in the United States (Scallan et al., 2011). Symptoms include: nausea, vomiting, diarrhea, abdominal pain, and weakness. Staphylococcal toxins are fast acting and can cause illness in as little as 30 minutes. Symptoms usually start within one to six hours after eating contaminated food. Everyone is susceptible to intoxication by *S. aureus* toxin, with more severe symptoms, including occasional death, occurring in infants, the elderly and debilitated persons.

3.3.2 Characteristics of Spore-Forming Foodborne Pathogens

Table 3-A in Appendix 3 contains information on the conditions that will limit growth for most of the spore-forming pathogens that are of greatest concern in food processing. Data shown are the minimum or maximum values – i.e., the extreme limits reported among the references cited. These values may have been obtained in laboratory media, which may be more favorable to growth than many foods. These values may not apply to your processing conditions.

***Bacillus cereus* (*B. cereus*)** is the bacterium responsible for *B. cereus* food poisoning. An estimated 63,400 foodborne cases of *B. cereus* food poisoning occur annually in the United States (Scallan et al., 2011). There are two forms of illness, associated with two different toxins. In one form of illness, *B. cereus* produces an emetic toxin in the contaminated food; the emetic toxin causes nausea and vomiting, starting from 30 minutes to 6 hours after consumption of the food. In the other form of illness, associated with an infection due to high numbers of *B. cereus* in the contaminated food, *B. cereus* produces a diarrheal toxin in the intestines of the affected consumer after the consumer ingests food; the diarrheal toxin causes diarrhea, starting from 6 to 15 hours after consumption. Symptoms in both forms of illness last about 24 hours. Everyone is susceptible to *B. cereus* food poisoning.

***Clostridium botulinum* (*C. botulinum*)** toxin is the toxin responsible for a severe paralytic illness called botulism. *C. botulinum* is found in soil and grows best in low oxygen conditions. The bacteria form spores that can survive in a dormant state until exposed to conditions that support their germination and growth, such as in inadequately processed low-acid canned foods. Foodborne botulism is caused by eating foods that contain the botulinum toxin, which is formed during growth of *C. botulinum*. There are seven types of botulism toxin designated by letters A through G; only types A, B, E and F have caused botulism in humans. An estimated 55 foodborne cases of botulism occur annually in the United States (Scallan et al., 2011). Symptoms include: weakness; vertigo; double vision; difficulty in speaking, swallowing, and breathing; abdominal swelling; constipation; paralysis; and, possibly, death. Symptoms start from 18 to 36 hours after eating a contaminated food, but can occur as early as 6 hours or as late as 10 days after exposure. Everyone is susceptible to intoxication by *C. botulinum* toxin; only a few micrograms of the toxin can cause illness. Mortality is high; without the antitoxin and respiratory support, death is likely.

***Clostridium perfringens* (*C. perfringens*)** is the bacterium responsible for perfringens food poisoning. *C. perfringens* causes illness when large numbers of the bacteria are consumed in contaminated food. The bacterium then produces enough toxin in the intestines to cause illness. *C. perfringens* spores can survive high temperatures. During cooling and holding of food at warm temperatures, the spores germinate and the resulting vegetative cells of the bacteria grow. An estimated 966,000 foodborne cases of perfringens food poisoning occur annually in the United States (Scallan et al., 2011). Symptoms include: abdominal cramps and diarrhea. Symptoms typically start from 8 to 12 hours after eating a contaminated food, but can occur as early as 6 hours after exposure and last for about a day. Everyone is susceptible to perfringens food poisoning, but it is more common in the young and elderly, who may experience more severe symptoms lasting for one to two weeks.

3.3.3 Potential Ingredient-Related Biological Hazards

See Table 3-2 in this chapter and Tables 1A through 1Q in Appendix 1 of this guidance for information that can help you identify potential ingredient-related biological hazards that may be associated with specific food products. See Chapter 4 – Preventive Controls, as well as

Chapters 6 through 13, for recommendations on control of some specific ingredient-related biological hazards.

3.3.4 Potential Process-Related Biological Hazards

The purpose of this section is to help you identify potential process-related biological hazards for the foods that you produce. See Chapter 4 – Preventive Controls, as well as Chapters 6 through 13, for recommendations on control of some specific process-related biological hazards.

Some process-related biological hazards can occur if something goes wrong with a process control. For example, pathogens that you intend to control by cooking could survive if your product is undercooked during application of a heat treatment; pathogens that you intend to control by refrigeration could multiply and/or produce toxin if there is a lack of proper refrigerated holding during product assembly; and pathogens that you intend to control by a_w could multiply and/or produce toxin if the product is not properly formulated (e.g., too little sugar is used, resulting in an increase in the a_w). Other process-related biological hazards are not related to something going wrong with a process control. For example, if you plan to use reduced oxygen packaging (ROP) to prevent the growth of spoilage organisms and extend the shelf life of the product, the extended shelf life provides more time for toxin production or pathogen growth if pathogens are present and temperatures are suitable for growth. As another example, if you manufacture a product by adding spices after a process control that would significantly minimize pathogens, pathogens in the added spices could introduce pathogens to the treated product. As yet another example, pathogens could be introduced to a treated product after packaging if there is a lack of container integrity.

In the following sections on process-related biological hazards, we describe examples of these kinds of process-related biological hazards.

3.3.4.1 Bacterial pathogens (vegetative and sporeforming) that survive after treatment

If a process that you design to kill bacterial pathogens and/or their spores does not work as intended, the bacterial pathogens and/or their spores that you intended to control can be present in your food product. The primary pathogens of concern are *L. monocytogenes*, *Salmonella* spp., *S. aureus* and *C. jejuni*, pathogenic strains of *E. coli*, *Yersinia enterocolitica* (*Y. enterocolitica), B. cereus C. perfringens, and C. botulinum*. See Appendix 3 of this guidance for limiting conditions for growth of bacterial pathogens.

See Chapter 4 of this guidance for an overview of recognized and established processing conditions to control pathogens and for factors to consider when designing your process to prevent problems. For example:

- Some foods heat faster than others. Bacterial pathogens in the cold spot of the food will be inactivated more slowly than those at the surface because those in the cold spot are subjected to less heat. If the minimum process for lethality is not achieved at the cold spot, pathogens may survive the treatment.
- Certain characteristics of food make it either easier or harder to destroy bacterial pathogens, if present. For example, pathogens are more easily destroyed in foods with an acidic pH; sugars and oils tend to shield pathogens from the effects of heat; and the presence of moisture, both in and

surrounding the food, make destruction easier. If these have not been taken into account in designing the process, pathogens may survive the treatment.

- Spores of bacterial pathogens are more heat tolerant than the vegetative cells of the same pathogen and different bacterial pathogens have different heat resistances (see Appendix 3 of this guidance). If the process is not designed to control the most resistant pathogen of concern in the food, pathogens may survive the treatment.

See also Chapter 6 – Use of Heat Treatments as a Preventive Control for more detailed recommendations to control process-related biological hazards through heat treatments.

3.3.4.2 Bacterial pathogens that grow and/or produce toxin

3.3.4.2.1 Due to lack of proper time/temperature control

Bacterial pathogens that are introduced from contaminated ingredients into a product that does not undergo a lethality process, or that survive a lethality process as a result of a problem with a process control, can multiply ("grow") and, depending on the pathogen, produce toxin as a result of time and temperature abuse of food products. Certain bacterial pathogens (e.g., *E. coli* O157:H7, *S. aureus,* and *L. monocytogenes)* grow well in time- and temperature-abused food. Time and temperature abuse occurs when a product is allowed to remain at temperatures favorable to bacterial pathogen growth for sufficient time to result in unsafe levels of the pathogens or their toxins in the product. Most bacterial pathogens will grow well in cooked foods that are temperature-abused if their growth is not otherwise controlled by means such as drying, salting, or acidification, because competing bacteria are significantly reduced by the cooking process. Uncooked foods that have high water activities and pH, such as batters, which are subjected to time/temperature abuse (e.g., using room-temperature batter for several hours), can support growth and toxin production by pathogens such as *S. aureus*.

Vegetative pathogens may grow in products during processing steps and may be ultimately destroyed by a lethal step such as cooking. However, too much bacterial growth before the lethal step may render the lethal process inadequate. Moreover, if the time and temperature abuse allows production of toxin, such as toxin production from *S. aureus* in temperature-abused custard pies, this toxin will not be destroyed by a heat step later in the process.

In evaluating the potential for bacterial pathogens to grow and/or produce toxin in your food products, you should consider the following factors:

- The types of pathogenic bacteria that are known or reasonably likely to be present;
- Whether those pathogens can grow in the food;
- The infective dose of the pathogenic bacteria;
- The expected initial level of the pathogenic bacteria in the food.

See Chapter 4 of this guidance for an overview of processing conditions to minimize pathogen growth by controlling temperatures to prevent pathogen growth and time of exposure to temperatures at which growth can occur. See also Chapter 7 – Use of Time/Temperature Control as a Process Control for more detailed recommendations to control process-related biological hazards through time/temperature controls. Tables 3-A and 3-B (Appendix 3 of this guidance) provide the limiting temperature conditions for growth of vegetative and sporeforming bacterial pathogens.

3.3.4.2.2 Due to lack of proper cooling after heat treatments

Depending upon the food and ingredients, heat treated foods can still possibly have viable forms (i.e., spores) of pathogenic bacteria present. Sometimes, vegetative cells that are particularly heat tolerant, (like *Listeria monocytogenes*) survive the cooking process; however, this should not be the case if the appropriate target pathogen was selected to be controlled by the applied process. More often, it is spores that survive the cooking process if they are present, and they begin to germinate when the product temperature begins to drop below 140°F. In addition, they will be present in the food during storage. Some spores such as those from pathogens such as non-proteolytic *C. botulinum* and some strains of *B. cereus* have the ability to germinate and grow at refrigeration temperatures, although long times are required. Other spores that remain in the food remain dormant until the product is temperature abused. In such an event, pathogenic spores that may be present are able to germinate, grow and possibly produce toxin due to the fact that most spoilage bacteria have been eliminated by the reduction step.

See Chapter 4 of this guidance for an overview of processing conditions to minimize pathogen growth by controlling temperatures during cooling after cooking. See also Chapter 7 – Use of Time/Temperature Control as a Process Control for more detailed recommendations to control process-related biological hazards through time/temperature controls.

3.3.4.2.3 Due to poor formulation control

Products most susceptible to biological hazards due to problems with formulation are RTE products that either do not receive a kill step in their process or that receive a kill step for vegetative pathogens but not spores and that may require refrigeration for safety during their manufacture and shelf life. For this category of products, product formulation can play a significant role in significantly minimizing or preventing hazards. For example, a naturally acidic product with a pH below 4.6 may rule out *C. botulinum* as a hazard requiring a preventive control, since this pH will prevent spore germination, growth, and toxin production. Formulation parameters such as pH, a_w, use of preservatives, and oxygen availability, can work in concert to establish an ecosystem that is designed to inhibit the growth of the pathogens that may be present. If not, just as described for foods that have been time and temperature abused, bacterial pathogen growth and toxin formation can result due to this lack of inhibition and control.

In determining the potential for a process-related hazard due to poor formulation control, we recommend that you know the formulations or ingredient lists of your incoming products, as well as the equilibrated pH, titratable acidity, a_w, percent moisture, percent sodium and percent sugar, as appropriate, of the finished combined product. Many of the products susceptible to biological hazards due to problems with formulation are made up of multiple ingredients, each with their own specific set of formulation parameters. Any one individual component not meeting the required formulation criteria to ensure that the designed preventive control system is achieved may result in a food that does not inhibit the growth or toxin formation of a pathogen that may be present in the food.

In determining the potential for a process-related biological hazard due to poor formulation control, we also recommend that you consider the interactions that may occur among the various products, raw materials, and other ingredients when combined. Layering product components of significantly different pH or a_w values alters the microenvironments at the interfaces of the components. A simple example is an éclair filled with a cream filling. The pH

and a_w at the interface of the pastry and the filling will be affected by the difference between the higher pH and lower a_w of the pastry and the potentially lower pH and higher moisture content of the filling, potentially resulting in an environment favorable to microbial growth. A microorganism that is in the filling may not grow due to the pH, but the pH of the pastry may favor growth of a microorganism at the interface during the product's shelf life. Characteristics such as oxygen-reduction (redox) potential and the effectiveness of antimicrobials are also likely to differ at component interfaces and may impact pathogen survival and growth.

In determining the potential for a process-related hazard due to poor formulation control, we also recommend that you consider how the equilibrium pH and a_w of the finished product compares to that of the individual components. If a finished formulated product is a more homogeneous mixture of the components, then the resulting final equilibrium pH and a_w may be significantly different from that of the individual components. A good example is hummus, which is typically made from chick peas (garbanzo beans), which may be rehydrated from a dry state, blended with acidifying agents, oils and spices and then pureed. The final product with a smooth texture will have an equilibrium pH, and possibly $a_{w,}$ different from the original ingredients. If a topping of pine nuts, or oil, or diced red peppers is added to the top in the container as "decoration" then those additions could then significantly change the microenvironment at the interface and may require a control (such as acidification).

See Chapter 4 of this guidance for an overview of formulation-based controls. See Chapter 8 – Use of Formulation as a Preventive Control for more detailed recommendations to control process-related biological hazards through product formulation.

3.3.4.2.4 Due to reduced oxygen packaging (ROP)

From a food safety standpoint, packaging serves two functions: (1) It prevents contamination of the food; and (2) it makes possible, or extends the effectiveness of, food preservation methods. For example, packaging can maintain the atmosphere in a controlled or modified atmosphere package or a vacuum package, or it can prevent rehydration of a dried food. All of these different packaging methods are grouped into a category that we call ROP. ROP is used to prevent the growth of spoilage organisms, thereby extending the shelf life of the product. There are some other product quality benefits as well, such as reductions in rancidity, shrinkage, and color loss.

However, ROP does not control the growth of all bacterial pathogens and can create a process-related biological hazard. The extended shelf life provides more time for toxin production or pathogen growth if pathogens are present and temperatures are suitable for growth. Lower oxygen levels favor pathogens that can grow in the absence of oxygen over the aerobic spoilage organisms that require oxygen for growth. For this reason, you may get toxin production before you get spoilage - something that is less likely to happen in traditional packaging.

The major concern with ROP is *C. botulinum,* although there may also be concerns with other pathogens such as *L. monocytogenes*, particularly in refrigerated RTE foods. You should not use ROP unless barriers for *C. botulinum* are present. These barriers include: a_w below 0.93; pH below 4.6; salt above 10%; thermal processing in the final container; and freezing with frozen storage and distribution. Each of these barriers by itself can be effective in the control of *C. botulinum* growth. Refrigeration below 38°F (3.33°C) can prevent growth of all strains of *C. botulinum,* but because temperatures above this are commonly employed for refrigeration,

temperature should not be relied on as the only control. Combinations of barriers that individually would not control growth of *C. botulinum* can work together to prevent growth.

For a further discussion on the potential for ROP to create a process-related biological hazard, see Annex 6 of the 2013 Food Code (FDA, 2013b).

3.3.4.3 Bacterial pathogens in ingredients added after process controls

The manufacture of certain RTE products involves, by design, the addition of ingredients after any process controls are applied. For example, the production of some fresh vegetable salad kits includes the addition to the final product, prior to packaging, of various ingredients such as nuts, dried berries, and seeds. The process control for the salad components (e.g., chlorine wash) is applied to the various fresh cut vegetables that are mixed in preparation for packaging, while the nuts, berries, and seeds are added just prior to packaging. As another example, the production of some fresh-baked pastry products includes the addition of toppings, such as frostings, nuts, dried fruit, confections (e.g., sprinkles). A facility that produces products containing ingredients added after a process control should consider the potential for the added components to be a process-related biological hazard as part of its hazard analysis.

3.3.4.4 Bacterial pathogens introduced after packaging due to lack of container integrity

Food manufactured and processed (e.g., heat treated) in a container and/or clean-filled after treatment can become contaminated if its container forms a leak or loses seal integrity, thereby exposing the processed food to a variety of biological hazards. The primary pathogens of concern include *C. botulinum*, *L. monocytogenes*, pathogenic strains of *E. coli*, *Salmonella* spp., *S. aureus*, and *B. cereus*.

The primary causes of recontamination of foods after a process control step and packaging are defective container closures and contaminated cooling water. Poorly formed or defective container closures can increase the risk of bacterial pathogens entering the container through container handling that occurs after the product has been filled and the container has been sealed. This risk is a particular concern during container cooling performed in a water bath. As the product cools, a vacuum is drawn in the container. Contaminated cooling water can enter through the container closure, especially if the closure is defective.

3.3.5 Potential Facility-Related Biological Hazards

Foodborne illnesses due to commercially produced foods have been traced to post-process contamination due to the poor implementation of CGMPs, such as by exposure or contact with contaminated equipment during processing such as conveying, holding, chilling or packaging. Examples of events and foodborne illness outbreaks due to contamination of RTE foods are quite extensive and readily available in scientific literature. Typically in these events, foods that were processed by some means (e.g., cooked, pasteurized, dried) to reduce the presence of microorganisms, in particular pathogens identified as hazards requiring a preventive control, were subsequently exposed to the environment where they were recontaminated with pathogens. As discussed in the following sections on facility-related biological hazards, there are challenges to prevent this from happening.

Table 3-3 provides a list of examples, adapted in part from ICMSF Book 7, Chapter 11 (ICMSF, 2002) and from FDA documents that highlight the public health impact of contamination of RTE foods with environmental pathogens.

Table 3-3. Examples of Pathogens Identified from Outbreaks Attributed to Contamination with Environmental Pathogens

Product	Environmental Pathogen	Details	Reference
Chocolate	*S.* Napoli	Possibly contaminated water used in double-walled pipes, tanks and other equipment	Gill, *et. al.* (1983)
Chocolate	*S.* Eastbourne	From processing environment	Craven, *et. al.* (1975)
Butter (from pasteurized cream)	*L. monocytogenes*	From processing environment	Lyytikainen *et. al.* (2000)
Peanut butter	*S.* Tennessee	From processing environment	FDA (2007a, 2007b)
Peanut butter	*Salmonella* spp.	From processing environment	Cavallaro et al. (2011); FDA (2009b, 2009c)
Whole white pepper	*S.* Rissen	From processing environment	FDA (2009d)
Cantaloupes	*L. monocytogenes*	From processing environment	FDA (2012a)
Peanut butter	*S.* Bredeney	From processing environment	FDA (2012b)
Soft cheeses (from pasteurized milk)	*L. monocytogenes*	From processing environment	FDA (2013c)
Soft cheese (from pasteurized milk)	*L. monocytogenes*	From processing environment	FDA (2014a)

The PCHF requirements specify that your hazard evaluation must include an evaluation of environmental pathogens whenever a ready-to-eat food is exposed to the environment prior to packaging and the packaged food does not receive a treatment or otherwise include a control measure (such as a formulation lethal to the pathogen) that would significantly minimize the pathogen. (See 21 CFR 117.130(c)(1)(ii).) Effectively designed and implemented CGMPs are key to keeping biological hazards out of your food products. However, experience has shown that application of CGMPs – even in combination with a HACCP plan - cannot guarantee that contamination of a processed food from the environment will not occur. This is one reason why the PCHF requirements specify that sanitation controls include procedures, practices, and processes to ensure that the facility is maintained in a sanitary condition adequate to significantly minimize or prevent hazards such as environmental pathogens (21 CFR 117.135(c)(3)). In addition, the PCHF requirements specify that, as appropriate to the facility,

the food, and the nature of the preventive control and its role in the facility's food safety system, you must conduct activities that include environmental monitoring, for an environmental pathogen or for an appropriate indicator organism, if contamination of an RTE food with an environmental pathogen is a hazard requiring a preventive control, by collecting and testing environmental samples.

In the following sections, we provide information to help you determine whether an environmental pathogen is a hazard requiring a preventive control in your facility. Although Table 3-3 includes some examples of outbreaks of foodborne illness caused by facility-related biological hazards other than environmental pathogens, we do not discuss those other facility-related biological hazards in this chapter.

3.3.5.1 Sources of facility-related biological hazards

The likelihood of product contamination with a facility-related environmental pathogen increases as the prevalence of the environmental pathogens in the processing environment increases. The prevalence of the environmental pathogens in the processing environment can be influenced by the raw materials used in the process, the type of process, and the hygienic practices applied to keep to keep the processing area clean and hygienic. Table 3-4 is a quick reference guide to help you identify some of the most common sources for facility-related hazards that can contaminate the food processing environment; Table 3-4 does not provide an exhaustive list of such pathogens.

Table 3-4. Quick Reference Guide for Common Sources of Facility-Related Biological Hazards

Source	Examples
Raw agricultural commodities	• Raw milk • Cocoa beans • Fruits and vegetables • Nuts • Unprocessed spices
Food handlers and maintenance personnel	• Transfer of biological hazards from one point to another on, for example, shoes and other clothing • Improper hand washing • Transfer of biological hazards to foods through improper handling or maintenance practices
Air and water	• Lack of appropriate air filtration for cooling, drying, air conveying • Improper air flow from "raw" to RTE areas • Aerosols from improper cleaning practices

Source	Examples
Insects and pests	• Flies • Cockroaches • Rodents
Transport equipment	• Forklifts • Trolleys • Racks • Carts

With these varied sources for potential contamination, it is easy to understand how a failure of one or more steps in your CGMPs can lead to contamination of the processing environment and, ultimately, your food products with facility-related biological hazards.

3.3.5.2 Transient vs. resident facility-related environmental pathogens

Once bacterial pathogens have been introduced into the processing environment, experience has shown that pathogens may be present as “transient” contamination or “resident” contamination within the facility.

3.3.5.2.1 Transient contamination

Bacterial pathogens, including environmental pathogens, are typically introduced into the processing facility through, for example, incoming raw materials, personnel, or pests. It is important to ensure that these microorganisms remain transient and do not become established in the environment where they can grow and multiply. Transient contaminants can, however, result in a diversity of pathogens in the processing environment that can show up in the processing lines and finished product. This phenomenon is typical for food operations using a wide variety of ingredients, in particular raw commodities, because these materials can contain very diverse microflora. Generally though, the proper application of cleaning and sanitizing in accordance with CGMPs is adequate to control the transient bacteria in the processing facility. So, contamination detected from day-to-day may be found to be quite diverse.

3.3.5.2.2 Resident contamination

Bacterial pathogens causing resident contamination can also be introduced into the processing facility, where the pathogens then become established in a harborage site, multiply, and persist for extended periods of time, even years. A harborage site, or niche, is a site in the environment or on equipment (e.g., junctions, cracks, holes, and dead-end areas) that enables the accumulation of residues (food debris, dust, and water) and permits the growth of microorganisms such as *L. monocytogenes* and *Salmonella*. These sites may be difficult to inspect or access and therefore can protect environmental pathogens during routine cleaning and sanitizing. Thus, while common cleaning and sanitation practices are adequate to control the presence of transient contaminants, such practices do not control the presence of resident contaminants once they have become established. Sanitation controls, including proper personnel practices and equipment and facility design, are key to preventing transient bacterial pathogens from becoming resident strains. Once an environmental pathogen has become

established as a "resident strain," there is a persistent contamination risk for foods processed in that facility. The facility will need to use intensified sanitation procedures to eliminate the contamination. Of all the bacterial pathogens, *Salmonella* and *L. monocytogenes* have the most extensive history of being able to set up residence in a processing facility. Although not as likely, the potential exists for the other pathogens discussed previously in this chapter to become established as resident contaminants.

Key determinants for the pathogens to become established in a food processing environment are: 1) The temperature at which the food processing environment is maintained; 2) the available moisture in the food processing environment; and 3) the availability of nutrients for growth. For processed foods, this typically translates into two primary categories of food processing environments by the nature of the products that are manufactured and packaged in a facility:

- Frozen/refrigerated and wet
- Warm/ambient and dry

In both cases, proper cleaning is needed to minimize nutrient availability. The pathogen most often associated with cold and wet processing environments is *L. monocytogenes,* and the pathogen most often associated with warm and dry processing environments is *Salmonella* (Scott et. al., 2009; ICMSF, 2005).

3.3.5.3 Facility-related environmental pathogens associated with wet vs. dry processing environments

Food processing operations can typically be classified into one of two simple categories – wet processing environments or dry processing environments (Table 3-5). This very simple distinction has significant implications for the strategy that must be applied to control food contamination from environmental pathogens.

Table 3-5. Some Examples of Foods Processed in Wet and Dry Processing Environments

Processing Environment Conditions	Examples of Foods
Wet	• Ice Cream • Refrigerated Dairy Products • Refrigerated Deli Salads • Refrigerated and Frozen Meals • Refrigerated Beverages (non-juice)
Dry	• Chocolate and Confections • Milk Powders • Baked Goods • Dehydrated Soups

Processing Environment Conditions	Examples of Foods
	• Powdered Beverages • Nut/nut products

3.3.5.3.1 Wet process environments

The most effective strategy to prevent the contamination of finished products with *L. monocytogenes* is to maintain an environment as dry as possible. Wet environments have some very obvious characteristics that lead to problems with contamination by *L. monocytogenes*, such as:

- Wet floors due to constant wet cleaning will facilitate the transfer of *Listeria* spp., including *L. monocytogenes,* from an environmental source to food contact surfaces;
- Wet floors can create harborage sites if they are not well maintained and have broken/cracked grout or tiles. These structures may provide protected harborage to environmental pathogens even when the floors are cleaned and sanitized.
- Condensation on overhead structures as a result of air temperature and humidity control issues and from use of water in cooking and cooling operations creates a means of transfer of *Listeria* spp., including *L. monocytogenes,* from non-food-contact surfaces to exposed product and equipment food-contact surfaces.
- Frost formation due to condensation at freezer entry and exit points provides an opportunity for moisture accumulation and a constant source of water for *Listeria* spp. to multiply.
- Inadequate sanitation practices on floor freezer and cooler units may provide the moisture to support *Listeria* spp., including *L. monocytogenes,* if water sources are not properly plumbed to hygienically designed drains.

Wet floors can serve as vectors for spreading *Listeria* spp. via the movement of people and equipment and material handling items such as totes and pallets. Wet floors can also serve as vectors for pathogen transfer when personnel walk through standing water on poorly designed floors and drains and during cleaning. *L. monocytogenes* does not spread alone through the air; however, in wet environments, aerosols from high pressure water hoses used during cleaning operations help spread *L. monocytogenes* throughout the environment and from one surface (e.g., floors) to another surface (e.g., food contact surfaces, such as conveyors, tables, and product containers). In many facilities, certain processing operations are inherently wet, such as product debagging, raw material preparation, mixing and formulation of liquid product components, cooking, and blanching. In these cases, the best that can be done is to control the personnel, equipment traffic, and cleaning practices that are involved with the specific operation. The intent is to minimize water accumulation and aerosol formation to prevent in-process and finished product recontamination.

We recommend that wet processing areas be dried out as much as possible. This continues to be an ongoing challenge for the food industry that has for many years depended upon the unlimited use of water for equipment and facility cleaning practices.

3.3.5.3.2 Dry process environments

Moisture control is critically important in preventing *Salmonella* contamination in low-moisture products (ICMSF, 2005). Water in the dry processing environment is one of the most significant risk factors (perhaps the single most important factor) for *Salmonella* contamination, because water allows for pathogen growth, significantly increasing the risk for product contamination. Water, present even in very small amounts for short, sporadic time periods, may allow *Salmonella* to grow in the environment. At times, moisture is obvious in the form of water droplets or puddles from wet cleaning or from other not-so-apparent sources such as high relative humidity or moisture accumulating inside of equipment.

Salmonella can, to varying degrees, be introduced into low-moisture product manufacturing facilities and become established in those environments. Harborage sites may develop and become a source of product contamination, unless the sites are identified and eliminated (CAC, 2008).

Growth of *Salmonella* is only possible in the presence of water. Because food particles and dust are normally expected to be present in processing areas, adequate nutrients are always available to microorganisms. Growth cannot occur, however, if the plant environment is sufficiently dry. The potential *Salmonella* harborage sites become more important when water is present for a sufficient period of time. The presence of water in the dry processing environment can result from improper use of water during cleaning, which has been linked to the occurrence and spread of *Salmonella* (CAC, 2008). Other events resulting in the presence of water in a dry area include condensate formation, leaking water or steam valves, infiltration of water following heavy rains (e.g., leaky roofs) and the use of water showers in the case of fire emergencies. (CAC, 2008). We recommend that you remove water immediately from the primary *Salmonella*-controlled hygiene areas (areas where RTE food is exposed to the environment) following such events in order to keep the plant environment as dry as possible.

You should maintain dry conditions at all times in primary *Salmonella*-controlled hygiene areas, except for the occasions when you have determined that controlled wet cleaning is necessary. Potential problems arise when there is visible water present in the dry areas or when there are areas in which standing water has dried out. *Salmonella* may be found both in wet spots and in spots where standing water has dried (Zink, 2007). The latter situation may present an additional risk of spread via the generation of airborne contaminated dust**.**

3.4 Chemical Hazards

You must conduct a hazard analysis to identify and evaluate known or reasonably foreseeable chemical hazards. See 21 CFR 117.130(b)(1)(ii). When your hazard analysis identifies a known or reasonably foreseeable chemical hazard that requires a preventive control, you must identify and implement a preventive control for the chemical hazard. See 21 CFR 117.135(a)(1).

The chemical hazards that are the focus of this section of this chapter include ingredient-related chemical hazards (i.e., pesticide and drug residues, heavy metals, environmental contaminants, histamine due to decomposition, natural toxins (e.g., mycotoxins), radiological hazards, unapproved food and color additives, food allergens, and substances associated with a food intolerance or food disorder) and process-related chemical hazards (i.e., food allergens, substances introduced by misformulation and the introduction of industrial chemicals or other contaminants from the food processing environment).

Food products can become contaminated with chemical hazards that are introduced at any stage in food production and processing. Some ingredient-related chemical hazards are natural components of food, such as food allergens, or are produced in the natural environment, such as mycotoxins, whereas other ingredient-related hazards (e.g., pesticides, drug residues, heavy metals, environmental contaminants) are contaminants of raw materials and other ingredients. Some process-related chemical hazards may be included in product formulation (e.g., sulfites that are a hazard for those consumers who are sensitive to them), whereas other process-related chemical hazards may be unintentionally introduced into food, such as industrial chemicals that are used in a facility for purposes other than food production. Process contaminants may also form during heating (e.g., acrylamide).[2] For further details on the sources of ingredient-related and process-related chemical hazards, see Tables 2A through 2Q and Tables 3A through 3Q of Appendix 1 of this guidance.

A chemical hazard may cause immediate effects, or may be associated with potential long-term effects after chronic exposure to the chemical. One example of an immediate effect is gastrointestinal illness such as nausea, which can be caused by elevated levels of industrial chemicals (such as caustic cleaning compounds). Caustic cleaning compounds can also cause burning of the mouth and esophagus. Ammonia in food contaminated by a refrigerant leak has caused gastrointestinal illness (stomachache and nausea) and headaches (Dworkin, et al. 2004). Sulfites have resulted in diarrhea, headache, difficulty breathing, vomiting, nausea, abdominal pain and cramps in sulfite-sensitive individuals (Timbo et al. 2004). Examples of long-term effects include impaired cognitive development in children chronically exposed to relatively low levels of lead (e.g., in contaminated candy) (FDA, 2006a) and liver cancer resulting from chronic exposure to the mycotoxin, aflatoxin (Williams et. al, 2004 and Shephard, 2008).

FDA has set action levels and tolerances for some contaminants (FDA, 2015f). They represent limits at or above which FDA will take legal action to remove products from the market. Where no established action level or tolerance exists, FDA may take legal action against the product at the minimal detectable level of the contaminant. Action levels and tolerances are established based on the unavoidability of the poisonous or deleterious substances and do not represent permissible levels of contamination where it is avoidable. For example, FDA has established an action level of 3 ppm polychlorinated biphenyl (PCB) residues in red meat on a fat basis (FDA, 1987). FDA also has issued for public comment a draft guidance for industry that would, when finalized, establish an action level of 100 ppb for inorganic arsenic in infant rice cereal (FDA 2016). FDA has established tolerances for polychlorinated biphenyls (PCB's) in foods such as milk and other dairy products, poultry, eggs, and infant and junior foods (see 21 CFR 109.30).

Further, under the Federal Food, Drug, and Cosmetic Act (FD&C Act), certain substances, such as food additives, color additives, new animal drugs, and pesticides require premarket approval before they may be legally used.

[2] Some processing contaminants are formed during the heating of certain ingredients or finished foods (e.g., acrylamide). We have not included such contaminants in Table 3-6 as potential process-related chemical hazards that may require a preventive control as part of a food safety plan under part 117 because we believe that more information is needed regarding appropriate levels and effective controls. As stated in our "Guidance for Industry: Acrylamide in Foods" (FDA, 2016a), we recommend that manufacturers evaluate approaches to acrylamide reduction that may be relevant to their particular processes and consider adopting approaches, if feasible, that reduce acrylamide levels in their products.

FDA also has issued guidances to provide information to industry on methods to reduce levels of specific chemicals in foods. For example, FDA has issued guidance providing information to help growers, manufacturers, and food service operators reduce acrylamide levels in certain foods (FDA, 2016a). Similarly, the Codex Alimentarius Commission has established a number of codes of practice for controlling mycotoxins, heavy metals, and other chemicals in foods (CAC, 2012).

Chemical residues in a food are not always considered hazards and their occurrence may be unavoidable. Because the particular chemical and its levels in the food determine whether it is a hazard, and because mechanisms whereby a chemical hazard can be introduced into a food product are both varied and dependent on the nature of the chemical, the preventive controls that you identify and implement to control specific chemical hazards should be based on the characteristics of those chemicals and the mechanisms whereby they could be introduced into your food product. In the following sections on chemical hazards, we describe some common preventive controls for controlling chemical hazards. For additional information on the control of chemical hazards, see Chapter 4 – Preventive Controls and Chapter 12 – Preventive Controls for Chemical Hazards.

In the remainder of this section on chemical hazards, we briefly describe characteristics of some chemical hazards that are of concern in foods and processing environments, including mechanisms whereby they can be introduced into a food product. We do not discuss seafood toxins in this guidance because seafood is exempt from the PCHF requirements; for a discussion of seafood toxins see our *Fish and Fishery Products Hazards and Controls Guidance* (FDA, 2011).

Table 3-6 is a quick reference guide to help you identify some of the most common sources of chemical hazards; Table 3-6 does not provide an exhaustive list of such hazards

Table 3-6. Quick Reference Guide for Common Sources of Chemical Hazards

Source	Examples
Ingredient-related chemical hazards	• Pesticide residues on produce raw agricultural commodities • Drug residues in milk • Heavy metals in or on produce raw agricultural commodities • Environmental contaminants (e.g., dioxins) • Mycotoxins in grains • Histamine in some aged cheeses • Radiological hazards in foods from areas after a nuclear accident • Unapproved food or color additives • Food allergens and substances associated with a food intolerance or food disorder (e.g., sulfites, gluten)

Source	Examples
Process-related chemical hazards	• Undeclared food allergens due to mislabeling or cross-contact • Improper addition of substances associated with a food intolerance (e.g., sulfites) • Improper use of a color additive such as Yellow No. 5 • Contamination with industrial chemicals such as cleaners or sanitizers • Radiological hazards from use of contaminated water supply
Facility-related chemical hazards	• Heavy metals due to leaching from equipment, containers, or utensils

3.4.1 Ingredient-Related Chemical Hazards

3.4.1.1 Pesticides

Pesticide residues may be of concern in food crops and in foods of animal origin (as a result of pesticide residues in animal food). The term pesticide is used for products such as insecticides, fungicides, rodenticides, insect repellants, herbicides or weed killers, and some antimicrobials that are designed to prevent, destroy, repel, or reduce all types of pests (See EPA "Setting Tolerances for Pesticide Residues in Foods") (EPA, 2015). Three federal government agencies share responsibility for the regulation of pesticides. Pesticides that have been registered (i.e., approved) with the U.S. Environmental Protection Agency (EPA) may be applied according to label directions directly to raw agricultural commodities or food (see 40 CFR 180). For a registered pesticide that could potentially result in residues in or on food, the EPA establishes a tolerance, which is the maximum amount of residue that is permitted in or on a food. FDA is responsible for enforcing pesticide tolerances for foods other than meat, poultry, and certain egg products, which are the responsibility of the U.S. Department of Agriculture Food Safety and Inspection Service (USDA FSIS) (FDA, 2012d). A detailed description of how FDA enforces pesticide residues in animal food is available in CPG Sec. 575.100 Pesticide Residues in Food and Feed – Enforcement Criteria (FDA, 2015e). If pesticide residues are present in food in the absence of, or in excess of, a tolerance, the food is deemed adulterated under section 402(a)(2)(B) of the FD&C Act (21 U.S.C. 342(a)(2)(B)). The most common reasons for adulteration of food products with pesticide residues are the improper treatment of raw materials with registered pesticides, and raw materials being exposed to prohibited pesticides.

Fruits and vegetables that have been grown in the United States usually are in compliance with EPA's pesticide tolerance regulations. If you obtain produce from a foreign country you should take steps to ensure that the imported produce will be in compliance with U.S. pesticide tolerance regulations, such as by considering pesticide residues to be chemical hazards that warrant preventive controls, such as supply-chain controls with a supplier verification program.

3.4.1.2 Animal drug residues

Animal drug residues may be of concern for foods of animal origin, including muscle meat, organ meat, fat/skin, eggs, honey, and milk. In the United States, animal drugs require approval by FDA before they can be administered to food-producing animals. Depending on the chemical property of the drug, residues of certain drugs can become concentrated during food manufacturing and processing. For example, if a fat-soluble, heat-stable drug residue is present in raw milk, the drug can get concentrated when the milk is converted to full fat cheese (Cerkvenik et al., 2004; Imperiale et al., 2004). Potential effects of drug residues range from short-term effects as a result of acute allergic reactions (e.g., penicillin) to long-term effects from drug resistant bacteria (Dayan, 1993). An example of an unapproved drug residue that has adulterated food is fluoroquinolone, which is an antibiotic that has not been approved for use on honey bees in the United States and has been detected in honey products from certain regions outside the United States (FDA, 2015a).

Drug residues in a food derived from an animal (such as milk) are considered a hazard if a tolerance has not been established for the particular drug-food combination, or if the tolerance level has been exceeded. Animal drugs used according to labeled directions should not result in residues in meat, poultry, milk, or egg products. When your hazard analysis identifies drug residues that require a preventive control, supply-chain controls with a supplier verification program could be an appropriate preventive control to manage the potential risk.

3.4.1.3 Heavy metals

Heavy metals, including lead, cadmium, arsenic, and mercury, may be of concern in certain foods as a result of agricultural practices (e.g., use of pesticides containing heavy metals or because crops are grown in soil containing elevated levels of heavy metals due to industrial waste), or the leaching of heavy metals from equipment, containers or utensils that come in contact with foods. Consumption of heavy metals in foods can lead to adverse health consequences. For example, lead exposure can impair cognitive development in children (FDA, 2006a). Consumption of inorganic arsenic has been associated with cancer, skin lesions, developmental effects, cardiovascular disease, neurotoxicity, and diabetes in humans (JEFCA, 2010).

When your hazard analysis identifies a heavy metal that requires a preventive control, the type of control would depend on how the heavy metal could get into your food product. In some cases, high levels of heavy metals may result from the environment (e.g., high lead levels in carrots that were grown in lead-contaminated soil). If your food product contains a food crop that is known to have been contaminated with a heavy metal through contaminated soil, a preventive control such as a supply-chain control with a verification program to ensure that the grower conducts an assessment of the growing region prior to its use for agriculture may be appropriate. In other cases, an unsafe level of a heavy metal such as lead could be introduced into a food product as a result of a food-contact surface constructed with lead solder. CGMP controls, such as the controls on equipment and utensils in 21 CFR 117.40, generally can control chemical hazards such as heavy metals that can leach from food-contact surfaces.

3.4.1.4 Environmental contaminants

Environmental contaminants may be of concern in certain foods as a result of their presence in the environment. When your hazard analysis identifies an environmental contaminant that

requires a preventive control, the type of control would depend on how the environmental contaminant could get into your food product. In some cases, high levels of environmental contaminants (e.g., dioxin) may result from accidental contamination of animal feed (WHO, 2014). In 2008, pork meat and pork products were recalled in Ireland when up to 200 times the safe limit of dioxins were detected in samples of pork, although risk assessments indicated no public health concern. The contamination was traced back to contaminated feed. In 1999, high levels of dioxins were found in poultry and eggs from Belgium and in several other countries. The cause was traced to animal feed contaminated with illegally disposed PCB-based waste industrial oil. Because dioxins tend to accumulate in the fat of food-producing animals, consumption of animal-derived foods (e.g., meat, poultry, eggs, fish, and dairy products) is considered to be the major route of human exposure, and FDA has developed a strategy for monitoring, method development, and reducing human exposure (FDA, 2002).

3.4.1.5 Mycotoxins and other natural toxins

Natural toxins, such as mycotoxins, histamines and other biogenic amines, and plant-produced substances (such as the toxin hypoglycin A found in the tropical fruit ackee) are well recognized as hazards in raw or processed agricultural commodities (FDA, 2005a; FDA 2005b; FDA, 2005c; FDA, 2005d).

Mycotoxins are a common group of natural toxins that include aflatoxin, fumonisin, deoxynivalenol (vomitoxin), ochratoxin, and patulin (see Table 3-7). Mycotoxins are toxic metabolites produced by certain fungi (i.e., molds) that can infect and proliferate on agricultural commodities (e.g., grains such as wheat and corn, peanuts, fruits, and tree nuts) in the field and during storage. Mycotoxins may produce various toxicological effects. Some mycotoxins are teratogenic, mutagenic, or carcinogenic in susceptible animal species and are associated with various diseases in domestic animals, livestock, and humans in many parts of the world. The occurrence of mycotoxins in human and animal foods is not entirely avoidable; small amounts of these toxins may be found on agricultural commodities. Occurrence of these toxins on commodities susceptible to mold infestation is influenced by environmental factors such as temperature, humidity, and the extent of rainfall during the pre-harvesting, harvesting, and post-harvesting periods. The molds that produce mycotoxins typically grow and become established in the agricultural commodity during stressful growing and holding conditions, such as insect damage to the crop, drought stress, and wet storage (e.g., from condensation). Although mycotoxins are not a hazard requiring a preventive control during times and locations with good growing and harvest conditions, a preventive control such as supply-chain controls with a supplier verification program may be appropriate if you use agricultural commodities susceptible to mycotoxin formation, because growing and harvest conditions vary from year to year.

Table 3-7 Common Mycotoxins Associated with Commodities

Mycotoxins	Commodities Associated with Mycotoxins
Aflatoxin	Peanuts, dried corn, tree nuts
Ochratoxin	Coffee, raisins, cereal grains
Fumonisins	Dried corn
Deoxynivalenol	Wheat, barley

Mycotoxins	Commodities Associated with Mycotoxins
Patulin	Apples

Histamines and other biogenic amines are produced from the breakdown of amino acids by bacteria in animal-derived foods (e.g., histamine is produced from the amino acid histidine). Effects of foodborne histamines or other biogenic amines generally are acute effects, including headache, nausea, heart palpitations, facial flushing, itching, urticaria (hives), and gastrointestinal upset. Consumption of certain cheeses, especially aged cheeses, has been associated with illness from histamines (Taylor and WHO, 1985; Stratton et. al, 1991). If you determine that cheeses you use as a raw material present a histamine hazard, you must identify and implement a preventive control (see 21 CFR 117.135(a)). If you purchase such cheeses, we recommend a supply-chain control with a supplier verification program as well as temperature controls to minimize growth of histamine-producing microorganisms.

An example of a natural toxin produced by a plant is hypoglycin A, a heat stable toxin found in the tropical fruit ackee. The level of hypoglycin A in the edible portion of the ackee fruit decreases as the fruit ripens. Only properly ripened and processed ackee products with hypoglycin A at negligible levels are safe for consumption (FDA, 2015f). Although some persons consume unripe ackee with no adverse effects, other persons who consume unripe ackee with hypoglycin A exhibit symptoms that range from mild (e.g., vomiting) to severe (e.g., vomiting with profound hypoglycemia, drowsiness, muscular exhaustion, and possibly coma and death).

3.4.1.6 Chemical hazards that may be intentionally introduced for purposes of economic gain

The PCHF requirements specify that you must consider, as part of your hazard identification, known or reasonably foreseeable hazards that may be intentionally introduced for purposes of economic gain (21 CFR 117.130(b)(2)(iii)). We recommend that you focus on circumstances where there has been a pattern of such adulteration in the past, suggesting a potential for intentional adulteration even though the past occurrences may not be associated with the specific supplier or the specific food product. Table 3-8 is a quick reference guide listing circumstances where there has been a pattern of such adulteration in the past. Additional resources include a free on-line food fraud database made available by the U.S. Pharmacopeial Convention (USP)[3] (USP, 2014 and USP, 2016), a report from the Congressional Research Service (Congressional Research Service, 2014), and a report that identifies 137 unique incidents in 11 food categories (Everstine et al., 2013).

[3] USP is a scientific nonprofit organization that sets standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements manufactured, distributed and consumed worldwide.

Table 3-8. Quick Reference Guide for Hazards That May Be Intentionally Introduced for Purposes of Economic Gain

Food Containing the Hazard	Hazard	Details	Reference
Milk	Melamine	Milk firms in one country added melamine, a nitrogen-rich industrial by-product, to diluted dairy products to increase the apparent protein content	FDA, 2008
Turmeric	Lead chromate	A chemical with a vibrant yellow color that has been used as an adulterant in turmeric to change the color of the spice to suggest that it is of a higher quality	FDA, 2013d
Paprika	Lead oxide	A red chemical that has been used as an adulterant in paprika to change the color of the spice to suggest that it is of a higher quality	Lead Action News, 1995
Chili powder	Sudan I	An orange-red powder that had been added to chili powder as a coloring agent, but is now banned in many countries because the International Agency for Research on Cancer has classified it as a category 3 carcinogen (not classifiable as to its carcinogenicity to humans)	United Kingdom Food Standards Agency, 2005

In determining whether a hazard that may be intentionally introduced for purposes of economic gain is a hazard requiring a preventive control, we recommend that your hazard analysis consider both the country of origin of an ingredient that may contain the hazard and any specific supplier associated with an ingredient containing that hazard. For example, one example listed in Table 3-8 is a widespread incident of economically motivated adulteration in which some milk firms in one country added melamine, a nitrogen-rich industrial by-product, to diluted dairy products to increase the apparent protein content (FDA, 2008). This adulteration resulted in significant public health consequences, with more than 290,000 ill infants and 6 deaths in that country. In light of this incident, we recommend that you include in your hazard analysis the potential for melamine to be an economically motivated adulterant in your food products when using milk products from a country where melamine adulteration has occurred and, based on the outcome of that hazard analysis, determine whether melamine is a hazard that must be addressed in your food safety plan. At present, we do not expect you to consider the potential for melamine to be a significant hazard when using domestic milk products, or milk products from other countries when there is no history of melamine adulteration associated with those countries.

If you determine through your hazard analysis that a hazard that may be intentionally introduced for purposes of economic gain is a hazard requiring a preventive control, we recommend that you address that hazard through your supply-chain program.

3.4.2 Chemical Hazards That Can Be Either Ingredient-Related or Process-Related

3.4.2.1 Food allergens

Researchers estimate that up to 15 million Americans and more than 17 million Europeans have food allergies (FARE, 2015). A number of foods contain allergenic proteins, which are natural constituents of the food that can pose a health risk to certain sensitive individuals. The symptoms of food allergies can include a tingling sensation in the mouth, swelling of the tongue and throat, nausea, difficulty in breathing, chest pain, hives, rash, itchy skin, vomiting, abdominal cramps, diarrhea, sudden drop in blood pressure, loss of consciousness, and, in severe cases, death. Symptoms of a food allergy usually come on suddenly, can be triggered by a small amount of food, and happen every time the food is eaten. The symptoms are the result of the body's immune system reacting to a specific food or an ingredient in the food.

Allergic consumers must avoid allergens to prevent potentially life threatening reactions. Undeclared food allergens are chemical hazards that can get into food because either: (1) The food manufacturer did not properly declare a food allergen ingredient on the product label; or (2) unintended (and, thus, undeclared) food allergens are present in a food due to incorrect labeling or due to allergen cross-contact.

This section of this chapter provides a general discussion of food allergen hazards and common mechanisms to control them. For more detailed information, see Chapter 11 – Food Allergen Controls, which provides a comprehensive guide to food allergen control. An additional resource is "Managing Allergens in Food Processing Environments," a publication of the Grocery Manufacturer's Association (GMA, 2009).

3.4.2.1.1 The "Big Eight" food allergens

The Food Allergen Labeling and Consumer Protection Act (FALCPA) of 2004 amended the FD&C Act and defined the following eight foods and any ingredients that contain protein derived from these eight foods (with certain exemptions noted in section 201(qq)(2) of the FD&C Act (21 U.S.C. 321(qq)(2)) as major food allergens: milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, and soybeans. The eight foods or food groups cause more than 90% of the food allergies in the United States (FDA, 2015c) and are commonly referred to as "the big eight" food allergens. FDA has published guidance on labeling the food allergens identified in FALCPA – See "Guidance for Industry: Questions and Answers Regarding Food Allergens, including the Food Allergen Labeling and Consumer Protection Act of 2004" (FDA, 2006b). Immediately below, we provide more information about each of "the big eight food allergens."

- **Crustacea:** The class of Crustacea, or shellfish, includes shrimp, crab, lobster, and crayfish. Crab and shrimp are the most commonly consumed shellfish in the United States. The major shellfish allergen is tropomyosin, a muscle protein that accounts for 20% of the dry weight of shrimp (GMA, 2009).

- **Egg:** Most egg allergic proteins are found in the egg white (albumin) rather than the yolk.
- **Fish:** Different fish species (e.g., bass, cod, and flounder) have been found to have structurally-related proteins, and this may explain why individuals with a fish allergy are allergic to multiple types of fish. Cooking may reduce the allergenicity of fish, but it does not eliminate it.
- **Milk (Dairy):** Cow's milk contains a number of different proteins that are grouped into two categories: caseins, which constitute 80% of the total protein, and whey proteins, which make up 20%.
- **Peanut:** Peanut seeds contain an average of about 29% protein, classified as albumins or globulins.
- **Soy:** Globulins are the major proteins in soybeans.
- **Tree Nuts:** Tree nuts include almonds, Brazil nuts, cashews, filberts/hazelnuts, macadamia nuts, pecans, pine nuts, pistachios, and walnuts. FDA lists the nuts considered "tree nuts" in its 2006 "Guidance for Industry: Questions and Answers Regarding Food Allergens, including the Food Allergen Labeling and Consumer Protection Act of 2004 (Edition 4)" (FDA, 2006b) and its 2013 Guidance for Industry: A Food Labeling Guide (FDA, 2013a).
- **Wheat:** Wheat proteins include the globulins, prolamins (i.e., glutenin and gliadin), and glutelins. About 25% of wheat-allergic children react to other cereal grains (i.e., barley, oats, or rye). Gluten is a mixture of proteins that occur naturally in wheat, rye, barley and crossbreeds of these grains. It is associated with celiac disease, which affects as many as 3 million people in the United States by the body's natural defense system attacking the lining of the small intestine and preventing the proper absorption of nutrients (FDA, 2015(d)).

3.4.2.1.2 Undeclared food allergen hazards due to incorrect label design

FALCPA also amended section 403 of the FD&C Act (21 U.S.C. 343) to prescribe certain requirements for what you must declare on the product label for any food product that contains any of the "big eight allergens," including allergenic whole foods (such as milk) and any ingredients that contain protein derived from these foods (such as casein derived from milk). See section 403(w) of the FD&C Act (21 U.S.C. 343(w)) and our guidance entitled "Guidance for Industry: Questions and Answers Regarding Food Allergens, including the Food Allergen Labeling and Consumer Protection Act of 2004" (FDA, 2006b).

An undeclared food allergen (including a food allergen contained in flavorings, colorings, and incidental additives) due to an incorrect label design that does not address all of the labeling requirements of FALCPA is a chemical hazard. See 21 CFR 117.130(b)(1)(ii).

3.4.2.1.3 Undeclared food allergen hazards due to incorrect application or use of a product label

If you apply the wrong label to a food, or use the wrong packaging (e.g., using packaging for "chocolate ice cream" rather than for "chocolate ice cream with almonds"), consumers who have a food allergy could purchase a food that would cause an allergic reaction. An undeclared food allergen due to applying the incorrect food label to a product, or using the wrong packaging, is a chemical hazard. See 21 CFR 117.130(b)(1)(ii).

3.4.2.1.4 Undeclared food allergen hazards due to allergen cross-contact

Cross-contact results from the unintentional incorporation of undeclared allergens into foods that are not intended to include those allergens. Cross-contact can occur either between foods that contain different food allergens or between foods with and without food allergens. Introduction of an allergen through cross-contact may occur during receiving, handling,

processing and storage of ingredients and foods, utensils, and packaging; through improper handling and cleaning of equipment, utensils, and facilities; and through improper facility design.

An undeclared food allergen due to allergen cross-contact is a chemical hazard. See 21 CFR 117.130(b)(1)(ii). Allergen cross-contact can result from:

- Failure to schedule the production of two different products appropriately, resulting in an allergen-containing product contaminating a product without food allergens.
- Failure to adequately clean between two different formulations of a product that do and do not contain allergens, resulting in an allergen-containing product contaminating a product without the allergen.
- Failure to store allergen-containing ingredients separately from ingredients that do not contain allergens, where leakage of allergen-containing materials results in contamination of the non-allergen containing product.
- Failure to handle powdered allergens in a way that prevents particles from blowing onto foods or food contact surfaces for foods that do not contain that allergen.

3.4.2.2 Food additives, color additives, and GRAS substances, including substances associated with food intolerance or food disorder

Under sections 201(s) and 409 of the FD&C Act (21 U.S.C 321(s) and 348, respectively), a substance that is added to food requires premarket review and approval as a food additive unless it satisfies the statutory exclusion from the definition of "food additive" for a substance that is generally recognized as safe (GRAS) under the conditions of its intended use (section 201(s) of the FD&C Act or is otherwise excepted from the statutory definition of food additive (e.g., as a color additive, as a dietary ingredient intended for use in a dietary supplement, or as a new animal drug).

Under sections 201(t) and 721 of the FD&C Act (21 U.S.C 321(t) and 379(e), respectively), a color additive requires premarket review and approval; there is no statutory GRAS exclusion applicable to a color additive.

Generally, a food additive, color additive, or GRAS substance is known to be safe for use in food only under specific conditions of use, such as a maximum level of use or use only in certain food categories. The potential risk to consumers increases when these substances are not properly controlled, such as exceeding the usage rates or accidentally introducing an additive into a food for which it was not approved.

For some consumers, certain substances (including substances that are lawfully used in food as food additives, color additives, GRAS substances, and components of whole foods such as milk) can cause hypersensitivity reactions because the substance irritates the stomach, or the body cannot properly digest it. The symptoms include nausea, abdominal pain, diarrhea, vomiting, gas, cramps or bloating, heartburn, headaches, irritability, or nervousness. Symptoms of food intolerance usually occur gradually, in comparison with the sudden onset from an allergic reaction, and may only occur when a lot of a food is consumed or the food is consumed often.

- **Lactose:** Some people are intolerant to lactose, a sugar that is a component of milk, because they lack the enzyme to digest lactose. The symptoms include abdominal pain, diarrhea, vomiting, gas, cramps or bloating. People who have a lactose intolerance avoid milk or milk products and rely on the allergen labeling for milk to identify the types of products that may cause them problems.

- **Sulfiting agents:** Sulfiting agents are used as chemical preservatives in various products. People sensitive to sulfiting agents can experience symptoms that range from mild to life-threatening reactions. As noted previously, sulfites have resulted in diarrhea, headache, difficulty breathing, vomiting, nausea, abdominal pain and cramps in sulfite-sensitive individuals (Timbo et al. 2004).
- The sulfiting agents permitted in foods that must be listed on the ingredient label, unless they are added to food as an "incidental substance," are: sulfur dioxide (21 CFR 182.3862), sodium sulfite (21 CFR 182.3798), sodium bisulfite (21 CFR 182.3739), sodium metabisulfite (21 CFR 182.3766), potassium bisulfite (21 CFR 182.3616), and potassium metabisulfite (21 CFR 182.3637). Sulfiting agents are considered to be incidental only if they have no technical effect in the finished food and are present at less than 10 parts per million (ppm) (21 CFR 101.100(a)(4)). The quantity of sulfiting agents added to food should not exceed the amount necessary to achieve the intended technical effect(s).
- **Yellow No. 5:** Yellow No. 5 (tartrazine) is a color additive subject to color certification under section 721(c) of the FD&C Act. (21 U.S.C. 379e) People sensitive to Yellow No. 5 can experience symptoms that range from mild to moderately severe. For example hives occur in some intolerant individuals, but in asthmatic individuals Yellow No.5 can trigger allergic-type reactions (including bronchial asthma). To help protect people who are sensitive to Yellow No. 5, FDA's regulation for Yellow No. 5 states that any food for human use that contains Yellow No. 5 must specifically declare the presence of the color additive by listing it as an ingredient (21 CFR 74.705(d)(2)). If Yellow No. 5 is added but is not declared, the product would be both misbranded under section 403(m) of the FD&C Act (21 U.S.C. 343(m) and adulterated under section 402(c) of the FD&C Act (21 U.S.C 342(c)).
- **Cochineal extract and carmine:** Cochineal extract and carmine are color additives permitted for use in foods in the United States under conditions of safe use listed in 21 CFR 73.100. For sensitive consumers, cochineal extract and carmine can cause severe allergic reactions, including anaphylaxis (74 FR 207, January 5, 2009). Although the color additives cochineal extract and carmine cause allergic reactions, they are not included in the eight major food allergens identified in FALCPA. As a result, the color additives cochineal extract and carmine are not included in the definition of "food allergen" in part 117 and are not subject to the food allergen controls specified in the PCHF requirements. In addition, FDA's specific labeling requirement in the color additive listing for cochineal extract and carmine (21 CFR 73.100(d)(2)), rather than the more general labeling requirements of FALCPA, govern the food labeling requirements cochineal extract and carmine. All human foods containing cochineal extract or carmine are required to declare the presence of the color additive by listing its respective common or usual name, "cochineal extract" or "carmine," in the statement of ingredients ((21 CFR 73.100(d)(2)). Additional information on the labeling requirements for these two color additives can be found in FDA industry guidance, *Cochineal Extract and Carmine: Declaration by Name on the Label of All Foods and Cosmetic Products That Contain These Color Additives; Small Entity Compliance Guide* (FDA, 2009a). Control strategies for cochineal extract and carmine are similar to those applied to food allergen labeling controls.

In addition, some consumers have celiac disease, which is a hereditary, chronic inflammatory disorder of the small intestine triggered by the ingestion of certain storage proteins (referred to as gluten) occurring in wheat, rye, barley, and crossbreeds of these grains. As discussed in section 3.4.2.1.1 of this chapter, celiac disease affects as many as 3 million people in the United States (FDA, 2015(d)).

3.4.2.2.1 Unapproved food additives and color additives

A substance (other than a food contact substance subject to a notification under section 409(h)) that is a food additive or a color additive must be used in accordance with a food additive regulation permitting that specific use or a color additive listing. Otherwise, the presence of that substance in food would make the food adulterated under section 402(a)(2)(C) of the FD&C Act

(21 U.S.C. 342(a)(2)(C)). Under the PCHF requirements, an unapproved food or color additive is a chemical hazard (see 21 CFR 117.130(b)(1)(ii)).

Some food and color additives are specifically prohibited from use in food because we have determined that the chemical additive poses a potential risk to public health (see 21 CFR part 189 and 21 CFR 81.10). Examples of such food and color additives are coumarin, safrole, and FD&C Red No. 4 (Red No. 4) (FDA, 2015b). We consider a prohibited food additive or color additive to be an unapproved food additive or color additive for the purposes of the PCHF requirements and, thus, to be a chemical hazard. You should consult 21 CFR if you have questions about the regulatory status or safety of a particular additive when formulating your food products. An additional resource for you is the *Food Additive Status List* on our website (FDA, 2014b).

3.4.2.2.2 Chemical hazards due to misformulation

A food ingredient can be a chemical hazard if it is added in excess of a maximum use level, regardless of whether the maximum use level is established due to food intolerance (such as for sulfites) or is otherwise a condition of safe use of a food additive, color additive, or GRAS substance. Control strategies to prevent misformulation of substances generally include process controls to ensure that excessive amounts are not added.

3.4.2.2.3 Chemical hazards due to incorrect labeling of substances associated with food intolerance or food disorder

Although the mechanisms whereby persons experience food intolerance or food disorder are different from the mechanisms that cause food allergy, reactions due to food intolerance or food disorder can cause significant health problems for those affected, and the principal means that consumers have to avoid the symptoms of food intolerance are the same means that consumers use to avoid symptoms of food allergy – i.e., avoid foods containing the substance that causes the problem. For example, people who are intolerant to lactose, a sugar that is a component of milk, avoid food products containing milk to avoid the symptoms associated with lactose intolerance. In addition, people who have celiac disease avoid food products containing wheat and other sources of gluten.

Undeclared substances associated with a food intolerance or food disorder are chemical hazards that can get into food because either: (1) The food manufacturer did not properly declare the substance on the product label; (2) unintended (and, thus, undeclared) substances are present in a food due to incorrect labeling. Control strategies to prevent incorrect labeling of substances associated with a food intolerance or food disorder are analogous to those used to prevent incorrect labeling of food allergens and, thus, you may find Chapter 11—Food Allergen Controls helpful in preventing incorrect labeling of substances associated with a food intolerance or food disorder. The preventive controls in that comprehensive guide to food allergen control do not explicitly address substances associated with food intolerance or food disorder, but may nonetheless be useful in addressing chemical hazards due to incorrect labeling of such substances.

3.4.2.4 Process contaminants produced during heating

There are several process-related contaminants that are produced during heating of specific ingredients or finished foods that may be a health (e.g., cancer) concern. For example,

acrylamide is formed during high-temperature cooking processes (including frying, roasting, or baking) due to interaction between sugars and amino acids that are naturally present in foods. Acrylamide is found mainly in foods made from plants, including potato products, grain products, and coffee.

As noted in footnote 8, we have not included such contaminants in Table 3-6 as potential process-related chemical hazards that may require a preventive control as part of a food safety plan under part 117 because we believe that more information is needed regarding appropriate levels and effective controls. We have published a guidance document, *Guidance for Industry: Acrylamide in Foods* (FDA, 2016a) to help growers, manufacturers, and food service operators reduce acrylamide levels in certain foods. Control strategies to reduce acrylamide in food may include controlling temperatures during cooking and ingredient substitution.

3.4.2.3 Radiological hazards

Radiological hazards rarely occur in the food supply; however, when they do occur, these hazards can present a significant risk when exposures occur over a period of time (WHO, 2011). Consuming food contaminated with radionuclides will increase the amount of radioactivity a person is exposed to, which could have adverse health effects. The health effect depends on the radionuclide and the amount of radiation to which a person is exposed. For instance, exposure to certain levels of radioactive iodine is associated with increased risk of thyroid cancer (WHO, 2011).

Radiological hazards can become incorporated into food through the use of water that contains the radionuclides during food production or manufacture. There are areas in the United States where high concentrations of some radionuclides, such as radium-226, radium-228, and uranium, can be detected in well water (Ayotte et al., 2007; Focazio et al., 2001). You should be aware of the condition of the water used for production and manufacture in your facilities. For example, if your facility uses well water and there are elevated levels of radionuclides in the well water, you should not use the water. The CGMPs require that water that contacts food, food-contact surfaces, or food-packaging materials be safe and of adequate sanitary quality (see 21 CFR 117.37(a)).

Radiological hazards also may result from accidental contamination, e.g., contamination arising from accidental release from a nuclear facility or from damage to a nuclear facility from a natural disaster. In 2011, following damage to a nuclear power plant during an earthquake and tsunami in Japan, radioactivity was subsequently detected in foods, particularly milk, vegetables, and seafood produced in areas neighboring the plant (WHO, 2011). You should be vigilant regarding accidental releases of radiological hazards and their potential to contaminate your food product, either directly due to contamination of natural resources near your facility or as a result of raw materials and other ingredients that you obtain from a region that has experienced an accidental release of radiation.

3.4.3 Facility-Related Chemical Hazards

Industrial chemicals or other contaminants from the food processing environment can contaminate food during production – e.g., if chemicals used to clean a production line are not adequately removed from the production line or if heavy metals are leaching from containers or utensils. In this guidance, we do not discuss preventive controls for facility-related chemical hazards such as cleaning chemicals and the leaching of heavy metals from containers or utensils, because such hazards are usually addressed through CGMPs.

3.5 Physical Hazards

You must conduct a hazard analysis to identify and evaluate known or reasonably foreseeable physical hazards (such as stones, glass, and metal fragments). See 21 CFR 117.130(b)(1)(iii). When your hazard analysis identifies a known or reasonably foreseeable physical hazard that requires a preventive control, you must identify and implement a preventive control for the physical hazard. See 21 CFR 117.135(a)(1).

Physical hazards are broadly classified as "hard/sharp" physical hazards and "choking" hazards. Both categories can cause injury to the consumer. These injuries may include dental damage, laceration of the mouth or throat, laceration or perforation of the intestine, and choking and may even lead to the death. Because physical hazards cover a broad range of contaminants, such as glass, metal, plastic, wood, and stones, such contamination can occur throughout the processing facility, including the receiving dock for ingredients and supplies.

In this section of this guidance we describe common physical hazards – i.e., metal, glass, and hard plastic physical hazards.

- **Metal:** Metal-to-metal contact during processing can introduce metal fragments into products. For example, metal fragments can break off during mechanical cutting and blending operations, and some metal equipment has parts that can break or fall off, such as wire-mesh belts. FDA's Health Hazard Evaluation Board (FDA, 2005e; Olsen, 1998) has supported regulatory action against products with metal fragments of 0.3 inches (7 mm) to 1.0 inches (25 mm) in length. Such fragments have been shown to be a hazard to consumers. Metal hazards can be controlled by the use of metal detection devices or by regular inspection of at-risk equipment for signs of damage.
- **Glass:** Glass fragments can be introduced into food whenever processing involves the use of glass containers. Normal handling and packaging methods, especially mechanized methods, can result in breakage. Ingesting glass fragments can cause injury to the consumer. FDA's Health Hazard Evaluation Board has supported regulatory action against products with glass fragments of the same size noted for metal. Most products packed in glass containers are intended to be a ready-to-eat (RTE) commodity. In your hazard analysis, you should consider the potential for glass fragments to originate from sources other than glass containers used in packaging. For example, some facilities that do not pack in glass prohibit the presence of glass in the production environment to reduce the risk of glass getting into the product. You can address glass fragments originating from sources such as overhead light fixtures through CGMPs.
- **Hard Plastic:** Hard plastic can be introduced into food when tools and equipment such as scoops, paddles, buckets or other containers develop fatigue, crack, and break as they wear. Hard plastic also can be introduced into food when plastic sieves and screens deteriorate. You should examine items to determine whether they are worn and remove worn items before they break, especially if they cannot be effectively cleaned (e.g., because of small cracks).

In general, there is overlap between facility-related physical hazards and process-related physical hazards. For example, equipment that has food-contact surfaces that break during food processing and result in physical debris being deposited in the food product can be considered a facility-related physical hazard (because the equipment is part of the facility) or a process-related physical hazard (because the equipment broke during processing). In general, in evaluating the potential for physical hazards in your food products, it does not matter whether you consider physical hazards to be facility-related or process-related. However, a few physical hazards can readily be classified as facility-related or process-related. For example, nuts and bolts used during maintenance procedures would be a facility-related hazard, but production equipment that has nuts and bolts that could fall out during production would be a process-related hazard.

Table 3-9 is a Quick Reference Guide to help you identify common sources of these physical hazards. See Chapter 13 – Preventive Controls for Physical Hazards for more detailed recommendations on control measures for physical hazards. In this guidance, we do not discuss ingredient-related physical hazards such as wood and stone, which are usually addressed through CGMPs or as a supply-chain control through your supplier program.

Table 3-9. Quick Reference Guide for Common Sources of Physical Hazards

Source	Metal – Ferrous & Non-ferrous	Plastic, Ceramic, and Glass	Other
Ingredient-related	• Farm field debris • Precut, ground, injected, sliced, items, where metal was not properly controlled by supplier.	• Farm field debris, • Packaging materials	• Pits or pit fragments, shells
Facility-related and process-related (processing/production environment, equipment, and pests (insects, birds, rodents, reptiles))	• Equipment • Grinders, slicers, knives • Sieves, screens, wire-mesh belts • Mixing paddles • Metal cans (shavings, lids) • Pumps • Cook Kettles with swept surface paddles • Drop buckets	• Equipment (inspection belts, small wares, buckets) • Facility (glass light fixtures, glass windows in doors, plastic strip curtains) • Glass containers • Scoops • Mixing paddles • Buckets	• Incomplete removal of pits or pit fragments, shells • Poor Design -- Particle size of food inappropriate for consumer – choking hazard
People-related (actions or behaviors)	• Jewelry • Hair pins	• Buttons • Zipper pulls	

3.6 References

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